UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL

FACULDADE DE MEDICINA

PROGRAMA DE PÓS-GRADUAÇÃO EM PSIQUIATRIA E CIÊNCIAS DO COMPORTAMENTO

TESE DE DOUTORADO

EFEITO DA RESISTÊNCIA À INSULINA EM PROCESSOS COGNITIVOS RELACIONADOS AO COMPORTAMENTO ALIMENTAR DE INDIVÍDUOS COM BAIXO PESO AO NASCER: EVIDÊNCIAS DO CICLO VICIOSO DA OBESIDADE

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Tese apresentada como requisito parcial para a obtenção do título de Doutor à Universidade Federal do Rio Grande do Sul, Faculdade de Medicina, Programa de Pós-Graduação em Psiquiatria e Ciências do Comportamento.

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CIP - Catalogação na Publicação

Lovato, Amanda Brondani Mucellini
Efeito da resistência à insulina em processos cognitivos relacionados ao comportamento alimentar de indivíduos com baixo peso ao nascer: evidências do ciclo vicioso da obesidade / Amanda Brondani Mucellini Lovato. -- 2018.
182 f.
Orientadora: Gisele Gus Manfro.

Coorientadora: Patrícia Pelufo Silveira.

Tese (Doutorado) -- Universidade Federal do Rio Grande do Sul, Faculdade de Medicina, Programa de Pós-Graduação em Psiquiatria e Ciências do Comportamento, Porto Alegre, BR-RS, 2018.

1. Retardo do Crescimento Intrauterino. 2. Comportamento Alimentar. 3. Hipocampo. 4. Resistência à Insulina. 5. Pesquisa Médica Translacional. I. Gus Manfro, Gisele, orient. II. Pelufo Silveira, Patrícia, coorient. III. Título.

Elaborada pelo Sistema de Geração Automática de Ficha Catalográfica da UFRGS com os dados fornecidos pelo(a) autor(a).

ATA AUTENTICADA

UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL
Faculdade de Medicina

Programa de Pós-Graduação em Psiquiatria e Ciências do Comportamento
PSIQUIATRIA - Doutorado
Ata de defesa de Tese

Aluno: Amanda Brondani Mucellini Lovato, com ingresso em 05/08/2013

Título: Efeito da resistência à insulina em processos cognitivos relacionados à alimentação de indivíduos com baixo peso ao nascer: evidências do ciclo vicioso da obesidade

Data: 08/01/2018
Horário: 08:00
Local: Auditório Tuiskon Dick - 2º andar do CPE (HCPA)

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Antonio Marcus de Andrade Paes	A	UFMA
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Conceito Geral da Banca: A
Data da homologação:

Porto Alegre, 04 de abril de 2018

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Porto Alegre - RS

Ao Giovanni e aos meus filhos,

sentido da minha vida.

AGRADECIMENTOS

A Deus Nosso Rei e Senhor, por conduzir pacientemente seus filhos ao Caminho, à Verdade e à Vida.

À Nossa Senhora Maria Santíssima, por todas as graças intermediadas.

Ao meu doce bebê Matias, pelo amor de filho, pela renovação do sentido da vida e pelas oportunidades de ser uma mãe melhor.

Ao meu amado esposo Giovanni, pela tenacidade, paciência e sacrifícios para que nossa família alcance o seu verdadeiro fim.

Aos meus pais Odemar e Anete, pelos sacrifícios, orações e amor.

À minha irmã Paula, pela dedicação, confiança e amizade.

Aos meus sogros Thomé e Rosângela Lovato, pela dedicação e pelos incentivos.

Aos membros da minha família distantes ou não mais presentes neste mundo, por tudo que transmitiram para a minha formação.

Aos meus amigos, especialmente ao Thales Lobo e à Grace Pardo, pelo carinho e colaboração.

À Profª Patrícia Pelufo Silveira, pelo incentivo, pela dedicação e pela fineza de raciocínio.

À Profª Gisele Gus Manfro, pela oportunidade, pela confiança e pela sabedoria.

Aos colegas do grupo DOHaD Roberta Dalle Molle, Daniela Laureano, Tânia Machado, Danitsa Rodrigues, Natasha de Oliveira, Roberta Reis, Márcio Alves, Fábio Cunha, Ana Carla da Cunha, Mariana Balbinot, Ana Paula Salvador, Patrícia Miguel, Cristian Figueroa, Adolfo Reis e Marilyn Agranonik, pelas parcerias e amizade.

Aos colegas do grupo PROTAIA, especialmente ao Prof. Giovanni Salum Jr., à Rudineia Toazza e à Andressa Bortoluzzi, pela receptividade, pela colaboração e pelo aprendizado.

Aos professores e colegas do Departamento de Bioquímica, especialmente à Profª Carla Dalmaz, à Danusa Arcego, à Natividade Pereira, à Ana Paula Toniazo e à Carine Lampert, pelos auxílios e aprendizados.

Aos professores Alexandre Franco, Augusto Buchweitz, Michael Meaney, Luciano Minuzzi e aos seus alunos, e ao Marouane Nassim e à Irina Pokhvisneva, por possibilitarem e facilitarem as análises estatísticas e de MRI.

Aos participantes voluntários do projeto de pesquisa clínica, pela confiança e pela colaboração para com nosso trabalho.

Aos funcionários dos Centros de Pesquisa Experimental e Clínica do HCPA e do Instituto do Cérebro do Rio Grande do Sul da PUCRS, especialmente ao Everaldo Almeida, ao Jeferson da Silva, à Marta Cioato e à Andrea Rambo, pela prontidão e pelo profissionalismo.

Aos coordenadores, professores e funcionários do Programa de Pós-Graduação em Psiquiatria e Ciências do Comportamento, especialmente à Claudia Grabinski, pela dedicação e pela excelência.

Aos professores componentes da banca examinadora Eugenio Grevet, Lisiane Bizarro, Antonio Marcus Paes e Luis Portela Roska, pela disponibilidade e pela competência na avaliação deste trabalho.

Ao CNPq, pela bolsa de doutorado.

Ao CNPq, à CAPES e ao HCPA, pelo auxílio financeiro para execução dos projetos de pesquisa e para a participação de eventos científicos.

À UFRGS e ao Programa de Pós-Graduação em Psiquiatria e Ciências do Comportamento, pela oportunidade de realizar o doutorado.

Orandum est ut sit mens sana in corpore sano.	Deve-se pedir em oração que a mente seja sã num corpo são.
fortem posce animum mortis terrore carentem,	Peça uma alma corajosa que careça do temor da morte,
qui spatium uitae extremum inter munera ponat	que ponha a longevidade em último lugar entre as bênçãos da natureza,
naturae, qui ferre queat quoscumque labores,	que suporte qualquer tipo de labores,
nesciat irasci, cupiat nihil et potiores	desconheça a ira, nada cobice e creia mais
Herculis aerumnas credat saeuosque labores	nos labores selvagens de Hércules do que
et uenere et cenis et pluma Sardanapalli.	nas satisfações, nos banquetes e camas de plumas de um rei oriental.
monstro quod ipse tibi possis dare; semita	Revelarei aquilo que podes dar a ti próprio;
Certe tranquillae per uirtutem patet unica uitae.	Certamente, o único caminho de uma vida tranquila passa pela virtude.

(Juvenal, 10.356-64)

Resumo

A programação do metabolismo e do comportamento alimentar e a posterior exposição a alimentos hiperpalatáveis possivelmente expliquem o risco aumentado para doenças crônicas relacionadas à obesidade dos indivíduos com baixo peso ao nascer. Especificamente, as evidências indicam que essa população é mais propensa à resistência à insulina e ao dano hipocampal e que a associação de ambos pode explicar, em parte, a disfunção no controle alimentar e na saúde metabólica. Os indivíduos com restrição fetal do crescimento, portanto, seriam mais propensos ao ciclo vicioso da obesidade: desde a infância, são mais sensíveis à insulina e preferem alimentos hiperpalatáveis aos saudáveis; a maior ingestão desses alimentos induz progressivamente à resistência à insulina; a alteração na sinalização de insulina hipocampal prejudica a formação da memória alimentar e o controle inibitório frente a pistas alimentares; o maior consumo crônico de alimentos hiperpalatáveis rompe o equilíbrio e, consequentemente, surgem as doenças metabólicas relacionadas à obesidade na vida adulta. A proposta deste trabalho foi introduzir a hipótese do ciclo vicioso da obesidade em indivíduos nascidos com baixo peso, investigando, através de um delineamento translacional, se a resistência à insulina estaria associada ao processamento cognitivo diferencial frente às pistas alimentares nos indivíduos nascidos pequenos para a idade gestacional. (a) Primeiramente, verificou-se o ciclo vicioso da obesidade em um estudo com adolescentes saudáveis, representantes de todo o espectro de peso ao nascer, analisando se a resistência à insulina periférica estaria associada ao comprometimento da memória alimentar implícita e à desativação de áreas cerebrais associadas ao controle inibitório em resposta a imagens de alimentos hiperpalatáveis. (b) Após, verificou-se se o baixo peso ao nascer estaria associado a um comportamento alimentar obesogênico e à alteração do tamanho hipocampal e da sensibilidade à insulina em adolescentes. (c) Por fim, em um modelo de desnutrição gestacional em roedores, analisou-se se o baixo peso ao nascer modifica o estado metabólico, o comportamento alimentar e a função insulínica hipocampal, e se o consumo de alimentos hiperpalatáveis incrementaria essas mudanças. Uma carta ao editor e um artigo de revisão foram escritos com base nessas premissas. No estudo clinico, foi encontrada que a maior resistência à insulina está associada ao comprometimento da memória alimentar implícita e que quanto maior a resistência à insulina, maior ativação de áreas cerebrais associadas à atenção e menor ativação das associadas ao controle inibitório frente a imagens de alimentos hiperpalatáveis. Esse estudo também mostrou que o baixo peso ao nascer está associado a uma

ingestão mais densamente calórica, ao comprometimento da memória alimentar implícita, à redução do volume do subículo hipocampal e que a resistência à insulina interage com o peso ao nascer ao modular a ingestão alimentar externa. Por fim, o estudo experimental evidenciou que o baixo peso ao nascer está associado ao aumento da fosforilação do receptor glutamatérgico hipocampal induzido por insulina, à resistência à insulina hipocampal e à menor ingestão e entropia do comportamento alimentar quando há mudança na previsibilidade alimentar. Além disso, o baixo peso ao nascer junto à ingestão crônica de dieta hiperpalatável está associado ao maior ganho de peso corporal e ao reconhecimento da novidade alimentar. Ao reunir essas evidências, esta tese aponta que a associação da resistência à insulina ao comprometimento hipocampal explica, em parte, a alteração do comportamento alimentar dos indivíduos nascidos com baixo peso. Em um ambiente repleto de pistas alimentares, a ruptura do controle cognitivo pode levar ao ganho de peso e comprometer a saúde metabólica desses sujeitos ao longo do tempo.

Palavras-chave: Retardo do Crescimento Intrauterino. Comportamento Alimentar. Hipocampo. Síndrome X Metabólica. Resistência à Insulina. Pesquisa Médica Translacional.

Abstract

Metabolic and feeding behavioral programming with subsequent exposure to hyperpalatable foods can possibly explain the increased risk for chronic diseases related to obesity in individuals with low birth weight. Evidence indicate that this population is more prone to insulin resistance and hippocampal damage and that their association may partly explain the dysfunction in feeding control and metabolic health. Individuals with fetal growth restriction, therefore, would be more prone to the vicious cycle of obesity, they are more sensitive to insulin and prefer to eat hyperpalatable foods over more healthy options since childhood; the increased intake of these foods progressively induces insulin resistance; the alteration in hippocampal insulin signaling impairs the formation of food memory and the inhibitory control towards food cues; the greater chronic consumption of hyperpalatable foods disrupts the balance, and consequently, metabolic diseases related to obesity appear in adult life. The purpose of this study was to introduce the hypothesis of the vicious cycle of obesity in low birth weight individuals, investigating, through a translational design, whether insulin resistance would be associated with differential cognitive processing of foods cues in individuals born small for gestational age. (a) First, the vicious cycle of obesity was verified in a study with healthy adolescents from the full birth weight spectrum, analyzing whether peripheral insulin resistance would be associated with eating memory compromising and deactivation of brain areas associated with inhibitory control in response to hyperpalatable foods pictures. (b) Afterwards, it was verified whether low birth weight would be associated with an obesogenic eating behavior and with changes in hippocampal size and insulin sensitivity in adolescents. (c) Finally, in a model of gestational malnutrition in rodents, it was analyzed whether low birth weight modifies metabolic status, eating behavior and hippocampal insulin function, and whether the consumption of hyperpalatable foods would exacerbate these changes. A letter to the editor and a review manuscript were written based on these assumptions. In the clinical study, it was found that higher insulin resistance is associated with inconsistencies in implicitly learned food preferences and that the greater the insulin resistance, the greater activation of brain areas associated with attention and the lower activation of those associated with inhibitory control facing hyperpalatable foods pictures. This study also showed that low birth weight is associated with higher caloric intake, inconsistencies in implicitly learned food preferences, reduced hippocampal subiculum volume, and that insulin resistance interacts with birth weight by modulating food intake. Finally, the experimental study showed that low birth

weight is associated with increased phosphorylation of the hippocampal glutamatergic receptor induced by insulin, hippocampal insulin resistance and lower intake and feeding behavior entropy when there is a change in food predictability. In addition, low birth weight along with chronic intake of hyperpalatable diet is associated with greater body weight gain and the recognition of novel foods. In gathering this evidence, this thesis points out that the association between insulin resistance and changes in hippocampus partly explains the altered eating behavior of low birth weight subjects. In an environment full of food cues, the disruption in cognitive control may lead to weight gain and compromise the metabolic health of these subjects over time.

Key-words: Fetal Growth Retardation. Feeding Behavior. Hippocampus. Metabolic Syndrome X. Insulin Resistance. Translational Medical Research.

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LISTA DE ABREVIATURAS E SIGLAS

Adlib	*Ad libitum* control chow feeding
Adlib-CON	Offspring from Adlib dams fed with CON
Adlib-HFS	Offspring from Adlib dams fed with HFS
AGA	Adequate for gestational age
Akt	Protein kinase-B
ANOVA	Analysis of variance test
BioDAQ®	Food intake monitoring system, Research Diets®
BMI	Body mass index
CA	*Cornu ammonis*
CAPES	Coordenação de Aperfeiçoamento de Pessoal de Nível Superior
CNPq	Conselho Nacional de Desenvolvimento Científico e Tecnológico
CNS	Central nervous system
COM	Control diet
CV	Coefficients of variation
DEBQ	Dutch eating behaviour questionnaire
DOHaD	Developmental Origins of Health and Disease
FEW	Family-wise error
FIPE	Fundo de Investimento em Pesquisa e Eventos
FR	Restricted control chow feeding during gestation
FR-CON	Offspring from FR dams fed with CON
FR-HFS	Offspring from FR dams fed with HFS
GluN2A ou NR2A, GluN2B ou NR2B	NMDAR subunits
GLUT	Glucose transporter
HCPA	Hospital de Clínicas de Porto Alegre
HFS	High-fat and sugar or hyperpalatable diet
HOMA-IR	Homeostasis assessment model-insulin resistance
IP	Intraperitoneally
IQ	Inteligence quotient
IR	Insulin receptor

IUGR	Intrauterine growth restriction
MAPK	Mitogen-activated protein kinase
MRI	Magnetic resonance imaging
NAcc	Nucleus accumbens
NMDA ou NMDAR	Glutamatergic N-Methyl-D-Aspartate receptor
PFC	Pre-frontal cortex
PI3K	Phosphatidylinositol 3 kinase
PND	Postnatal day
PSD	Post-synaptic density
RCIU	Restrição do crescimento intrauterino
RM	Repeated measures
SD	Standard deviation
SGA	Small for gestational age
SOCS-3	Suppressor of cytokine signaling 3
STZ	Streptozotocin
T2DM	Type II diabetes *mellitus*
VTA	Ventral tegmental area
WASI	Wescheler Abreviated Scale of Inteligence

SUMÁRIO

1. INTRODUÇÃO

Esta tese inicia com a exposição de um referencial teórico sobre o impacto do baixo peso ao nascer no metabolismo e no neurodesenvolvimento do indivíduo, com uma correspondência publicada na revista *The Lancet,* comentando o tema, seguido da hipótese de um mecanismo cerebral envolvido na programação do comportamento alimentar dos indivíduos que sofreram redução do crescimento fetal, com um artigo de revisão publicado na revista *Neuroscience & Biobehavioral Reviews* sobre o assunto. Posteriormente, apresentam-se dois artigos em versões pré-submissão em que foram apresentados e discutidos os resultados da hipótese testada em humanos e roedores. Por fim, reúne e conclui os achados, apontando possíveis perspectivas sobre o tema proposto.

1.1. O BAIXO PESO AO NASCER

A restrição do crescimento intrauterino (RCIU) é definida como o crescimento fetal inferior ao esperado pelo potencial inerente de uma criança. A melhora do cuidado médico perinatal ocorrido na metade do século passado foi a principal responsável pelo aumento da sobrevivência dos indivíduos nascidos com RCIU (1), cuja prevalência é estimada entre 10 e 15% dos recém-nascidos (2). No entanto, a incidência de tais casos varia de acordo com a população, a localização geográfica e as curvas de crescimento utilizadas como referência. A presença da RCIU na população está concentrada principalmente na Ásia, que representa quase 75% de todas as crianças afetadas por essa condição, seguida da África e América Latina, que representam 20% e 5% dos casos, respectivamente (3,4).

Para ser diagnosticada corretamente, é necessário o acompanhamento por ultrassonografia durante a gestação. Entretanto, é comum que o peso ao nascer seja a única informação disponível para o registro de dados clínicos e, assim, os bebês geralmente são classificados com RCIU quando nascem com peso menor ao décimo percentil do peso da população específico para sexo e idade gestacional (5–7). Essa classificação pode ser arbitrária, pois, dependendo dos padrões de crescimento estabelecidos, alguns indivíduos podem ser considerados *small for gestational age* (SGA) ou pequenos para a idade

gestacional, mas não com RCIU, porque seu peso ao nascer se encontra dentro do intervalo normal (igual ou maior ao décimo percentil). É importante reconhecer que o diagnóstico de verdadeiros indivíduos com RCIU é desafiador na prática clínica, já que tanto crianças nascidas com peso menor que o décimo percentil podem não apresentar patologias relacionadas ao baixo peso ao nascer, quanto crianças que nasceram com o peso adequado para a idade gestacional podem não ter alcançado seu crescimento intrínseco (8–10). Nesta tese, entretanto, como foram utilizados bancos de dados onde havia apenas o peso ao nascer e a idade gestacional como informações sobre o crescimento fetal, os termos RCIU, baixo peso ao nascer e pequeno para a idade gestacional foram utilizados indiferentemente.

A etiologia da RCIU pode ser materna, fetal, placentária e genética (11) e, na maioria dos casos, é o resultado de uma disfunção na perfusão placentária-fetal, levando a circulação fetal à hipóxia e à acidose (12). Uma má nutrição gestacional e o baixo peso pré-gestacional são os maiores determinantes para a restrição de crescimento fetal nos países em desenvolvimento, enquanto que nos países desenvolvidos o fator mais importante é o tabagismo, seguido de uma má nutrição gestacional (13).

A RCIU representa uma adaptação a um ambiente pré-natal adverso que gera processos compensatórios no feto, resultando num sobrevivente intacto, porém sob risco de desfechos mórbidos (14). Ela é caracterizada como simétrica se peso, comprimento e circunferência da cabeça são proporcionalmente menores que o padrão, ou assimétrica quando a circunferência da cabeça está dentro dos limites normais. A restrição assimétrica geralmente ocorre na fase hipertrófica ou tardia da gestação e é causada por um prejuízo na função uteroplacentária ou uma deficiência nutricional em que o crescimento fetal é normal até que a taxa de crescimento exceda o suprimento nutricional. Como consequência, a formação de glicogênio e gordura fetal é afetada, assim como o crescimento de músculos e ossos, a fim de redistribuir o débito cardíaco prioritariamente ao coração e ao cérebro (15).

No período perinatal, a RCIU aumenta as chances para mortalidade fetal e neonatal e para convulsões, hemorragia pulmonar, hipertensão pulmonar persistente, síndrome do desconforto respiratório, aspiração de mecônio, imunodeficiência, disfunção renal, paralisia cerebral, distúrbios hematológicos, hipotermia, hipoglicemia/hiperglicemia, hipocalcemia,

baixa ferritina sérica, policitemia/hiperviscosidade, enterocolite necrosante/intolerância alimentar, retinopatia de prematuridade, asfixia perinatal e infecções (11,16). Em longo prazo, as consequências da RCIU incluem o déficit de crescimento estatural, osteoporose, disfunção imunológica, doença reativa das vias aéreas, puberdade precoce, doenças renais e hepáticas, alguns tipos de câncer e menor vida útil, dentre outras implicações discutidas a seguir.

A programação metabólica na adversidade fetal

A RCIU pode ser vista como um período de fome fisiológica crônica, já que a escassez de recursos nutricionais durante a vida gestacional torna os indivíduos mais eficientes na aquisição e no estoque de energia (17–19). Essa estratégia é o resultado de mudanças estruturais e funcionais permanentes em órgãos responsáveis pela regulação nutricional e metabólica, como cérebro, fígado, tecido adiposo, músculo e pâncreas (20), levando, por exemplo, ao aumento da sensibilidade periférica à insulina para utilização da glicose, ao aumento da glicogênese hepática, à diminuição da sensibilidade à insulina para a síntese proteica nos músculos e ao comprometimento do desenvolvimento pancreático. De acordo com a hipótese do *thrifty phenotype* ou fenótipo poupador, essas adaptações favorecem a sobrevivência em curto prazo em um ambiente pós-natal pobre nutricionalmente (19), promovendo a melhor utilização da energia, reduzindo a demanda por aminoácidos e elevando a glicemia para manter o suprimento suficiente ao coração e ao cérebro.

Em contrapartida, conforme a hipótese *developmental origins of health and disease* (DOHaD) ou origens desenvolvimentistas da saúde e da doença, o ajuste funcional e estrutural predispõe o indivíduo a disfunções e doenças crônicas não transmissíveis na idade adulta (21,22). Para garantir a sobrevivência na adversidade, ocorre um crescimento assimétrico, com tecidos musculares e subcutâneos sofrendo a restrição mais pronunciadamente. Em condições de desnutrição pós-natal, essa adaptação leva os tecidos fetais a terem suas funções metabólicas basais dependentes da energia à custa do crescimento corporal (23). Entretanto, quando o suprimento nutricional aumenta, ocorre a absorção de energia além das necessidades e capacidades metabólicas, predispondo os

indivíduos pequenos para a idade gestacional à resistência à insulina, diabetes *mellitus* tipo II, adiposidade abdominal, doenças cardiovasculares e síndrome metabólica na idade adulta (24–29).

Além disso, o ambiente pós-natal do mundo moderno, com oferta excessiva de alimentos hiperpalatáveis, ricos em açúcar, gordura e/ou sal, densamente calóricos e pobres nutricionalmente, dispensa o consumo de alimentos *in natura* mais saudáveis e é um dos principais contribuintes para o desenvolvimento de doenças relacionadas à síndrome metabólica na população em geral – e mais ainda em indivíduos predispostos a elas, como os nascidos com RCIU (30,31). Baseada nisso, foi escrita uma correspondência à revista *The Lancet*, que se encontra no item 4.1. desta tese, salientando que os cuidados pré-gestacionais e pré-natais adequados são ainda a melhor estratégia para evitar as consequências da programação fetal na saúde em longo prazo (32).

A propensão à resistência à insulina

Um grande número de estudos epidemiológicos evidenciou a forte associação existente entre a RCIU e o subsequente desenvolvimento de diabetes *mellitus* tipo II na idade adulta (18,25,33,34). Os dados de modelos animais de RCIU induzido por desnutrição proteica sustentam esses achados (35,36) e indicam que essa associação seja mediada pelo *catch-up growth* ou crescimento de recuperação ocorrido no início da vida (37). Esse crescimento ocorre geralmente nos recém-nascidos com RCIU que receberam alimentação normal após o nascimento, levando a um ganho de massa gorda desproporcionalmente maior em comparação ao ganho de massa magra (38).

Sabe-se que a resistência à insulina e a disfunção das células-β das ilhotas pancreáticas são as duas principais características da diabetes *mellitus* tipo II (39,40). Em humanos predispostos a desenvolverem essa doença, como os com baixo peso ao nascer, o desequilíbrio na secreção e na ação da insulina pode ser detectado muito tempo antes da falência pancreática, mesmo que as células-β sejam capazes de secretar insulina suficientemente para compensar tanto o defeito no mecanismo de ação, quanto para manter a glicemia em níveis normais (definição de resistência à insulina). Contudo, a

sobrecarga das células-β induz a redução da secreção de insulina em níveis adequados, tendo como consequência a hiperglicemia.

Em seres humanos saudáveis, a elevação da glicemia induz o aumento da secreção de insulina e a proliferação de células-β (41,42), porém esse achado não é evidenciado em estudos com modelos animais de RCIU (43). Além disso, a proporção de células-β pancreáticas é diminuída nos fetos de roedores que sofreram restrição de crescimento, permanecendo reduzida durante todo o percurso da vida (35,36). Essa incapacidade de incrementar adequadamente a quantidade de células-β poderia ser decorrente tanto da menor proliferação celular, quanto da aumentada taxa de apoptose (44,45) e provavelmente possam ser consequência de modificações na regulação epigenética da expressão de genes implicados no metabolismo da glicose ocorrida durante a adversidade intrauterina (46–48), o que não parece ocorrem com as células-α e PP, responsáveis pela secreção pancreática de glucagon e somatostina (49,50).

Os efeitos da poupança cerebral ou *brain sparing*

A priorização da redistribuição do débito cardíaco ao cérebro na RCIU assimétrica é conhecida como poupança cerebral ou *brain sparing* (51), resultando em um índice de cefalização (circunferência da cabeça dividida pelo peso ao nascer) extremamente alto. Embora esse remanejamento tenha sido inicialmente considerado um mecanismo de proteção, ultimamente é considerado um indicador precoce de dano cerebral associado ao risco aumentado para alterações no neurodesenvolvimento (52–57). As implicações neurológicas da RCIU abrangem baixos escores em testes cognitivos, dificuldades escolares ou necessidade de educação especial, transtornos perceptivos, incluindo pior percepção visual-motora, menor escore de inteligência, disfunção motora fina e grossa e paralisia cerebral. Além disso, o baixo peso ao nascer está associado ao maior risco para transtornos psiquiátricos, como ansiedade, esquizofrenia, depressão e transtorno bipolar, baixa habilidade social e acadêmica e reduzida capacidade de trabalho, sendo que a incidência do comprometimento cognitivo grave é baixa, porém há um aumento na incidência de pequenos desvios cognitivos quando comparados com a população em geral (58–67).

Os mecanismos implicados na vulnerabilidade neurocomportamental da RCIU não são claros, mas as evidências sugerem que eles estejam associados a alterações na estrutura cerebral, com redução do volume intracraniano e da matéria cinzenta cortical (68). A RCIU também está associada a uma maturação anormal dos oligodendrócitos, resultando em uma reduzida mielinização e menor volume da matéria branca cerebral (69). Além disso, estudos em humanos e em modelos animais com RCIU mostraram que o hipocampo, reconhecido pelo papel em codificar, armazenar e evocar as informações relacionadas com aprendizagem e memória, é uma das áreas mais afetadas nessa condição. As subestruturas do hipocampo *Cornus Ammonis* (CA) 1, CA3 e giro denteado, além do subículo da formação hipocampal, são as regiões mais vulneráveis à hipóxia-isquemia, uma consequência inerente à insuficiência uteroplacentária (70). As principais mudanças estruturais sofridas pelo hipocampo na RCIU incluem redução no número de células e na matéria branca, além de alteração na composição celular e na morfologia dendrítica (71–73) Existem também evidências de modificações na expressão genética e proteica de fatores neurotróficos, de receptores glutamatérgicos e de proteínas da densidade pós-sináptica associadas ao baixo peso ao nascer, levando a mudanças da função sináptica hipocampal (74–77).

A neurobiologia do comportamento alimentar na restrição de crescimento fetal

O comportamento alimentar é moldado por elementos genéticos, fisiológicos, cognitivos, ambientais, psicossociais e culturais. Sua formação é iniciada desde a vida *in utero* (78,79) e os eventos que ocorrem durante o desenvolvimento fetal podem alterar permanentemente as vias cerebrais relacionadas ao consumo e ao gasto energético, comprometendo as preferências alimentares durante todo o percurso de vida (80–83).

Existem evidências de que os indivíduos com RCIU comem mais (84,85) e se exercitam menos (86–88), bem como também tem preferência específica para os alimentos hiperpalatáveis. Desde o primeiro dia da vida, é possível detectar diferenças na resposta hedônica ao sabor do doce de acordo com o grau de RCIU em recém-nascidos pré-termo e a termo (89–91). Durante a infância, é possível detectar maior impulsividade frente ao alimento doce (92) e maiores dificuldades alimentares em crianças nascidas pequenas para a

idade gestacional (93–96). Além disso, ao longo da vida, o baixo peso ao nascer está associado a uma programação das preferências alimentares, com o aumento do consumo de alimentos ricos em carboidratos e gordura, em comparação a frutas e vegetais (31,97–102). Estudos recentes têm também verificado um comportamento alimentar característico em modelos animais: ratos com RCIU comem mais alimentos hiperpalatáveis e apresentam alterações de comportamento em tarefas que utilizam estes alimentos como recompensa (103–106), sugerindo que estes animais com RCIU sejam mais orientados para a recompensa alimentar (104,105).

Evidências mostraram que a deficiência nutricional na vida precoce promove o aumento da ingestão alimentar e da ativação de neurônios rostrais e mediais do núcleo do trato solitário em resposta à estimulação por alimento na fase adulta, indicando que o tronco encefálico é uma região vulnerável às influências da manipulação nutricional nos estágios precoces de desenvolvimento, tendo efeitos no controle alimentar em longo-prazo (107). Além disso, existe associação da deficiência nutricional perinatal com uma menor saciedade em resposta à leptina e a uma sinalização prejudicada deste hormônio no núcleo arqueado (108–111), assim como maior resposta a sinais motivadores do apetite, como a grelina (112). A adversidade neonatal também está associada a uma expressão aumentada de neuropeptídeos orexígenos em comparação aos anorexígenos (113–117) e a uma disfunção da diferenciação e proliferação celular hipotalâmica (118,119), o que poderia explicar o aumento celular nos núcleos paraventricular, arqueado e ventromedial, que estão envolvidos no controle homeostático da ingestão alimentar. A alteração nos níveis de insulina e leptina ocorrida pela deficiência nutricional durante a gestação também parece contribuir para a disfunção hipotalâmica (118–120). Além disso, o *catch-up growth* pode exacerbar a disfunção metabólica ao longo da vida (121–123), modificando a expressão de receptores de sinalizadores envolvidos no controle do apetite, como a insulina, a leptina, a serotonina e a dopamina no hipotálamo (124). Alguns estudos mostraram que ratos com deficiência nutricional *in utero* têm alterações na expressão de genes e proteínas relacionados à sinalização dopaminérgica na área tegmental ventral, no núcleo accumbens e no córtex pré-frontal, regiões envolvidas no processamento do valor de recompensa (103,104,125). Existem também evidências de que a RCIU programe a sinalização opioide no sistema mesocorticolímbico, influenciando a resposta comportamental aguda frente ao

sabor doce (126,127). Portanto, esses resultados apontam que o desequilíbrio entre os sistemas de controle homeostático, hedônico e de recompensa podem estar associados com o consumo excessivo de alimentos hiperpalatáveis dos indivíduos que sofreram RCIU.

A alteração no comportamento alimentar na RCIU também pode ser explicada por uma disfunção no eixo hipotálamo-pituitária-adrenal, já que esses indivíduos possuem maior nível de corticosterona em diferentes idades (128–130), além de menor expressão de receptores de glicocorticoides e mineralocorticoides no hipocampo (131). Essas alterações podem levar a uma hiperatividade crônica desse eixo neuroendócrino, contribuindo para a programação de doenças metabólicas crônicas, assim como para uma resposta alterada ao estresse, o que pode influenciar o comportamento alimentar (132,133).

Além dessas evidências, o distinto comportamento alimentar dos indivíduos com baixo peso ao nascer possivelmente também venha em decorrência da disfunção de áreas envolvidas com processos cognitivos relacionados à alimentação. Por exemplo, há evidências de alteração da ativação (134) e da sinalização molecular (135) de áreas corticais em humanos e roedores, sendo que essa modificação está associada a uma atitude mais impulsiva frente aos alimentos. Sabe-se também que o hipocampo é uma das estruturas encefálicas que mais sofrem prejuízo com a exposição à desnutrição no período neonatal (136,137) e estaria envolvido com os desvios cognitivos apresentados pelos sujeitos que sofreram adversidade no ambiente pré-natal (52,138–140). Estudos recentes mostram que o hipocampo é fundamental para o controle inibitório frente a estímulos alimentares (141–143) e que essa estrutura cerebral tem papel fundamental na aquisição e evocação de memórias relacionadas à alimentação, na percepção de saciedade, na estimativa do tamanho e duração das refeições e no controle da ingestão induzida pelo estresse (144). Ainda, a resistência à insulina pode estar intimamente relacionada à disfunção hipocampal e ao desequilíbrio do comportamento alimentar na RCIU. Isso aumentaria o risco para o desenvolvimento de distúrbios metabólicos e adiposidade, conhecido como *vicious cycle of obesity* ou ciclo vicioso da obesidade. Este assunto será mais bem detalhado no artigo de revisão no item 4.2., que foi publicado na revista *Neuroscience & Biobehavioral Reviews* (145).

1.2. PROCESSOS COGNITIVOS RELACIONADOS À ALIMENTAÇÃO

A cada momento em que se ingere um alimento, existe a oportunidade de associá-lo às *food cues* ou pistas alimentares, que são os sinais preditivos da alimentação, como o odor, o sabor e o visual da comida, assim como o local, o horário, as emoções e os pensamentos antecipatórios à refeição (146). As respostas fisiológicas (como aumento da salivação, da insulinemia e da glicemia) ou psicológicas (como o desejo e o prazer de comer) que ocorrem durante a ingestão alimentar podem também acontecer na presença de qualquer estímulo preditivo do consumo. Esse fenômeno caracteriza a fase cefálica do comportamento alimentar e é conhecido como *food cue reactivity* ou responsividade à pista alimentar ou, então, como *external eating* ou alimentação induzida por estímulos externos (147,148). O aprendizado da associação entre os sinais preditivos e o consumo alimentar é uma forma de condicionamento clássico: as pistas alimentares (estímulo condicionado) tornam-se sinais para o consumo de alimentos (estímulo incondicionado) e a mera presença do estímulo preditivo do alimento passa a ser suficiente para induzir o aparecimento das expectativas e o desejo de ingeri-lo (149).

Muitos fatores influenciam a forma como os indivíduos respondem às pistas alimentares (143). Por exemplo, os alimentos são mais atrativos e saborosos quando se está com fome, sugerindo que os sistemas neurais hedônicos e de recompensa (áreas mesocorticolímbicas) interagem com os circuitos das vias homeostáticas do metabolismo (áreas tronco encefálicas e hipotalâmicas), influenciando no desejo e no prazer pela comida (150). Quando saciadas, pessoas obesas respondem mais fortemente às pistas alimentares do que as pessoas magras, indicando que o excesso de peso está associado a mudanças nos mecanismos cerebrais de recompensa dos alimentos (151–153). Além disso, variações genéticas da sinalização opioide e dopaminérgica parecem promover uma responsividade diferencial às pistas alimentares (154).

Vários estudos de neuroimagem sugerem que a capacidade de resistir a uma recompensa imediata em prol de um objetivo de longo prazo (como manter o peso corporal ou emagrecer) depende da ativação equilibrada de dois sistemas neurais: um sistema de decisão executiva envolvido no controle de impulsos, que corresponde à ativação das regiões lateral e medial do córtex pré-frontal, e um sistema para predizer o valor desta

recompensa, que corresponde à ativação do córtex orbitofrontal, do córtex pré-frontal ventromedial, do estriado e o do hipocampo (155–158). Além disso, tem-se sugerido que o equilíbrio entre os sistemas de controle inibitório e o de recompensa é afetado quando há outras demandas cognitivas concorrentes (159), ou quando há tentativas repetidas de autocontrole (160), talvez explicando porque os comedores restritivos muitas vezes exibem eventual ingestão excessiva e ganho de peso (161). Esse desequilíbrio entre os sistemas inibitório e o de recompensa também esclarece por que algumas pessoas são mais propensas a comer mais e ganhar mais peso do que outras (162–164). No entanto, ainda não está claro se as dificuldades com a inibição da responsividade às pistas alimentares preveem aumentos no peso corporal ou se esse o controle reduzido é uma consequência da obesidade.

Os processos de memória são fundamentais para o aprendizado dos desfechos prazerosos e saciadores da alimentação, pois as associações entre as pistas alimentares, o comportamento alimentar e as repercussões do consumo ao longo de experiências repetidas são armazenadas e sustentam a responsividade às pistas alimentares (143). Há evidências de que a memória de trabalho é importante para determinar a atenção que se presta às pistas alimentares, o que significa que pensar em um alimento aumenta a chances de perceber os estímulos no ambiente e a responder às pistas alimentares em comparação ao não pensar no alimento (165). Além disso, os estudos também sugerem que a memória episódica afeta as escolhas alimentares e as decisões sobre o quê, quanto e quando comer, pois, quando um alimento é identificado por uma pista no ambiente, a expectativa de sua ingestão é baseada em experiências passadas armazenadas, e outras informações, como o lugar, o momento e o contexto específico da alimentação também são evocadas (166,167). Usar estas memórias episódicas simula mentalmente o desfecho da escolha a ser tomada, permitindo selecionar o melhor resultado para determinado momento. Um importante ponto a ser considerado é que, com o passar do tempo, o comportamento frente às pistas alimentares torna-se mais habitual e as simulações baseadas nas memória ocorrem automática e inconscientemente quando em frente a uma escolha alimentar (168).

Ao reunir as evidências, o que se sugere é que as informações sobre refeições anteriores são combinadas com as informações sobre o estado interno pós-prandial atual, a

fim de ser feita uma previsão da saciedade e da recompensa futura, o que, então, modula a responsividade às pistas alimentares. Baseada nisso, a tendência para o consumo exagerado ou maior preferência por alimentos hiperpalatáveis pode resultar de um desequilíbrio entre o controle cognitivo alimentar (que depende da memória alimentar) e a responsividade habitual às pistas alimentares (169), provavelmente devido ao prejuízo nos processos de memória alimentar. Em um ambiente repleto de pistas de alimentos hiperpalatáveis, a ruptura do controle cognitivo pode levar ao ganho de peso ao longo do tempo e os estudos mostram que, de fato, o excesso de peso e a obesidade estão associados a problemas de aprendizagem e memória (170–175). Mais detalhes sobre a associação entre a memória alimentar e a obesidade são apresentados no artigo de revisão no item 4.2 desta tese (145).

1.3. MODELOS ANIMAIS DE RESTRIÇÃO DE CRESCIMENTO FETAL

A pesquisa científica com animais ocorre apenas quando é relevante para o avanço do conhecimento científico, considerando-se a impossibilidade de utilização de métodos alternativos, e essas técnicas devem ser refinadas a fim de reduzir o número e o desconforto dos animais utilizados para pesquisa (176,177). Para induzir a RCIU, os modelos animais são divididos em três categorias de intervenção: materna (por exemplo, pela limitação do consumo alimentar total ou proteico e pela diminuição da irrigação sanguínea no útero), placentária (por insultos de hipóxia) e fetal (através de manipulação genética ou infecções). As espécies mais utilizadas são ratos e camundongos, mas também existem pesquisas em cobaias, coelhos, cães, ovelhas, cabras, porcos, cavalos, babuínos e macacos Rhesus (178).

Há uma série de fatores espécie-específicos a serem considerados ao usar animais que mimetizem a gravidez humana, sendo que o número de filhotes por gestação, a forma de placentação, a duração da gestação, o parto e o desenvolvimento fetal *versus* neonatal afetam a escolha do modelo. Os roedores apresentam uma fisiologia semelhante aos humanos e a sua utilização em experimentos é vantajosa devido ao curto tempo de maturidade sexual (em torno de 60 dias), de ciclo estral (4 a 5 dias), de gestação (em torno de 21 dias) e do grande tamanho das ninhadas (em média, 8 filhotes por gestação), facilitando a observação entre gerações (179).

1.4. JUSTIFICATIVA

A literatura sugere que a programação do metabolismo e do comportamento alimentar e a posterior exposição a alimentos hiperpalatáveis possivelmente expliquem o risco aumentado para doenças crônicas relacionadas à obesidade dos indivíduos com baixo peso ao nascer. Especificamente, as evidências indicam que essa população é mais propensa à resistência à insulina e ao dano hipocampal e que a união desses fatores pode explicar, em parte, a disfunção no controle alimentar e na saúde metabólica.

Considerando a prevalência significativa de RCIU na população, a busca pelos mecanismos neurobiológicos envolvidos na programação do comportamento alimentar pelo ambiente intrauterino e pelo período pós-natal podem auxiliar na busca por intervenções precoces que estabeleçam o equilíbrio alimentar e a saúde ao longo da vida dos indivíduos nascidos pequenos para a idade gestacional.

2. OBJETIVOS

2.1. OBJETIVO GERAL

O objetivo geral deste trabalho foi testar a hipótese do ciclo vicioso da obesidade em indivíduos nascidos com baixo peso, investigando, através de um delineamento translacional, se a resistência à insulina estaria associada ao processamento cognitivo diferencial frente aos alimentos nestes sujeitos.

2.2. OBJETIVOS ESPECÍFICOS

a) Verificar o ciclo vicioso da obesidade, analisando se a resistência à insulina periférica estaria associada ao comprometimento da memória alimentar implícita e à desativação de áreas cerebrais associadas ao controle inibitório em resposta a imagens de alimentos hiperpalatáveis (parte I do artigo clínico em adolescentes representantes de todo o espectro de peso ao nascer);
b) Investigar se o baixo peso ao nascer estaria associado a um comportamento alimentar obesogênico e à alteração do tamanho hipocampal e da sensibilidade à insulina (parte II do artigo clínico em adolescentes nascidos com peso adequado ou pequeno para a idade gestacional);
c) Avaliar se o baixo peso ao nascer modificaria o estado metabólico, o comportamento alimentar e a função insulínica hipocampal, e se o consumo de alimentos hiperpalatáveis incrementaria essas mudanças (estudo experimental em um modelo de desnutrição gestacional em roedores).

3. CONSIDERAÇÕES ÉTICAS

A pesquisa experimental seguiu as Diretrizes e Normas Nacionais e Internacionais, especialmente a Lei nº 11.794, de 08 de outubro de 2008, que estabelece os procedimentos para uso cientifico de animais, e foi aprovada pela Comissão de Ética de Animais do Grupo de Pesquisa e Pós-Graduação do HCPA (número do projeto de pesquisa no GPPG: 13-0544) (Anexo 7.1).

A pesquisa clínica foi realizada de acordo com a Resolução 196/96 do Conselho Nacional de Saúde, além dos próprios regulamentos do Serviço de Gestão em Pesquisa do HCPA, aprovada pelo Comitê de Ética em Pesquisa do Grupo de Pesquisa e Pós-Graduação do HCPA (número do projeto de pesquisa no GPPG: 12-0254) e cadastrada na Plataforma Brasil (número do Certificado de Apresentação para Apreciação Ética: 5278112500005327) (Anexos 7.2 e 7.3).

4. ARTIGOS

4.1. CORRESPONDÊNCIA

Correspondence

obesity in women in developing countries might impact negatively on existing maternal health services in low-resource settings. Women with obesity have greater risk of pre-eclampsia, gestational diabetes, premature delivery, macrosomia, dystocia, post-partum haemorrhage, and miscarriage,[2] and their babies are at a 62% increased risk of dying within 48 hours after birth compared with newborn babies of mothers without obesity.[3] Caesarean section rates are higher in women with obesity, with three times more emergency caesarean sections, often associated with intra-operative and postoperative complications.[2,4]

For more on the 1000 Days Initative see http://www.thousanddays.org/

Additional equipment required includes larger cuffs for measuring blood pressure or theatre tables stable enough to tolerate additional weight. Skilled personnel are required for registering fetal heart beats, finding veins, or positioning in some women with obesity. Caesarean sections can be more difficult and additional help is often required to retract abdominal tissues. For spinal and epidural anaesthesia, failures and repeated pricking have been reported,[5] but longer spinal needles for such cases are often not available in low-resource settings. Post-partum and breastfeeding problems because of mechanical and endocrinological issues[6] in women with obesity require attentive nursing support. Based on these observations, targeted actions are required, as the problem of obesity in developing countries will rapidly increase in the coming years and services have to be prepared to avoid obesity related maternal morbidity and mortality.

For the *Lancet* Obesity Series see http://www.thelancet.com/series/obesity-2015

We declare no competing interests.

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1 Diez WH, Baur LA, Hall K, et al. Management of obesity: improvement of health-care training and systems for prevention and care. *Lancet* 2015; **385**: 2521–33.

2 Ramsay JE, Greer I, Sattar N. Obesity and reproduction. *BMJ* 2006; **333**: 1159–62.

3 Cresswell JA, Campbell OM, De Silva MJ, Filippi V. Effect of maternal obesity on neonatal death in sub-Saharan Africa: multivariable analysis of 27 national datasets. *Lancet* 2012; **380**: 1325–30.

4 Lynch CM, Sexton DJ, Hession M, Morrison JJ. Obesity and mode of delivery in primigravid and multigravid women. *Am J Perinatol* 2008; **25**: 163–67.

5 Dresner M, Brocklesby J, Bamber J. Audit of the influence of body mass index on the performance of epidural analgesia in labour and the subsequent mode of delivery. *BJOG* 2006; **113**: 1178–81.

6 Yu CK, Teoh TG, Robinson S. Obesity in pregnancy. *BJOG* 2006; **113**: 1117–25.

The recent Obesity Series published in *The Lancet* considered the bigger picture of environmental factors. The authors of the Series emphasised and proposed important obesity prevention measures, including changing the environment, stimulating the expression of healthy food preferences, and establishing smart food policies.[1,2] Some individual factors play an essential part in the development of obesity and therefore should also be a target for obesity prevention. For example, it is well established that alterations in fetal growth increase the risk for developing obesity and its metabolic consequences later in life.[3,4] We and other groups have showed that fetal growth restriction modifies food preferences and feeding behaviour,[3] increasing spontaneous intake of highly palatable foods in individuals over the life-course. As acknowledged by Corinna Hawkes and colleagues,[1] although food preferences can be modified over time, they are often resistant to change. To us, the small picture—a healthy fetal life, optimised through adequate prenatal care—is essential to avoid the long-term consequences of fetal programming on childhood and adult health, including obesity.

It is important to avoid the idea that fetal growth restriction is simply the result of an inappropriate caloric intake during pregnancy. Many maternal factors affect fetal growth, such as hypertension, diabetes, smoking, and obesity.[4] Most of these conditions are treatable with good and frequent prenatal care. Despite being acknowledged in large campaigns such as the 1000 Days Initiative real prenatal care improvements are still very timid. In Brazil, for example, less than 62% of livebirths were preceded by at least 7 prenatal visits.[5] Besides health promotion and surveillance, prenatal care should be a time for parental orientation and teaching about breastfeeding, ideal weaning time and healthy weaning foods, which in the long term will also affect obesity risk. To provide such support, professional training is necessary, but not always available—this is another point where intervention or policy could have an enormous effect.

We declare no competing interests.

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1 Hawkes C, Smith TG, Jewell J, et al. Smart food policies for obesity prevention. *Lancet* 2015; **385**: 2410–21.

2 Portella AK, Silveira PP. Neurobehavioral determinants of nutritional security in fetal growth-restricted individuals. *Ann NY Acad Sci* 2014; **1331**: 15–33.

3 Silveira PP, Agranonik M, Faras H, et al. Preliminary evidence for an impulsivity-based thrifty eating phenotype. *Pediatr Res* 2012; **71**: 293–98.

4 Visentin S, Grumolato F, Nardelli GB, Di Camillo B, Grisan E, Cosmi E. Early origins of adult disease: low birth weight and vascular remodeling. *Atherosclerosis* 2014; **237**: 391–99.

5 Brasil Ministério da Saúde. Datasus. Indicadores Regionais, Estaduais e Nacionais do rol de Diretrizes, Objetivos, Metas e Indicadores 2013-2015. http://www2.datasus.gov.br/DATASUS/index.php?area=02 (accessed March 23, 2015).

The Lancet Series on obesity missed an important opportunity to more fully address non-Western food and the implications for policy and consumer engagement. While citing a few low-income and middle-income country examples, and noting the need for sociocultural dimensions

Mucellini, Amanda Brondani; Manfro, Gisele Gus ; Silveira, Patrícia Pelufo. (2015) Tackling obesity: challenges ahead. *Lancet* (British edition), v. 386, p. 740. http://dx.doi.org/10.1016/S0140-6736(15)61538-0

Fator de impacto: 47.831 (2016)

Title: Tackling obesity: Challenges ahead

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Key-words: Obesity programming; Prevention; Prenatal care.

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Disclosure: The authors declare no conflicts of interest.

In the recent Obesity Series published in The Lancet, the authors, considering the bigger picture of environmental factors, emphasized and proposed important obesity prevention measures, including changing the environment, stimulating the expression of healthy food preferences, establishing smart food policies, among others[1]. We highlight, however, that some individual factors play an essencial role in the risk for obesity and therefore should also be a target for obesity prevention. For instance, it is well established that alterations in fetal growth increase the risk for developing obesity and its metabolic consequences later in life. We and other groups have showed that fetal growth restriction modifies food preferences[2], as well as feeding behavior[3], increasing the spontaneous intake of highly palatable foods in individuals over the life-course. As well acknowledged by Hawkes et al[1], although food preferences can be modified over time, they are often persistent and

resistant to change. To us, the “small picture” – a healthy fetal life, optimized through adequate prenatal care – is essential to avoid the long-term consequences of fetal programming on childhood/adult health, including obesity.

It is important to avoid the misleading idea that fetal growth restriction is simply the result of an inappropriate caloric intake during pregnancy. Many prevalent maternal conditions as hypertension, diabetes and smoking affect fetal growth[4]. Even obese mothers can have fetal growth restricted newborns. Most of these conditions are amenable with good and frequent prenatal care. Despite being acknowledged in large campaigns such as the 1000 Days Initiative, real prenatal care improvements are still very timid. In Brazil, for instance, less than 62% of live births were preceded by at least 7 prenatal visits[5]. Besides health promotion and surveillance, prenatal care should be a time for parental orientation and teaching about breastfeeding, ideal weaning time and healthy weaning foods, which in the long term will also affect obesity risk. To provide such support, high professional training about these issues is necessary, but not always available – and this is another point where intervention/policy could have an enormous impact down the road.

1. Hawkes C, Smith TG, Jewell J, et al. Smart food policies for obesity prevention. *Lancet* 2015.

2. Ayres C, Agranonik M, Portella AK, Filion F, Johnston CC, Silveira PP. Intrauterine growth restriction and the fetal programming of the hedonic response to sweet taste in newborn infants. *International journal of pediatrics* 2012; **2012**: 657379.

3. Silveira PP, Agranonik M, Faras H, et al. Preliminary evidence for an impulsivity-based thrifty eating phenotype. *Pediatric research* 2012; **71**(3): 293-8.

4. Visentin S, Grumolato F, Nardelli GB, Di Camillo B, Grisan E, Cosmi E. Early origins of adult disease: low birth weight and vascular remodeling. *Atherosclerosis* 2014; **237**(2): 391-9.

5. Datasus. BMdS. Indicadores regionais, estaduais e nacionais do rol de diretrizes, objetivos, metas e indicadores 2013-2015. 2015 (accessed March 22, 2015.

4.2. ARTIGO DE REVISÃO

Neuroscience and Biobehavioral Reviews 77 (2017) 165–176

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review article

Hippocampal insulin resistance and altered food decision-making as players on obesity risk

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ARTICLE INFO

Article history:
Received 23 November 2016
Received in revised form 17 March 2017
Accepted 19 March 2017
Available online 22 March 2017

Keywords:
Feeding behavior
Cognitive decline
Metabolic syndrome

ABSTRACT

There are increasing evidences that hippocampus can modulate the decision of what, when and how much to eat, in addition to its already recognized role in learning and memory processes. Insulin also has been linked to brain functions such as feeding behavior and the imbalance of its mechanism of action on hippocampus is being related to cognitive dysfunction. The discussion here is whether changes in insulin action could contribute to intake dysregulation and obesogenic behavior as a primary consequence of impairing hippocampal functioning, aside from the role of this hormone on obesity development through peripheral metabolic pathways. Excess intake of high-fat and high-sugar diets leads to insulin resistance, which disrupts hippocampal function. Hippocampal physiology is sensitive to signals of hunger and satiety, inhibiting the ability of food cues to evoke appetite and eating, therefore alterations in hippocampal integrity could affect food inhibitory control leading to increased intake and obesity.

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1. Obesity: a growing concern

Obesity is considered pandemic as it occurs in a wide geographical area affecting an exceptionally high proportion of the population (Wylie-Rosett, 2004). The higher frequency of obesity was first observed in the United States but has spread to other industrialized countries and also occurs in developing countries

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http://dx.doi.org/10.1016/j.neubiorev.2017.03.011
0149-7634/

Mucellini, A. B., Fonseca, N. K. de O. da, Manfro, G. G., & Silveira, P. P. (2017). Hippocampal insulin resistance and altered food decision-making as players on obesity risk. *Neuroscience and Biobehavioral Reviews*, *77*, 165–176. https://doi.org/10.1016/j.neubiorev.2017.03.011

Fator de impacto: 8.299 (2016)

Title: Hippocampal insulin resistance and altered food decision-making as players on obesity risk

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Abstract

There are increasing evidences that hippocampus can modulate the decision of what, when and how much to eat, in addition to its already recognized role in learning and memory processes. Insulin also has been linked to brain functions such as feeding behavior and the

imbalance of its mechanism of action on hippocampus is being related to cognitive dysfunction. The discussion here is whether changes in insulin action could contribute to intake dysregulation and obesogenic behavior as a primary consequence of impairing hippocampal functioning, aside from the role of this hormone on obesity development through peripheral metabolic pathways. Excess intake of high-fat and high-sugar diets leads to insulin resistance, which disrupts hippocampal function. Hippocampal physiology is sensitive to signals of hunger and satiety, inhibiting the ability of food cues to evoke appetite and eating, therefore alterations in hippocampal integrity could affect food inhibitory control leading to increased intake and obesity.

Key- words: Feeding behavior; cognitive decline; metabolic syndrome.

Obesity: a growing concern

Obesity is considered pandemic as it occurs in a wide geographical area affecting an exceptionally high proportion of the population (Wylie-Rosett, 2004). The higher frequency of obesity was first observed in the United States but has spread to other industrialized countries and also occurs in developing countries such as Brazil (Caballero, 2007). In 2014, 39% of the adults worldwide were overweight, and 13% were obese; rates that were twice as big as observed since 1980 (WHO, 2016)..

Obesity is characterized by body mass index of >30 kg per m2, which is mainly the result of an increase in fat mass. This condition occurs when there is an unbalance between calories that are consumed as compared to what is wasted and it can negatively affect health and decrease longevity (Flegal et al., 2013; Mitchell et al., 2011). The reasons why excessive intake occurs and how it leads to obesity are not fully understood, but it is known to involve genetic, physiological, metabolic, behavioral and cultural factors.

The concern about obesity relies on the fact that it is considered the fifth largest risk factor for disease worldwide, being a major risk factor for non-communicable diseases (Dulloo et al., 2010; Keller and Lemberg, 2003; WHO, 2016). Excess fat, especially in the central region of the body, is related to the most prevalent and costly current medical

problems such as type 2 diabetes, coronary artery disease, gastrointestinal problems, respiratory complications, osteoarthritis and various types of cancer (Haslam and James, 2005; WHO, 2016). Furthermore, obesity is closely associated with metabolic syndrome, which is characterized by hyperinsulinemia, insulin resistance, glucose intolerance, atherogenic dyslipidemia, hypertension, and increased expression of pro-thrombotic and pro-inflammatory markers (Olufadi and Byrne, 2008).

Obesity is also related to brain vulnerability and cognitive disorders, both in humans (Bruce-Keller et al., 2009; Galioto et al., 2013; Whitmer et al., 2005; Wolf et al., 2007) and in rodents (Bruce-Keller et al., 2009; Greenwood and Winocur, 2001; Winocur and Greenwood, 2005). As showed in many studies, obese humans (Benito-Leon et al., 2013) and rodents (Goldbart et al., 2006; Jurdak et al., 2008; Molteni et al., 2002; Park et al., 2010; Winocur and Greenwood, 1999) that consume hyperlipidemic and hypercaloric diets had inferior performance on learning and memory tests as compared to those with normal weight and to those who eat more healthy diets. In addition, clinical studies in humans show that abdominal fat and high body mass index are associated with reduced brain volume (Debette et al., 2010) and specific cortical thinning (Medic et al., 2016).

According to Sethi and Vidal-Puig (2007), there is an increased uptake of nutrients from the circulation to the periphery, particularly in insulin sensitive tissues shortly after food intake. During periods of fasting, the movement of molecules takes place in the opposite direction. In obesity, however, this bidirectional energy flow is altered due to endocrine dysfunction of adipose tissue and therefore decreases the effectiveness of endocrine mechanisms in the tissues (Caimari et al., 2010; Kahn et al., 2006; Lopez et al., 2003). Adipose tissue has humoral and hormonal regulation, and numerous functions, for example, insulation, physical barrier to trauma, energy storage and protein secretion with autocrine, paracrine and endocrine action. Secreted proteins, also called adipokines, can impact on biological aspects, including energy homeostasis, immune, cardiovascular, reproductive and neurological functions (Bruce-Keller et al., 2009; Sethi and Vidal-Puig, 2007). The extra supply of glucose and free fatty acids through exaggerated food intake with consequent increase in adipokines secretion (such as leptin and others) by adipose tissue growth, contributes to the onset of insulin resistance. This condition is characterized by

reduced biological action of insulin on target cells, with dysfunctions on uptake, metabolism and glucose storage at physiological concentrations of insulin (Kahn and Flier, 2000; Zeyda and Stulnig, 2009).

Many researchers are nowadays focusing in the association between insulin and the neurophysiology of hippocampus, an important region for learning and memory development and also eating behavior (Biessels and Reagan, 2015). Aside from the peripheral role of insulin on obesity development, we aim to discuss here a different way by which this hormone may, by acting centrally, influence obesogenic behavior and lead to excessive calorie intake. It is important to understand how metabolic and neural signals interact with each other on eating behavior. Thus, in this review we will focus on insulin action in the hippocampus and its consequent impaired memory related to food intake as well as the association between eating inhibition and insulin resistance.

Regulation of eating behavior

Animals must get enough food from its environment for its energy expenditure as an essential requirement for survival. The physiological state that makes an animal or a man seek food is called hunger. However, feeding behavior is not only an event that occurs to satiate hunger and that ends when hunger is finished throughout a metabolic feedback. A better way to describe feeding behavior is that it is controlled by homeostatic (bottom-up) but also hedonic (top-down) mechanisms, involving emotional, reward and cognitive factors.

Although the arcuate nucleus of the hypothalamus is one of the main areas of the central nervous system (CNS) responsible for the control of intake and energy homeostasis, feeding behavior is also modulated by the predicted reward values processed predominantly by the cortico-limbic structures (Berthoud, 2011). Deregulation of these systems leads to changes in consumption and predicts weight gain and obesity (Davis et al., 2011; Levitan et al., 2004; Silveira et al., 2016).

Memory of eating and obesity

In addition to the vast evidence that impulsive eating can result from an over-activation or a faulty signaling in the reward system components (Hebebrand et al., 2014; Johnson and Kenny, 2010; Luo et al., 2013; Volkow et al., 2011), some studies show that uncontrolled eating behavior can also be a result of a failure in cognitive inhibitory control related to food (Batterink et al., 2010; Bruce et al., 2010; He et al., 2014; Rangel, 2013). Food and its stimuli are cues that may evoke vigorous appetitive and consummatory responding on some occasions and little or no responding at other times. Thus, animals engage in appetitive and eating behavior until they become satiated and then refrain from making these responses until satiety wanes (Davidson et al., 2007; Davidson and Martin, 2014). Therefore, under conditions of negative energy balance, appetitive behaviors and food intake produce the rewarding effects of returning to homeostasis; however, once homeostasis is achieved, these behaviors no longer produce rewarding postingestive outcomes and could instead be followed by unpleasant consequences. According to some authors (Davidson et al., 2005), animals learn to anticipate both of these outcomes, and based on these associations, the food cues should excite or activate the stored representation of that reward (i.e., its memory) on subsequent occasions.

It has been shown that increasing awareness of food as it is eaten (Higgs and Woodward, 2009; Wansink and Payne, 2007), as well as simple recall of foods eaten at the last eating occasion decrease food intake in the following meal (Higgs, 2002). Robinson and colleagues (Robinson et al., 2013) suggest that these processes enhance episodic memory representation of the food consumed, and this information is used to process subsequent decisions about how much to eat (Brunstrom et al., 2012; Higgs, 2002; Higgs et al., 2012). Distraction exerts a greater influence on later intake than it does on immediate consumption, suggesting a larger effect as the memory of that eating episode fades (Robinson et al., 2013). In addition, it was shown that overweight adolescents have a memory bias in the recollection of high caloric food cues (that was not associated with better memory in general), suggesting a more elaborative encoding of this type of information or a bias at the retrieval stage of memory processing (Soetens and Braet, 2007).

Satiety regulation is a dynamic interaction process of peripheral signals such as hormones and different brain structures and neurotransmitter systems also involving the hippocampus. The hippocampus, classically associated with memory, is also recognized as a feeding behavior modulator (Parent et al., 2014) once it has many receptors for pre and post-prandial signals, such as insulin, leptin, ghrelin, glucose, cholecystokinin, glucocorticoids, NPY, galanin and bombesin (Lathe, 2001). In addition, the hippocampus receives neural signals related to food stimuli from different brain regions, such as the arcuate nucleus, nucleus of the solitary tract, insula and orbitofrontal cortex

(Wang et al., 2006) and sends efferent projections to other regions that can influence ingestive behavior, such as the hypothalamus, stria terminalis, and nucleus accumbens (Hsu et al., 2015; Kahn and Shohamy, 2013).

Hippocampal connectivity with striatum and neocortex throughout projections of parahippocampal region can also contribute directly to value assignment and decision-making in general, even without conscious awareness, dynamically modulating value representations during learning itself, allowing value to spread and biasing decisions without effortful retrieval at the time of decision (Wimmer and Shohamy, 2012). These properties could well influence food intake as the hippocampus has been suggested to be a discriminatory retention region for food cues. It is involved in the learned anticipatory response to environmental cues associated with eating (Davidson et al., 2007) and the inhibitory control of food intake and appetitive behavior depends on its structural integrity (Hebben et al., 1985; Rozin et al., 1998).

The influence of the hippocampus on food intake is mediated by adiposity signals, being related to the connection to the hypothalamus, and playing a role in body weight changes (Davidson et al., 2007), as shown in several rodent studies (Davidson et al., 2010; Forloni et al., 1986). Interestingly, overeating impairs hippocampal functioning, which contributes to the development and/or maintenance of diet-induced obesity in rodents (Davidson et al., 2013; Kanoski and Davidson, 2011). Hippocampal dysfunction increases meal frequency, total energy intake, and weight gain in rats (Davidson et al., 2010; Davidson et al., 2005). In humans, the famous H.M. case illustrates the importance of the hippocampus to integrate the information of internal metabolic states and willingness to eat; H. M., a patient that became amnesic after a bilateral resection in the medial temporal lobe region for epilepsy, had altered perception of internal states and would eat a second full dinner 1 min after he had completed the first one (Hebben et al., 1985).

Given that a host of life events that can impair hippocampal function, including excess intake of sugars and fats as shown in animal studies (Davidson et al., 2013; Freeman et al., 2011; Goldbart et al., 2006; Kanoski and Davidson, 2011; Kanoski et al., 2010; McNay et al., 2010; Molteni et al., 2002; Morris et al., 2016; Park et al., 2010; Tozuka et al., 2009) it is possible that diet-induced obesity is caused, at least in part, by impaired hippocampal inhibition of meal onset (Parent et al., 2014). Eating high-fat and high-sugar diets may impair hippocampal inhibitory control of eating behavior, perhaps because it becomes insensitive to satiety states and does not properly store information related to previous meal. The so called “western” diet seems to reduce hippocampus’ ability to resist

the environmental food cues (Davidson et al., 2007; Davidson and Martin, 2014) and increases the chance of overeating, excess weight gain, and more severe forms of cognitive impairment.

Physiological role of insulin

Insulin, a molecule composed by two polypeptide chains of 21 and 30 amino acids (Reid et al., 1968), is produced by pancreatic islets beta cells and is secreted into circulation with anabolic functions. This hormone promotes the deposition of substrates in the form of nutrients in tissues and, on the other hand, inhibits catabolism. Insulin promotes the transport of mainly glucose (but also amino acids and free fatty acids) from the extracellular compartment to inside the cells with consequent decrease in their circulating levels (Dimitriadis et al., 2011). Moreover, it can regulate the rate of carbohydrates used by most cells. Immediately after a high carbohydrate meal, the glucose absorbed into the blood may induce a rapid secretion of insulin (Aronoff et al., 2004) that promotes glucose uptake, storage and utilization by almost all body tissues, especially skeletal muscle, adipose tissue and liver (Pansuria et al., 2012). Also, insulin is responsible for inhibiting liver, kidney and small intestine glucose production in order to maintain glucose homeostasis (Wilcox, 2005).

Once released into the blood, insulin binds to a specific plasma membrane glycoprotein receptors on its target cells. Insulin receptor (IR) activation induces autophosphorylation of the tyrosine residues of the docking protein known as insulin receptor substrate (IRS), and leads to activation of several signaling cascades including phosphoinositide 3 kinase (PI3K)/Akt (at the metabolic tissue) and the mitogen-activated protein kinase (MAPK) pathways (Dimitriadis et al., 2011), that may increase or decrease the expression and the activity of IR. IR stimulates rapid glucose uptake in muscle, adipocytes, pancreatic and hepatic cells via translocation of glucose transporter type 4 (GLUT4) vesicles (Saltiel and Kahn, 2001) and also controls glycogen/lipid/protein synthesis, specific gene expression and energy metabolism (Pansuria et al., 2012). The MAPK pathway transmits a signal surface to the nucleus, controlling different biological responses such as cell growth, proliferation, differentiation, and cell death (Zhang et al., 2011). Of the six IRS families

described, IRS-1 and IRS-2 are involved in most of the effects of insulin in these two signaling pathways.

Insulin in the central nervous system

For a long time, it was believed that the brain was not insulin-dependent, but insulin and its receptors are found in abundance in the olfactory bulb, hypothalamus, and hippocampus, among other regions, both in humans and in rodents (Havrankova et al., 1978; Hill et al., 1986; Schulingkamp et al., 2000). Insulin is actively transported across the blood-brain barrier and it may even be produced locally in the brain, although most brain insulin is thought to be originated from the systemic circulation (Bingham et al., 2002; Ghasemi et al., 2013). Elevations in circulating insulin can alter brain function, augmenting the counter regulatory response to hypoglycemia (Fruehwald-Schultes et al., 1999). Physiologically relevant increases in plasma insulin levels also stimulate the translocation of GLUT4 to the plasma membrane in many CNS areas (McEwen and Reagan, 2004), even if the carrier is not as abundant in the CNS as GLUT1 and GLUT3 (Blazquez et al., 2014).

Many studies have shown a relationship between IR signaling and ion channels and receptors expression at synapses in various regions of the CNS, suggesting that insulin and IR can regulate synaptic plasticity and cognitive functions (Biessels and Reagan, 2015; Gispen and Biessels, 2000). Their location on hippocampal glutamatergic synapses indicates a role of insulin in the transmission and synaptic plasticity and modulation of learning and memory (Irvine et al., 2011; Muller et al., 2011; Skeberdis et al., 2001). In addition, IRS-1 inhibition is described in Alzheimer's disease and related animal models (Bomfim et al., 2012; Moloney et al., 2010), and the reversion of this inhibition improves cognitive outcomes in mice (Bomfim et al., 2012). It is also recognized the trophic function of insulin referred to proliferation, differentiation, and neurite growth (Lee et al., 2011; Xu et al., 2004).

Astrocytes are also known to express both IR and insulin signaling pathway proteins (Stern et al., 2014). Neurons from CNS depend on astrocytes for energy metabolism, maintenance of the blood-brain barrier, vascular reactivity, regulation of extracellular glutamate levels, protection from reactive oxygen species, amyloid-beta peptides, and

spread of inflammatory cells (Koistinaho et al., 2004; Zonta et al., 2003). Diabetes-related disturbances in the brain are associated with changes in astrocytes activity and can be prevented with insulin treatment (Coleman et al., 2010).

Moreover, insulin receptor signaling controls vessel dilation and contraction and regulates monocyte differentiation into macrophages (Baron, 1994; Laakso and Kuusisto, 2014; Pansuria et al., 2012), explaining why people with type II diabetes mellitus (T2DM) are more susceptible to central lesions, white matter hyperintensities, and brain atrophy than people without T2DM (de Bresser et al., 2010). Patients with T2DM also have increased levels of amyloid polypeptide deposits in and around blood vessels, which may be involved with their risk to develop vascular and neurological pathologies (Oskarsson et al., 2015). Insulin has also been shown to be important in maintaining the integrity and permeability of the blood-brain barrier (Hawkins et al., 2007; Sartorius et al., 2015).

Insulin in the hypothalamus and mesocorticolimbic system

Insulin is the major postprandial hormone and acts by moderating satiety signals generated by a meal in the brain tissue (Schwartz et al., 2000; Woods et al., 1998). It influences the amount of food consumed in a meal and also contributes to body weight regulation and reproduction (Bruning et al., 2000; Rodin et al., 1985).

Insulin is involved in feeding control and energy balance by regulating orexigenic and anorexigenic neurons (Palou et al., 2009). The IR is expressed by neurons in the arcuate nucleus and found both in POMC and AgRP neurons. In general, NPY/AgRP neurons are directly inhibited by insulin (as by leptin), while POMC/CART neurons are stimulated by these hormones (Mayer and Belsham, 2009). During the cephalic phase of eating behavior, peripheral changes in the insulin to glucose ratio are detected by these hypothalamic neurons, stimulating appetite by increasing the expression of both NPY and AgRP and decreasing POMC and CART expression (Berthoud and Jeanrenaud, 1982; Palou et al., 2009). During the gastric phase, insulin secretion is stimulated by gastrointestinal hormones such as CCK, but the release of insulin is higher when food is absorbed in the intestine (intestinal phase) and glucose levels rise. This increase in insulin due to increased glycemia during

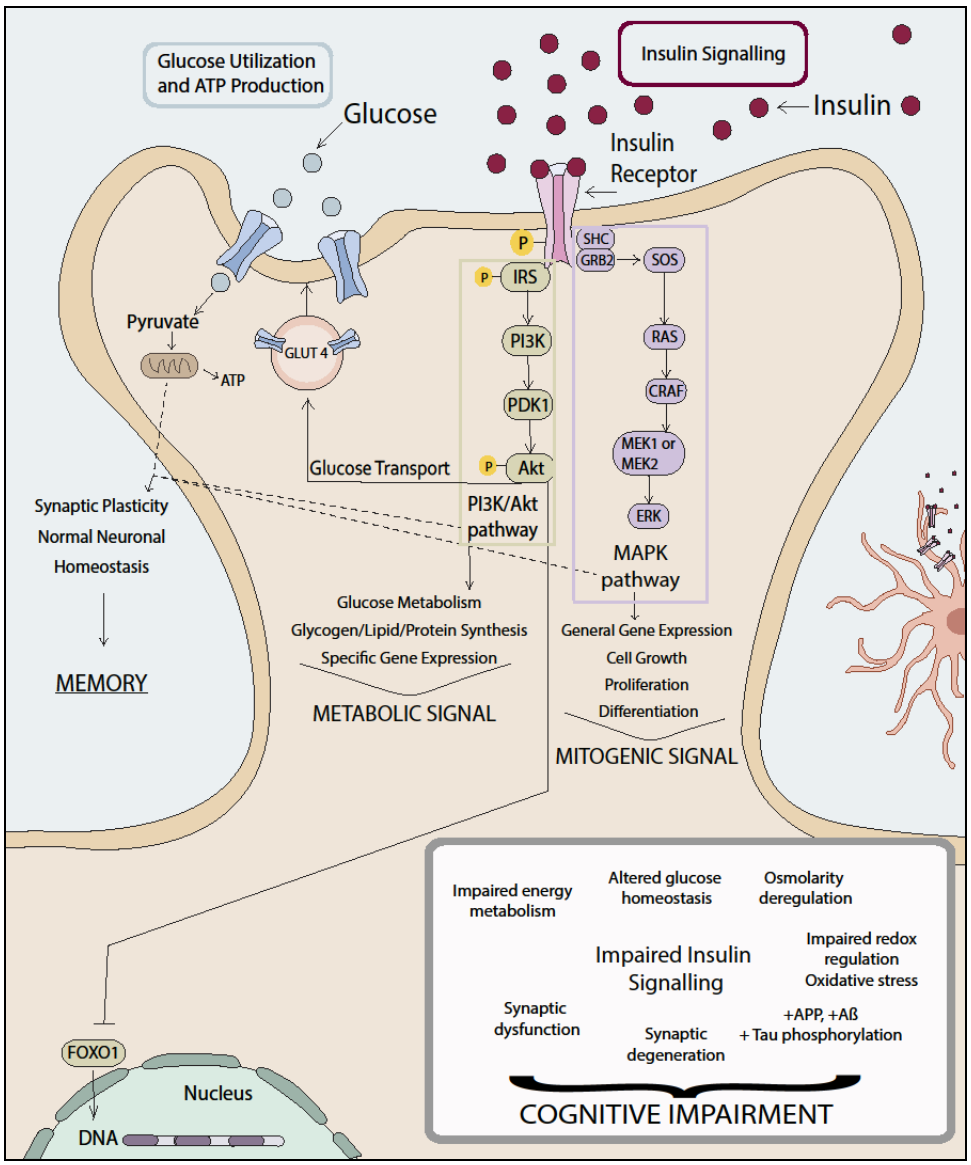

Figure 1. Insulin receptor activation on central nervous system (more specifically, in the hippocampus). Pancreas-derived insulin binds to receptors on endothelial cells of the blood-brain barrier, where it is transported into the brain interstitial fluid by a saturable process of receptor-mediated transcytosis. As soon as insulin binds its receptors (distributed throughout the cerebral cortex, hippocampus, hypothalamus, amygdala, olfactory bulb and septum) they become activated as a tyrosine kinase, leading to autophosphorylation of the IR subunits and phosphorylation of the tyrosine residues of its docking protein (insulin receptor substrate). This activates both the phosphoinositide 3 kinase (PI3K)/Akt and the mitogen-activated protein kinase (MAPK) pathways. The PI3K/Akt pathway seems to be associated with metabolic signaling, including an increase of glucose transporter from the GLUT4 translocation and subsequent conversion to ATP, while the MAPK pathway is associated with mitogenic signaling. Both these pathways of insulin signaling and glucose utilization are recognitablezed to be important for neuronal function and required for neuronal synaptic plasticity and for learning and memory. Impaired insulin signaling leads to synaptic dysfunction and altered glucose homeostasis that impacts energy metabolism, osmolarity, redox balance and could contribute to increased depots of amyloid precursor protein (APP), Aβ accumulation and tau hyperphosphorylation. These alterations lead to cognitive impairment and are accompanied by astrogliosis and possibly by neuroinflamation. Insulin receptor substrate (IRS); Phosphoinositide-dependent kinase-1 (PDK1); Protein kinase B (AKT); Phosphatidylinositol 3 kinase (PI3K); Growth factor receptor-bound protein 2 (GRB2); Son of Sevenless (SOS); Mitogen-activated protein kinase kinase (MEK); Extracellular signal-regulated kinase (ERK); Mitogen-activated protein kinase (MAPK); Forkhead box protein O1 (FOXO1). Adapted from (Verdile et al., 2015) and (Duarte, 2015).

postprandial state has an anorexigenic effect by acting on the same NPY and POMC hypothalamic neurons (Langhans et al., 2001; Palou et al., 2009). On the other hand, animals that lack or are insensitive to insulin are known to be hyperphagic and to gain weight, thus central administration of this hormone can reduce food intake and body weight (Gomez-Pinilla, 2008; Schwartz et al., 2000; Stockhorst et al., 2004).

Moreover, food intake is regulated via insulin in the mesolimbic system (Figlewicz, 2003; Figlewicz and Benoit, 2009), since there are IRs in the ventral tegmental area (VTA) and ventral striatum (Li et al., 2009; Mebel et al., 2012; Woods et al., 2016) as shown in experimental studies. Insulin suppresses dopamine release in the VTA, which decreases food "wanting" (Mebel et al., 2012). The decreased sensitivity to insulin in CNS limbic regions results in increased food consumption and in inaccurate valuation of foods, contributing to impulsive eating and obesity (Figlewicz et al., 2004; Woods et al., 2016). Another way by which insulin influences feeding behavior is modifying the sensory properties of food, by acting on olfactory mucosa and decreasing olfactory perception in rodents (Savigner et al., 2009) and humans (Ketterer et al., 2011).

Recent fMRI studies in humans suggest the existence of functional connections between the hypothalamus and different parts of the fronto-striatal circuitry of the brain (Kullmann et al., 2014). In addition, glucose ingestion increases the functional connectivity between the hypothalamus and the striatum, possibly via insulin (Page et al., 2013). Activity in the putamen, orbitofrontal cortex and insula correlate positively with enhanced peripheral insulin sensitivity via intranasal insulin application in humans (Heni et al., 2012; Kullmann et al., 2013a).

Finally, the prefrontal cortex plays an important role modulating feeding behavior and choices in humans, being involved in inhibitory control (lateral prefrontal cortex) (Hare et al., 2009) and reward-based decision-making (orbito-frontal cortex and anterior cingulate) (Rolls, 2004). All prefrontal regions are responsive to insulin (Guthoff et al., 2010; Heni et al., 2014a; Heni et al., 2012; Karczewska-Kupczewska et al., 2013; Kroemer et al., 2013; Page et al., 2013; Page et al., 2011). Exogenous intranasal insulin administration causes a decrease in the response of the prefrontal cortex to food pictures (Guthoff et al., 2010), and insulin increases after a glucose load are associated with reduced activation in frontal and limbic

regions (Kroemer et al., 2013). Therefore, brain insulin signaling in the striatal-frontal regions seems to act on value attribution and decision making negatively modulating food intake.

Insulin in the hippocampus

Insulin improves cognitive performance in humans and animals, including young healthy adults (Kern et al., 2001) and individuals with Alzheimer's disease (Chen et al., 2016; Freiherr et al., 2013), young rats (Haj-ali et al., 2009), aged rodents (Haas et al., 2016; Maimaiti et al., 2016) and animal experimental models with insulin resistance (Greenwood and Winocur, 2001; McNay et al., 2010). Studies using intranasal insulin administration show that this hormone is involved in cognition and particularly memory development (for a review, see (Ott et al., 2012)). Intracerebroventricular injection of insulin immediately after inhibitory avoidance training leads to memory enhancement 24h after training in rodents (Park et al., 2000). Intracerebroventricular or hippocampal injection of insulin also enhances spatial working memory and water maze memory dependent of PI-3K, increasing local glycolytic metabolism (Haj-ali et al., 2009; McNay et al., 2010; Stern et al., 2014). Furthermore, this hormone promotes neural growth in the hippocampus and the impairment of central insulin receptors is associated with learning and memory deficits (Stockhorst et al., 2004). Additionally, hippocampal-dependent spatial learning tasks, such as the Morris water maze, increase the hippocampal IR signaling in rodents (Zhao et al., 1999). These data highlight that IR cascade activation in the hippocampus is associated with cognitive performance (Cholerton et al., 2013).

The hippocampal development is particularly sensitive to changes in glucose homeostasis (Amin et al., 2013). As in the periphery, central insulin action results in translocation of the neuronal insulin-sensitive GLUT4 to the plasma membrane of hippocampal neurons (Grillo et al., 2009), which increases their glucose uptake. It also decreases glucose extracellular levels, and increases lactate levels in the extracellular space, indicating an increase in local glycolytic metabolism (McNay et al., 2010). Hippocampal cell culture experiments suggest that the dendritic distribution of insulin receptors is in accordance with a synaptic localization (De Felice et al., 2009; Zhao et al., 2008). Insulin also induces synaptogenesis, modulates the synaptic function, and regulates dendritic spine formation and excitatory synapse development in hippocampal neurons through the

activation of PI3K/mTOR pathway (Lee et al., 2011; Lee et al., 2005) and upregulation of tau protein (Nemoto et al., 2011).

N-Methyl-D-Aspartate receptors (NMDARs) are part of the ionotropic glutamate receptors family and glutamate is known as the major excitatory neurotransmitter of the nervous system (Paoletti et al., 2013). The specific patterns of neuronal activity occurring by calcium flow through these receptors are converted into long-term changes in synapse structure and function, essential for memory, behavioral inhibition and other cognitive functions (Baker and Kim, 2002; Taylor et al., 2014). In hippocampal synapses, the NMDARs complex in the post-synaptic density (PSD) is a structure intimately involved in the regulation of synaptic plasticity (Gardoni et al., 2002). The impairment of synaptic plasticity in streptozotocin (STZ)-induced diabetic rats is associated to an inappropriate level of NMDARs stimulation required for the induction phase of long-term potentiation. In fact, insulin can potentiate current flow through NMDA, and the Tyr-phosphorylation of the subunits GluN2A and GluN2B of the NMDARs, an important component of signal transduction mechanisms occurring in PSD, is mediated by insulin in hippocampal slices (Christie et al., 1999). Additionally, IR and the insulin receptor substrate-1, 2 and p58/p53 (IRS-1, 2, and p58/p53) are components of PSD (Abbott et al., 1999). In mice that lack IRS-2, there is a deficit in NMDA receptor-dependent synaptic plasticity in the hippocampus, with concomitant deficits in the modulation of synaptic plasticity, and these changes are associated with reduced basal phosphorylation of the NMDA receptor subunit GluN1 as well as downstream targets of the PI3K pathway (Costello et al., 2012). This suggests that insulin modulates synapse plasticity by stimulating long-term depression and potentiation, which are involved in memory representation (Feldman, 2009) reviewed in (Moult and Harvey, 2008).

The expression and concentration of GluN2B are significantly reduced in hippocampal PSD in STZ-treated rats (Di Luca et al., 1999; Muller et al., 2011) (Di Luca et al., 1999; Muller et al., 2011), but insulin can prevent the decreased Tyr-phosphorylation in hippocampal pyramidal cells of these animals (Gardoni et al., 2002). The disturbances of the NMDARs on STZ-diabetes are the result of a slowly progressive process, rather than an acute insult caused by hyperglycaemia, and at least part of the learning and plasticity deficits in STZ-rats may be a direct consequence of disturbances at the level of the NMDARs complex.

Interestingly, human fMRI studies show a significant positive correlation between fasting plasma insulin levels and hippocampal activity after stimulation with high-caloric food images strongly suggesting a link between insulin signaling pathways, hippocampal activation, and craving behavior to food cues in humans (Avena et al., 2008; Hargrave et al., 2016; Pelchat et al., 2004; Wallner-Liebmann et al., 2010). Hippocampal neighboring gyri (parahippocampal and fusiform gyri) are linked to neural pathways of visual recognition, especially visual food cues (Kullmann et al., 2013b; van der Laan et al., 2011), being particularly sensitive to insulin. These findings corroborate the idea that the hippocampus participates in the identification of external signs of food and that insulin is closely linked with that role of the hippocampus in feeding behavior, possibly reducing the attention to food cues (Kullmann et al., 2016).

Implications of insulin resistance

There are many factors that can explain the mechanisms of insulin resistance, including obesity, inflammation, mitochondrial dysfunction, hyperinsulinemia, lipotoxicity/ hyperlipidemia, genetic background, endoplasmic reticulum stress, aging, oxidative stress, fatty liver, hypoxia, lipodystrophy, and pregnancy (Ye, 2013). In obesity, the increase in glucose and free fatty acids by high food intake, as well as by adipose tissue growth products including hormones such as leptin and cytokines, contribute to the onset of insulin resistance (Kahn et al., 2006). In obese individuals, adipose tissue releases increased amounts of non-esterified fatty acids, glycerol, hormones, pro-inflammatory cytokines, and other factors that are involved in the development of insulin resistance (Hotamisligil, 2003).

This dysfunction occurs when insulin-sensitive tissues progressively become less responsive to insulin and, consequently, insulin-induced glucose uptake is impaired. The failure may be the result of changing insulin signaling in target tissues (reduced concentration and kinase activity of IR, limited concentration and phosphorylation of IRS-1 and 2 of PI activity 3-kinase, low GLUT4 translocation and diminished activity of intracellular enzymes). In addition there is a down-regulation of GLUT4 in adipocytes (Petersen and Shulman, 2006). Thus, there is a dysfunction in glucose uptake, metabolism and storage

under physiological concentrations of insulin and, therefore, increased production of this hormone by the pancreas (Kahn and Flier, 2000). In many progressive cases, the lipids deposits into pancreatic islet cells impair the ability of beta cells to maintain enhanced insulin secretion, leading to glucose intolerance and type 2 diabetes (Cerf, 2013; Haslam and James, 2005).

Central implications of insulin resistance

In humans, one of the first studies to show that, the brain was unresponsive to insulin in situations of obesity was published in 2006 (Tschritter et al., 2006). The benefits promoted by insulin centrally are not found in situations of resistance of this hormone (Biessels and Reagan, 2015; Kullmann et al., 2016; Lee et al., 2016; Stoeckel et al., 2016). In this condition, glucose metabolism and insulin signaling are impaired in many brain regions, including those involved in learning and memory, such as the hippocampus (Biessels and Reagan, 2015; Pearce et al., 2012). Patients with type II diabetes have reduced performance in almost all neuropsychological tests, especially in memory, information processing speed and executive function (Moheet et al., 2015). In obesity and Alzheimer's disease, and aging itself, there is a change in the ratio of central and peripheral levels of insulin, wherein the concentration of the hormone in the periphery is higher as compared to healthy and younger individuals (Rani et al., 2016; Stockhorst et al., 2004). It is also known that there is lower transport of peripheral insulin to the brain under these conditions, although some studies show that the reduction of insulin signaling is not generalized to all brain regions and for all existing signaling pathways at the same time (Steculorum et al., 2014).

In human neuroimaging studies, patients with obesity or type II diabetes exhibit reduction in gray matter volume and in cortical thickness, as well as loss of white matter integrity (Bischof and Park, 2015; Brundel et al., 2014), particularly in limbic structures such as the hippocampus and amygdala (den Heijer et al., 2003; Hajek et al., 2014; Manschot et al., 2006). They also have altered brain activation and functional connectivity in different brain networks, including areas involved with working memory (Qiu et al., 2016; Zhang et al., 2016). Reduction in the volume of the hippocampal formation is seen in individuals with impaired glucose tolerance and insulin resistance (Convit et al., 2003; Ursache et al., 2012),

and deficits in hippocampal-based memory performance and preservation of other cognitive domains are observed in these patients (Gold et al., 2007). Obese adolescents with type II diabetes have reduced cognitive performance in verbal memory and psychomotor efficiency, accompanied by reduced white matter volume and increased ventricles observed on MRI (Yau et al., 2010). In postmenopausal women, it was found a negative correlation between insulin resistance indexes such as HOMA-IR (Homeostasis Model of Assessment - Insulin Resistance) and hippocampal volume, as well as cognitive performance in tests of declarative and non-declarative memory (Rasgon et al., 2011). Patients with type II diabetes (Hoogenboom et al., 2014; Musen et al., 2012) and obese individuals (Kullmann et al., 2012) show diminished connectivity in the default mode network (DMN), a network including the precuneus, prefrontal cortex, lateral temporal cortex and hippocampus, that is essential for higher cognitive processes such as memory and cognitive function. Interestingly, the use of insulin in type II diabetes patients increases the functional connectivity between the hippocampus and frontal regions (Gottschalk and Ellger, 2015; Zhang et al., 2015), and this enhanced functional connectivity correlates with better performance in cognitive tests (Zhang et al., 2015).

Insulin resistance reduces peripheral insulin transport and its uptake into the brain (Plum et al., 2005; Stockhorst et al., 2004), turning the neurons less able to use glucose. In animal studies, this cell disorder is associated to impairment in normal neural transmission and electrophysiology, as well as to learning and memory due to hippocampus damage (Amin et al., 2013; Gardoni et al., 2002; Grillo et al., 2009). This is in accordance to other studies using the consumption of high-fat and/or high-sugar diets in animal models of obesity and insulin resistance (Davidson et al., 2012; Dinel et al., 2011; Jurdak et al., 2008; Kanoski et al., 2010; Kohjima et al., 2010; Molteni et al., 2002; Stranahan et al., 2008; Winocur and Greenwood, 2005). Insulin-induced long-term depression is attenuated in these animals (Mielke et al., 2005), especially in the hippocampus (Pratchayasakul et al., 2011), suggesting that brain insulin resistance contributes to cognitive impairment.

The combination of impaired insulin receptor signaling and decreased insulin transport across the blood-brain barrier (Davidson et al., 2012; Kanoski et al., 2010) can lead to hippocampal insulin resistance (Biessels and Reagan, 2015), which includes decreases in

insulin-stimulated phosphorylation of IR and Akt, less insulin-stimulated translocation of GLUT4, as well as increased serine phosphorylation of IRS-1, a marker of insulin resistance (Arnold et al., 2014; Mielke et al., 2005). Experimental studies in rodents show that this imbalance of insulin mechanism of action on the hippocampus can be explained by mitochondrial dysfunction, increased reactive oxygen species production, caspases inhibition, disturbances in the expression of apoptosis regulator genes, impairments in hypothalamic–pituitary–adrenal axis function, and neuroinflammation (Boitard et al., 2014; Dinel et al., 2011; Morrison et al., 2010; Pipatpiboon et al., 2013; Piroli et al., 2007; Sadeghi et al., 2016). However, these factors may also act independently of IR, causing hippocampal neuroplasticity deficits and neuronal apoptosis in obesity and elderly (Tucsek et al., 2014). Together, these phenomena increase neuronal damage and collaborate for the low cognitive performance in obese individuals.

Additionally, it was found that obesity and insulin resistance result in reduced hippocampal expression and signaling of the brain derived neurotrophic factor (BDNF) in several studies (Molteni et al., 2002; Park et al., 2010; Tozuka et al., 2009), which is known to play important roles in proliferation, differentiation and survival of neurons during development, as well as in the synaptic activity and plasticity in many groups of mature neurons, being also anorexigenic (Lebrun et al., 2006). On the other hand, treatment with hypoglycemic agents and insulin sensitizers, as peroxisome proliferator-activated receptor-γ (PPARγ) agonist, metformin, and inhibitors of dipeptidyl peptidase 4 (DPP-4), reduces brain mitochondrial dysfunction and reverses memory impairments in high-fat induced insulin resistant rats (Pintana et al., 2012; Pipatpiboon et al., 2013; Pipatpiboon et al., 2012).

Network hubs and modulators

As reviewed in the previous sections, a decreased connectivity within the default mode network, including the hippocampus, posterior cingulate cortex/precuneus and prefrontal regions in seen in patients with type II diabetes (Hoogenboom et al., 2014; Musen et al., 2012) and could explain the cognitive deficits associated with this condition. This core network has a functional connection to both lateral and medial hypothalamus (Kullmann et

al., 2014), and this may constitute the link between the peripheral metabolism and higher cognitive function and its effects on food choices and feeding behavior.

Another possible link between peripheral metabolism and eating behavior central control relies on the mesocorticolimbic pathways, as the VTA dopaminergic neurons have insulin receptors (Figlewicz, 2003; Li et al., 2009), and activity in the striatum correlates with enhanced peripheral insulin sensitivity (Heni et al., 2012). Insulin acting on these neurons could modulate feeding preferences as suggested in experimental studies (Portella et al., 2015).

Elevated proinflammatory cytokines, such as TNF alfa, interfere with insulin signaling and contribute to insulin resistance (Ferreira et al., 2014). Peripheral chronic low-grade inflammation is a feature of obesity and type II diabetes, being associated with hypothalamic gliosis (Thaler et al., 2012), loss of hypothalamic structural integrity (Cazettes et al., 2011; Puig et al., 2015), and inferior cognitive performance (Puig et al., 2015). Therefore, inflammation is an important modulator of insulin action and a possible link between metabolic disorders and cognitive decline.

Impaired brain insulin action could also result from insulin resistance at the blood-brain barrier (Verdile et al., 2015), or changes in the transport ratio of insulin across the blood-brain barrier (Heni et al., 2014b; Sartorius et al., 2015). These processes are seen during aging (Shah and Mooradian, 1997). In animal models, exposure to high-fat diets leads to increased blood-brain barrier permeability and cognitive dysfunction (Davidson et al., 2012; Pallebage-Gamarallage et al., 2012), suggesting that blood-brain barrier injury is another contributing factor to the development and progression of cognitive impairment in insulin resistant states.

Hippocampal insulin resistance and altered food decision-making – role on obesity risk

In this review, we propose to approximate two sets of evidence that appeared to have a very reasonable association. On the one hand, the contribution of the hippocampus on

food decision-making and, on the other, the role of insulin in the healthy functioning of the hippocampus. Both phenomena collaborate to balance food intake and body dimension. However, a disruption of the equilibrium that occurs in insulin resistant states may lead to a vicious cycle of obesity (Davidson et al., 2005; Davidson and Martin, 2014; Kanoski and Davidson, 2011): diets rich in fat and sugar induce an increase in adipose tissue; this leads progressively to insulin resistance, at least in some regions of the CNS; hippocampus is affected by the imbalance in insulin receptor signaling; the memory related to food is altered; there is no further inhibition to food stimuli, even when already satiated; hyperphagia leads to obesity in a feed forward process.

We reviewed evidence showing that hippocampal damage can disrupt interoceptive state signals ability to modulate eating behavior, leading to increased appetitive responding. Findings that satiety neuropeptides such as insulin play a role in the performance of hippocampal-dependent learning and memory processes encourage speculation that the effects of these neuropeptides on food intake might be based in part on their effects on behavioral inhibition processes that are mediated by the hippocampus (Benoit et al., 2010; Wimmer and Shohamy, 2012). Additionally, there are evidences that insulin resistance can be strongly involved with hippocampal damage.

Individuals vulnerable to uncontrolled eating show insulin resistance in the prefrontal cortex (Kullmann et al., 2015) and hippocampus (Convit et al., 2003) and altered measures of cognition related to eating behavior, such as disinhibition and food craving. The homeostatic control of food intake works in close interaction to regions involved in decision-making and value attribution (Berthoud, 2012). Therefore, in agreement with Biessels & Reagan (Biessels and Reagan, 2015), we can suggest that memory impairment for a consumed meal, which can harm the stability of feeding patterns (Epstein et al., 2010), is an early sign associated with hippocampal insulin resistance. This specific cognitive deficit may contribute to increased food intake, leading to overeating, obesity and higher insulin resistance in long term, as a “vicious cycle” model proposed by Martin and Davidson (Davidson and Martin, 2014; Martin and Davidson, 2014). The development of tools and protocols to detect subtle behavioral characteristics associated with increased risk for developing obesity and related metabolic disturbances (e.g. behavioral tasks and cognitive testing that could lead to a

better comprehension of the role of memory on food patterns) can be of interest for target prevention and counseling.

Funding: The authors appreciate support by the National Council for Technological and Scientific Development (CNPq). The financial supporters played no role in the design or writing of this review.

Conflicts of interest: All authors declare no conflicts of interest.

References

Abbott, M.A., Wells, D.G., Fallon, J.R., 1999. The insulin receptor tyrosine kinase substrate p58/53 and the insulin receptor are components of CNS synapses. J Neurosci 19, 7300-7308.

Amin, S.N., Younan, S.M., Youssef, M.F., Rashed, L.A., Mohamady, I., 2013. A histological and functional study on hippocampal formation of normal and diabetic rats. F1000Res 2, 151.

Arnold, S.E., Lucki, I., Brookshire, B.R., Carlson, G.C., Browne, C.A., Kazi, H., Bang, S., Choi, B.R., Chen, Y., McMullen, M.F., Kim, S.F., 2014. High fat diet produces brain insulin resistance, synaptodendritic abnormalities and altered behavior in mice. Neurobiol Dis 67, 79-87.

Aronoff, S.L., Berkowitz, K., Shreiner, B., Want, L., 2004. Glucose Metabolism and Regulation: Beyond Insulin and Glucagon. Diabetes Spectrum 17, 183-190.

Avena, N.M., Rada, P., Hoebel, B.G., 2008. Evidence for sugar addiction: Behavioral and neurochemical effects of intermittent, excessive sugar intake. Neurosci Biobehav R 32, 20-39.

Baker, K.B., Kim, J.J., 2002. Effects of stress and hippocampal NMDA receptor antagonism on recognition memory in rats. Learning & memory 9, 58-65.

Baron, A.D., 1994. Hemodynamic actions of insulin. The American journal of physiology 267, E187-202.

Batterink, L., Yokum, S., Stice, E., 2010. Body mass correlates inversely with inhibitory control in response to food among adolescent girls: an fMRI study. Neuroimage 52, 1696-1703.

Benito-Leon, J., Mitchell, A.J., Hernandez-Gallego, J., Bermejo-Pareja, F., 2013. Obesity and impaired cognitive functioning in the elderly: a population-based cross-sectional study (NEDICES). Eur J Neurol 20, 899-906, e876-897.

Benoit, S.C., Davis, J.F., Davidson, T.L., 2010. Learned and cognitive controls of food intake. Brain research 1350, 71-76.

Berthoud, H.R., 2011. Metabolic and hedonic drives in the neural control of appetite: who is the boss? Current opinion in neurobiology 21, 888-896.

Berthoud, H.R., 2012. The neurobiology of food intake in an obesogenic environment. The Proceedings of the Nutrition Society 71, 478-487.

Berthoud, H.R., Jeanrenaud, B., 1982. Sham feeding-induced cephalic phase insulin release in the rat. The American journal of physiology 242, E280-285.

Biessels, G.J., Reagan, L.P., 2015. Hippocampal insulin resistance and cognitive dysfunction. Nat Rev Neurosci 16, 660-671.

Bingham, E.M., Hopkins, D., Smith, D., Pernet, A., Hallett, W., Reed, L., Marsden, P.K., Amiel, S.A., 2002. The role of insulin in human brain glucose metabolism: an 18fluoro-deoxyglucose positron emission tomography study. Diabetes 51, 3384-3390.

Bischof, G.N., Park, D.C., 2015. Obesity and Aging: Consequences for Cognition, Brain Structure, and Brain Function. Psychosom Med 77, 697-709.

Blazquez, E., Velazquez, E., Hurtado-Carneiro, V., Ruiz-Albusac, J.M., 2014. Insulin in the brain: its pathophysiological implications for States related with central insulin resistance, type 2 diabetes and Alzheimer's disease. Front Endocrinol (Lausanne) 5, 161.

Boitard, C., Cavaroc, A., Sauvant, J., Aubert, A., Castanon, N., Laye, S., Ferreira, G., 2014. Impairment of hippocampal-dependent memory induced by juvenile high-fat diet intake is

associated with enhanced hippocampal inflammation in rats. Brain, behavior, and immunity 40, 9-17.

Bomfim, T.R., Forny-Germano, L., Sathler, L.B., Brito-Moreira, J., Houzel, J.C., Decker, H., Silverman, M.A., Kazi, H., Melo, H.M., McClean, P.L., Holscher, C., Arnold, S.E., Talbot, K., Klein, W.L., Munoz, D.P., Ferreira, S.T., De Felice, F.G., 2012. An anti-diabetes agent protects the mouse brain from defective insulin signaling caused by Alzheimer's disease- associated Abeta oligomers. J Clin Invest 122, 1339-1353.

Bruce, A.S., Holsen, L.M., Chambers, R.J., Martin, L.E., Brooks, W.M., Zarcone, J.R., Butler, M.G., Savage, C.R., 2010. Obese children show hyperactivation to food pictures in brain networks linked to motivation, reward and cognitive control. International journal of obesity 34, 1494-1500.

Bruce-Keller, A.J., Keller, J.N., Morrison, C.D., 2009. Obesity and vulnerability of the CNS. Biochim Biophys Acta 1792, 395-400.

Brundel, M., Kappelle, L.J., Biessels, G.J., 2014. Brain imaging in type 2 diabetes. European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology 24, 1967-1981.

Bruning, J.C., Gautam, D., Burks, D.J., Gillette, J., Schubert, M., Orban, P.C., Klein, R., Krone, W., Muller-Wieland, D., Kahn, C.R., 2000. Role of brain insulin receptor in control of body weight and reproduction. Science 289, 2122-2125.

Brunstrom, J.M., Burn, J.F., Sell, N.R., Collingwood, J.M., Rogers, P.J., Wilkinson, L.L., Hinton, E.C., Maynard, O.M., Ferriday, D., 2012. Episodic memory and appetite regulation in humans. PloS one 7, e50707.

Caballero, B., 2007. The global epidemic of obesity: an overview. Epidemiologic reviews 29, 1-5.

Caimari, A., Oliver, P., Rodenburg, W., Keijer, J., Palou, A., 2010. Feeding conditions control the expression of genes involved in sterol metabolism in peripheral blood mononuclear cells

of normoweight and diet-induced (cafeteria) obese rats. The Journal of nutritional biochemistry 21, 1127-1133.

Cazettes, F., Cohen, J.I., Yau, P.L., Talbot, H., Convit, A., 2011. Obesity-mediated inflammation may damage the brain circuit that regulates food intake. Brain research 1373, 101-109.

Cerf, M.E., 2013. Beta cell dysfunction and insulin resistance. Front Endocrinol (Lausanne) 4, 37.

Chen, Y., Zhang, J., Zhang, B., Gong, C.X., 2016. Targeting Insulin Signaling for the Treatment of Alzheimer's Disease. Curr Top Med Chem 16, 485-492.

Cholerton, B., Baker, L.D., Craft, S., 2013. Insulin, cognition, and dementia. European journal of pharmacology 719, 170-179.

Christie, J.M., Wenthold, R.J., Monaghan, D.T., 1999. Insulin causes a transient tyrosine phosphorylation of NR2A and NR2B NMDA receptor subunits in rat hippocampus. J Neurochem 72, 1523-1528.

Coleman, E.S., Dennis, J.C., Braden, T.D., Judd, R.L., Posner, P., 2010. Insulin treatment prevents diabetes-induced alterations in astrocyte glutamate uptake and GFAP content in rats at 4 and 8 weeks of diabetes duration. Brain research 1306, 131-141.

Convit, A., Wolf, O.T., Tarshish, C., de Leon, M.J., 2003. Reduced glucose tolerance is associated with poor memory performance and hippocampal atrophy among normal elderly. Proc Natl Acad Sci U S A 100, 2019-2022.

Costello, D.A., Claret, M., Al-Qassab, H., Plattner, F., Irvine, E.E., Choudhury, A.I., Giese, K.P., Withers, D.J., Pedarzani, P., 2012. Brain deletion of insulin receptor substrate 2 disrupts hippocampal synaptic plasticity and metaplasticity. PloS one 7, e31124.

Davidson, T.L., Hargrave, S.L., Swithers, S.E., Sample, C.H., Fu, X., Kinzig, K.P., Zheng, W., 2013. Inter-relationships among diet, obesity and hippocampal-dependent cognitive function. Neuroscience 253, 110-122.

Davidson, T.L., Kanoski, S.E., Chan, K., Clegg, D.J., Benoit, S.C., Jarrard, L.E., 2010. Hippocampal lesions impair retention of discriminative responding based on energy state cues. Behav Neurosci 124, 97-105.

Davidson, T.L., Kanoski, S.E., Schier, L.A., Clegg, D.J., Benoit, S.C., 2007. A potential role for the hippocampus in energy intake and body weight regulation. Curr Opin Pharmacol 7, 613-616.

Davidson, T.L., Kanoski, S.E., Walls, E.K., Jarrard, L.E., 2005. Memory inhibition and energy regulation. Physiology & behavior 86, 731-746.

Davidson, T.L., Martin, A.A., 2014. Obesity: Cognitive impairment and the failure to 'eat right'. Curr Biol 24, R685-687.

Davidson, T.L., Monnot, A., Neal, A.U., Martin, A.A., Horton, J.J., Zheng, W., 2012. The effects of a high-energy diet on hippocampal-dependent discrimination performance and blood-brain barrier integrity differ for diet-induced obese and diet-resistant rats. Physiology & behavior 107, 26-33.

Davis, C., Zai, C., Levitan, R.D., Kaplan, A.S., Carter, J.C., Reid-Westoby, C., Curtis, C., Wight, K., Kennedy, J.L., 2011. Opiates, overeating and obesity: a psychogenetic analysis. International journal of obesity 35, 1347-1354.

de Bresser, J., Tiehuis, A.M., van den Berg, E., Reijmer, Y.D., Jongen, C., Kappelle, L.J., Mali, W.P., Viergever, M.A., Biessels, G.J., Utrecht Diabetic Encephalopathy Study, G., 2010. Progression of cerebral atrophy and white matter hyperintensities in patients with type 2 diabetes. Diabetes care 33, 1309-1314.

De Felice, F.G., Vieira, M.N., Bomfim, T.R., Decker, H., Velasco, P.T., Lambert, M.P., Viola, K.L., Zhao, W.Q., Ferreira, S.T., Klein, W.L., 2009. Protection of synapses against Alzheimer's-linked toxins: insulin signaling prevents the pathogenic binding of Abeta oligomers. Proc Natl Acad Sci U S A 106, 1971-1976.

Debette, S., Beiser, A., Hoffmann, U., Decarli, C., O'Donnell, C.J., Massaro, J.M., Au, R., Himali, J.J., Wolf, P.A., Fox, C.S., Seshadri, S., 2010. Visceral fat is associated with lower brain volume in healthy middle-aged adults. Annals of neurology 68, 136-144.

den Heijer, T., Vermeer, S.E., van Dijk, E.J., Prins, N.D., Koudstaal, P.J., Hofman, A., Breteler, M.M., 2003. Type 2 diabetes and atrophy of medial temporal lobe structures on brain MRI. Diabetologia 46, 1604-1610.

Di Luca, M., Ruts, L., Gardoni, F., Cattabeni, F., Biessels, G.J., Gispen, W.H., 1999. NMDA receptor subunits are modified transcriptionally and post-translationally in the brain of streptozotocin-diabetic rats. Diabetologia 42, 693-701.

Dimitriadis, G., Mitrou, P., Lambadiari, V., Maratou, E., Raptis, S.A., 2011. Insulin effects in muscle and adipose tissue. Diabetes research and clinical practice 93 Suppl 1, S52-59.

Dinel, A.L., Andre, C., Aubert, A., Ferreira, G., Laye, S., Castanon, N., 2011. Cognitive and emotional alterations are related to hippocampal inflammation in a mouse model of metabolic syndrome. PloS one 6, e24325.

Duarte, J.M., 2015. Metabolic Alterations Associated to Brain Dysfunction in Diabetes. Aging Dis 6, 304-321.

Dulloo, A.G., Jacquet, J., Solinas, G., Montani, J.P., Schutz, Y., 2010. Body composition phenotypes in pathways to obesity and the metabolic syndrome. International journal of obesity 34 Suppl 2, S4-17.

Epstein, L.H., Salvy, S.J., Carr, K.A., Dearing, K.K., Bickel, W.K., 2010. Food reinforcement, delay discounting and obesity. Physiology & behavior 100, 438-445.

Feldman, D.E., 2009. Synaptic mechanisms for plasticity in neocortex. Annual review of neuroscience 32, 33-55.

Ferreira, S.T., Clarke, J.R., Bomfim, T.R., De Felice, F.G., 2014. Inflammation, defective insulin signaling, and neuronal dysfunction in Alzheimer's disease. Alzheimer's & dementia : the journal of the Alzheimer's Association 10, S76-83.

Figlewicz, D.P., 2003. Insulin, food intake, and reward. Semin Clin Neuropsychiatry 8, 82-93.

Figlewicz, D.P., Bennett, J., Evans, S.B., Kaiyala, K., Sipols, A.J., Benoit, S.C., 2004. Intraventricular insulin and leptin reverse place preference conditioned with high-fat diet in rats. Behav Neurosci 118, 479-487.

Figlewicz, D.P., Benoit, S.C., 2009. Insulin, leptin, and food reward: update 2008. American journal of physiology. Regulatory, integrative and comparative physiology 296, R9-R19.

Flegal, K.M., Kit, B.K., Orpana, H., Graubard, B.I., 2013. Association of all-cause mortality with overweight and obesity using standard body mass index categories: a systematic review and meta-analysis. Jama 309, 71-82.

Forloni, G., Fisone, G., Guaitani, A., Ladinsky, H., Consolo, S., 1986. Role of the hippocampus in the sex-dependent regulation of eating behavior: studies with kainic acid. Physiology & behavior 38, 321-326.

Freeman, L.R., Small, B.J., Bickford, P.C., Umphlet, C., Granholm, A.C., 2011. A high-fat/high-cholesterol diet inhibits growth of fetal hippocampal transplants via increased inflammation. Cell Transplant 20, 1499-1514.

Freiherr, J., Hallschmid, M., Frey, W.H., 2nd, Brunner, Y.F., Chapman, C.D., Holscher, C., Craft, S., De Felice, F.G., Benedict, C., 2013. Intranasal insulin as a treatment for Alzheimer's disease: a review of basic research and clinical evidence. CNS Drugs 27, 505-514.

Fruehwald-Schultes, B., Kern, W., Deininger, E., Wellhoener, P., Kerner, W., Born, J., Fehm, H.L., Peters, A., 1999. Protective effect of insulin against hypoglycemia-associated counterregulatory failure. The Journal of clinical endocrinology and metabolism 84, 1551-1557.

Galioto, R.M., Alosco, M.L., Spitznagel, M.B., Stanek, K.M., Gunstad, J., 2013. Cognitive reserve preserves cognitive function in obese individuals. Neuropsychol Dev Cogn B Aging Neuropsychol Cogn 20, 684-699.

Gardoni, F., Kamal, A., Bellone, C., Biessels, G.J., Ramakers, G.M., Cattabeni, F., Gispent, W.H., Di Luca, M., 2002. Effects of streptozotocin-diabetes on the hippocampal NMDA receptor complex in rats. J Neurochem 80, 438-447.

Ghasemi, R., Dargahi, L., Haeri, A., Moosavi, M., Mohamed, Z., Ahmadiani, A., 2013. Brain insulin dysregulation: implication for neurological and neuropsychiatric disorders. Mol Neurobiol 47, 1045-1065.

Gispen, W.H., Biessels, G.J., 2000. Cognition and synaptic plasticity in diabetes mellitus. Trends in neurosciences 23, 542-549.

Gold, S.M., Dziobek, I., Sweat, V., Tirsi, A., Rogers, K., Bruehl, H., Tsui, W., Richardson, S., Javier, E., Convit, A., 2007. Hippocampal damage and memory impairments as possible early brain complications of type 2 diabetes. Diabetologia 50, 711-719.

Goldbart, A.D., Row, B.W., Kheirandish-Gozal, L., Cheng, Y., Brittian, K.R., Gozal, D., 2006. High fat/refined carbohydrate diet enhances the susceptibility to spatial learning deficits in rats exposed to intermittent hypoxia. Brain research 1090, 190-196.

Gomez-Pinilla, F., 2008. Brain foods: the effects of nutrients on brain function. Nat Rev Neurosci 9, 568-578.

Gottschalk, A., Ellger, B., 2015. Whenever you lose connection, take intranasal insulin? Diabetes 64, 687-688.

Greenwood, C.E., Winocur, G., 2001. Glucose treatment reduces memory deficits in young adult rats fed high-fat diets. Neurobiol Learn Mem 75, 179-189.

Grillo, C.A., Piroli, G.G., Hendry, R.M., Reagan, L.P., 2009. Insulin-stimulated translocation of GLUT4 to the plasma membrane in rat hippocampus is PI3-kinase dependent. Brain research 1296, 35-45.

Guthoff, M., Grichisch, Y., Canova, C., Tschritter, O., Veit, R., Hallschmid, M., Haring, H.U., Preissl, H., Hennige, A.M., Fritsche, A., 2010. Insulin modulates food-related activity in the central nervous system. The Journal of clinical endocrinology and metabolism 95, 748-755.

Haas, C.B., Kalinine, E., Zimmer, E.R., Hansel, G., Brochier, A.W., Oses, J.P., Portela, L.V., Muller, A.P., 2016. Brain Insulin Administration Triggers Distinct Cognitive and Neurotrophic Responses in Young and Aged Rats. Mol Neurobiol 53, 5807-5817.

Haj-ali, V., Mohaddes, G., Babri, S.H., 2009. Intracerebroventricular insulin improves spatial learning and memory in male Wistar rats. Behav Neurosci 123, 1309-1314.

Hajek, T., Calkin, C., Blagdon, R., Slaney, C., Uher, R., Alda, M., 2014. Insulin resistance, diabetes mellitus, and brain structure in bipolar disorders. Neuropsychopharmacol 39, 2910-2918.

Hare, T.A., Camerer, C.F., Rangel, A., 2009. Self-control in decision-making involves modulation of the vmPFC valuation system. Science 324, 646-648.

Hargrave, S.L., Jones, S., Davidson, T.L., 2016. The Outward Spiral: A vicious cycle model of obesity and cognitive dysfunction. Curr Opin Behav Sci 9, 40-46.

Haslam, D.W., James, W.P., 2005. Obesity. Lancet 366, 1197-1209.

Havrankova, J., Roth, J., Brownstein, M., 1978. Insulin receptors are widely distributed in the central nervous system of the rat. Nature 272, 827-829.

Hawkins, B.T., Lundeen, T.F., Norwood, K.M., Brooks, H.L., Egleton, R.D., 2007. Increased blood-brain barrier permeability and altered tight junctions in experimental diabetes in the rat: contribution of hyperglycaemia and matrix metalloproteinases. Diabetologia 50, 202-211.

He, Q., Xiao, L., Xue, G., Wong, S., Ames, S.L., Schembre, S.M., Bechara, A., 2014. Poor ability to resist tempting calorie rich food is linked to altered balance between neural systems involved in urge and self-control. Nutrition journal 13, 92.

Hebben, N., Corkin, S., Eichenbaum, H., Shedlack, K., 1985. Diminished ability to interpret and report internal states after bilateral medial temporal resection: case H.M. Behav Neurosci 99, 1031-1039.

Hebebrand, J., Albayrak, O., Adan, R., Antel, J., Dieguez, C., de Jong, J., Leng, G., Menzies, J., Mercer, J.G., Murphy, M., van der Plasse, G., Dickson, S.L., 2014. "Eating addiction", rather than "food addiction", better captures addictive-like eating behavior. Neurosci Biobehav Rev 47, 295-306.

Heni, M., Kullmann, S., Ketterer, C., Guthoff, M., Bayer, M., Staiger, H., Machicao, F., Haring, H.U., Preissl, H., Veit, R., Fritsche, A., 2014a. Differential effect of glucose ingestion on the neural processing of food stimuli in lean and overweight adults. Human brain mapping 35, 918-928.

Heni, M., Kullmann, S., Ketterer, C., Guthoff, M., Linder, K., Wagner, R., Stingl, K.T., Veit, R., Staiger, H., Haring, H.U., Preissl, H., Fritsche, A., 2012. Nasal insulin changes peripheral insulin sensitivity simultaneously with altered activity in homeostatic and reward-related human brain regions. Diabetologia 55, 1773-1782.

Heni, M., Schopfer, P., Peter, A., Sartorius, T., Fritsche, A., Synofzik, M., Haring, H.U., Maetzler, W., Hennige, A.M., 2014b. Evidence for altered transport of insulin across the blood-brain barrier in insulin-resistant humans. Acta Diabetol 51, 679-681.

Higgs, S., 2002. Memory for recent eating and its influence on subsequent food intake. Appetite 39, 159-166.

Higgs, S., Robinson, E., Lee, M., 2012. Learning and Memory Processes and Their Role in Eating: Implications for Limiting Food Intake in Overeaters. Current Obesity Reports 1, 91-98.

Higgs, S., Woodward, M., 2009. Television watching during lunch increases afternoon snack intake of young women. Appetite 52, 39-43.

Hill, J.M., Lesniak, M.A., Pert, C.B., Roth, J., 1986. Autoradiographic localization of insulin receptors in rat brain: prominence in olfactory and limbic areas. Neuroscience 17, 1127-1138.

Hoogenboom, W.S., Marder, T.J., Flores, V.L., Huisman, S., Eaton, H.P., Schneiderman, J.S., Bolo, N.R., Simonson, D.C., Jacobson, A.M., Kubicki, M., Shenton, M.E., Musen, G., 2014.

Cerebral white matter integrity and resting-state functional connectivity in middle-aged patients with type 2 diabetes. Diabetes 63, 728-738.

Hotamisligil, G.S., 2003. Inflammatory pathways and insulin action. International journal of obesity and related metabolic disorders : journal of the International Association for the Study of Obesity 27 Suppl 3, S53-55.

Hsu, T.M., Hahn, J.D., Konanur, V.R., Noble, E.E., Suarez, A.N., Thai, J., Nakamoto, E.M., Kanoski, S.E., 2015. Hippocampus ghrelin signaling mediates appetite through lateral hypothalamic orexin pathways. Elife 4.

Irvine, E.E., Drinkwater, L., Radwanska, K., Al-Qassab, H., Smith, M.A., O'Brien, M., Kielar, C., Choudhury, A.I., Krauss, S., Cooper, J.D., Withers, D.J., Giese, K.P., 2011. Insulin receptor substrate 2 is a negative regulator of memory formation. Learning & memory 18, 375-383.

Johnson, P.M., Kenny, P.J., 2010. Dopamine D2 receptors in addiction-like reward dysfunction and compulsive eating in obese rats. Nat Neurosci 13, 635-641.

Jurdak, N., Lichtenstein, A.H., Kanarek, R.B., 2008. Diet-induced obesity and spatial cognition in young male rats. Nutr Neurosci 11, 48-54.

Kahn, B.B., Flier, J.S., 2000. Obesity and insulin resistance. J Clin Invest 106, 473-481.

Kahn, I., Shohamy, D., 2013. Intrinsic connectivity between the hippocampus, nucleus accumbens, and ventral tegmental area in humans. Hippocampus 23, 187-192.

Kahn, S.E., Hull, R.L., Utzschneider, K.M., 2006. Mechanisms linking obesity to insulin resistance and type 2 diabetes. Nature 444, 840-846.

Kanoski, S.E., Davidson, T.L., 2011. Western diet consumption and cognitive impairment: links to hippocampal dysfunction and obesity. Physiology & behavior 103, 59-68.

Kanoski, S.E., Zhang, Y., Zheng, W., Davidson, T.L., 2010. The effects of a high-energy diet on hippocampal function and blood-brain barrier integrity in the rat. Journal of Alzheimer's disease : JAD 21, 207-219.

Karczewska-Kupczewska, M., Tarasow, E., Nikolajuk, A., Stefanowicz, M., Matulewicz, N., Otziomek, E., Gorska, M., Straczkowski, M., Kowalska, I., 2013. The effect of insulin infusion on the metabolites in cerebral tissues assessed with proton magnetic resonance spectroscopy in young healthy subjects with high and low insulin sensitivity. Diabetes care 36, 2787-2793.

Keller, K.B., Lemberg, L., 2003. Obesity and the metabolic syndrome. Am J Crit Care 12, 167-170.

Kern, W., Peters, A., Fruehwald-Schultes, B., Deininger, E., Born, J., Fehm, H.L., 2001. Improving influence of insulin on cognitive functions in humans. Neuroendocrinology 74, 270-280.

Ketterer, C., Heni, M., Thamer, C., Herzberg-Schafer, S.A., Haring, H.U., Fritsche, A., 2011. Acute, short-term hyperinsulinemia increases olfactory threshold in healthy subjects. International journal of obesity 35, 1135-1138.

Kohjima, M., Sun, Y., Chan, L., 2010. Increased food intake leads to obesity and insulin resistance in the tg2576 Alzheimer's disease mouse model. Endocrinology 151, 1532-1540.

Koistinaho, M., Lin, S., Wu, X., Esterman, M., Koger, D., Hanson, J., Higgs, R., Liu, F., Malkani, S., Bales, K.R., Paul, S.M., 2004. Apolipoprotein E promotes astrocyte colocalization and degradation of deposited amyloid-beta peptides. Nat Med 10, 719-726.

Kroemer, N.B., Krebs, L., Kobiella, A., Grimm, O., Vollstadt-Klein, S., Wolfensteller, U., Kling, R., Bidlingmaier, M., Zimmermann, U.S., Smolka, M.N., 2013. (Still) longing for food: insulin reactivity modulates response to food pictures. Human brain mapping 34, 2367-2380.

Kullmann, S., Frank, S., Heni, M., Ketterer, C., Veit, R., Haring, H.U., Fritsche, A., Preissl, H., 2013a. Intranasal insulin modulates intrinsic reward and prefrontal circuitry of the human brain in lean women. Neuroendocrinology 97, 176-182.

Kullmann, S., Heni, M., Hallschmid, M., Fritsche, A., Preissl, H., Haring, H.U., 2016. Brain Insulin Resistance at the Crossroads of Metabolic and Cognitive Disorders in Humans. Physiol Rev 96, 1169-1209.

Kullmann, S., Heni, M., Linder, K., Zipfel, S., Haring, H.U., Veit, R., Fritsche, A., Preissl, H., 2014. Resting-state functional connectivity of the human hypothalamus. Human brain mapping 35, 6088-6096.

Kullmann, S., Heni, M., Veit, R., Ketterer, C., Schick, F., Haring, H.U., Fritsche, A., Preissl, H., 2012. The obese brain: association of body mass index and insulin sensitivity with resting state network functional connectivity. Human brain mapping 33, 1052-1061.

Kullmann, S., Heni, M., Veit, R., Scheffler, K., Machann, J., Haring, H.U., Fritsche, A., Preissl, H., 2015. Selective insulin resistance in homeostatic and cognitive control brain areas in overweight and obese adults. Diabetes care 38, 1044-1050.

Kullmann, S., Pape, A.A., Heni, M., Ketterer, C., Schick, F., Haring, H.U., Fritsche, A., Preissl, H., Veit, R., 2013b. Functional network connectivity underlying food processing: disturbed salience and visual processing in overweight and obese adults. Cerebral cortex 23, 1247-1256.

Laakso, M., Kuusisto, J., 2014. Insulin resistance and hyperglycaemia in cardiovascular disease development. Nature reviews. Endocrinology 10, 293-302.

Lathe, R., 2001. Hormones and the hippocampus. J Endocrinol 169, 205-231.

Lebrun, B., Bariohay, B., Moyse, E., Jean, A., 2006. Brain-derived neurotrophic factor (BDNF) and food intake regulation: a minireview. Auton Neurosci 126-127, 30-38.

Lee, C.C., Huang, C.C., Hsu, K.S., 2011. Insulin promotes dendritic spine and synapse formation by the PI3K/Akt/mTOR and Rac1 signaling pathways. Neuropharmacology 61, 867-879.

Lee, C.C., Huang, C.C., Wu, M.Y., Hsu, K.S., 2005. Insulin stimulates postsynaptic density-95 protein translation via the phosphoinositide 3-kinase-Akt-mammalian target of rapamycin signaling pathway. The Journal of biological chemistry 280, 18543-18550.

Lee, S.H., Zabolotny, J.M., Huang, H., Lee, H., Kim, Y.B., 2016. Insulin in the nervous system and the mind: Functions in metabolism, memory, and mood. Mol Metab 5, 589-601.

Levitan, R.D., Masellis, M., Basile, V.S., Lam, R.W., Kaplan, A.S., Davis, C., Muglia, P., Mackenzie, B., Tharmalingam, S., Kennedy, S.H., Macciardi, F., Kennedy, J.L., 2004. The dopamine-4 receptor gene associated with binge eating and weight gain in women with seasonal affective disorder: an evolutionary perspective. Biol Psychiatry 56, 665-669.

Li, Y., South, T., Han, M., Chen, J., Wang, R., Huang, X.F., 2009. High-fat diet decreases tyrosine hydroxylase mRNA expression irrespective of obesity susceptibility in mice. Brain research 1268, 181-189.

Lopez, I.P., Marti, A., Milagro, F.I., Zulet Md Mde, L., Moreno-Aliaga, M.J., Martinez, J.A., De Miguel, C., 2003. DNA microarray analysis of genes differentially expressed in diet-induced (cafeteria) obese rats. Obes Res 11, 188-194.

Luo, S., Romero, A., Adam, T.C., Hu, H.H., Monterosso, J., Page, K.A., 2013. Abdominal fat is associated with a greater brain reward response to high-calorie food cues in Hispanic women. Obesity (Silver Spring) 21, 2029-2036.

Maimaiti, S., Anderson, K.L., DeMoll, C., Brewer, L.D., Rauh, B.A., Gant, J.C., Blalock, E.M., Porter, N.M., Thibault, O., 2016. Intranasal Insulin Improves Age-Related Cognitive Deficits and Reverses Electrophysiological Correlates of Brain Aging. J Gerontol A Biol Sci Med Sci 71, 30-39.

Manschot, S.M., Brands, A.M., van der Grond, J., Kessels, R.P., Algra, A., Kappelle, L.J., Biessels, G.J., Utrecht Diabetic Encephalopathy Study, G., 2006. Brain magnetic resonance imaging correlates of impaired cognition in patients with type 2 diabetes. Diabetes 55, 1106-1113.

Martin, A.A., Davidson, T.L., 2014. Human cognitive function and the obesogenic environment. Physiology & behavior 136, 185-193.

McEwen, B.S., Reagan, L.P., 2004. Glucose transporter expression in the central nervous system: relationship to synaptic function. European journal of pharmacology 490, 13-24.

McNay, E.C., Ong, C.T., McCrimmon, R.J., Cresswell, J., Bogan, J.S., Sherwin, R.S., 2010. Hippocampal memory processes are modulated by insulin and high-fat-induced insulin resistance. Neurobiol Learn Mem 93, 546-553.

Mebel, D.M., Wong, J.C., Dong, Y.J., Borgland, S.L., 2012. Insulin in the ventral tegmental area reduces hedonic feeding and suppresses dopamine concentration via increased reuptake. The European journal of neuroscience 36, 2336-2346.

Medic, N., Ziauddeen, H., Ersche, K.D., Farooqi, I.S., Bullmore, E.T., Nathan, P.J., Ronan, L., Fletcher, P.C., 2016. Increased body mass index is associated with specific regional alterations in brain structure. International journal of obesity 40, 1177-1182.

Mielke, J.G., Taghibiglou, C., Liu, L., Zhang, Y., Jia, Z., Adeli, K., Wang, Y.T., 2005. A biochemical and functional characterization of diet-induced brain insulin resistance. J Neurochem 93, 1568-1578.

Mitchell, N.S., Catenacci, V.A., Wyatt, H.R., Hill, J.O., 2011. Obesity: overview of an epidemic. The Psychiatric clinics of North America 34, 717-732.

Moheet, A., Mangia, S., Seaquist, E.R., 2015. Impact of diabetes on cognitive function and brain structure. Annals of the New York Academy of Sciences 1353, 60-71.

Moloney, A.M., Griffin, R.J., Timmons, S., O'Connor, R., Ravid, R., O'Neill, C., 2010. Defects in IGF-1 receptor, insulin receptor and IRS-1/2 in Alzheimer's disease indicate possible resistance to IGF-1 and insulin signalling. Neurobiol Aging 31, 224-243.

Molteni, R., Barnard, R.J., Ying, Z., Roberts, C.K., Gomez-Pinilla, F., 2002. A high-fat, refined sugar diet reduces hippocampal brain-derived neurotrophic factor, neuronal plasticity, and learning. Neuroscience 112, 803-814.

Morris, M.J., Le, V., Maniam, J., 2016. The impact of poor diet and early life stress on memory status. Current Opinion in Behavioral Sciences 9, 144-151.

Morrison, C.D., Pistell, P.J., Ingram, D.K., Johnson, W.D., Liu, Y., Fernandez-Kim, S.O., White, C.L., Purpera, M.N., Uranga, R.M., Bruce-Keller, A.J., Keller, J.N., 2010. High fat diet increases

hippocampal oxidative stress and cognitive impairment in aged mice: implications for decreased Nrf2 signaling. J Neurochem 114, 1581-1589.

Moult, P.R., Harvey, J., 2008. Hormonal regulation of hippocampal dendritic morphology and synaptic plasticity. Cell Adh Migr 2, 269-275.

Muller, A.P., Gnoatto, J., Moreira, J.D., Zimmer, E.R., Haas, C.B., Lulhier, F., Perry, M.L., Souza, D.O., Torres-Aleman, I., Portela, L.V., 2011. Exercise increases insulin signaling in the hippocampus: physiological effects and pharmacological impact of intracerebroventricular insulin administration in mice. Hippocampus 21, 1082-1092.

Musen, G., Jacobson, A.M., Bolo, N.R., Simonson, D.C., Shenton, M.E., McCartney, R.L., Flores, V.L., Hoogenboom, W.S., 2012. Resting-state brain functional connectivity is altered in type 2 diabetes. Diabetes 61, 2375-2379.

Nemoto, T., Yanagita, T., Satoh, S., Maruta, T., Kanai, T., Murakami, M., Wada, A., 2011. Insulin-induced neurite-like process outgrowth: acceleration of tau protein synthesis via a phosphoinositide 3-kinase~mammalian target of rapamycin pathway. Neurochem Int 59, 880-888.

Olufadi, R., Byrne, C.D., 2008. Clinical and laboratory diagnosis of the metabolic syndrome. J Clin Pathol 61, 697-706.

Oskarsson, M.E., Paulsson, J.F., Schultz, S.W., Ingelsson, M., Westermark, P., Westermark, G.T., 2015. In vivo seeding and cross-seeding of localized amyloidosis: a molecular link between type 2 diabetes and Alzheimer disease. The American journal of pathology 185, 834-846.

Ott, V., Benedict, C., Schultes, B., Born, J., Hallschmid, M., 2012. Intranasal administration of insulin to the brain impacts cognitive function and peripheral metabolism. Diabetes, obesity & metabolism 14, 214-221.

Page, K.A., Chan, O., Arora, J., Belfort-Deaguiar, R., Dzuira, J., Roehmholdt, B., Cline, G.W., Naik, S., Sinha, R., Constable, R.T., Sherwin, R.S., 2013. Effects of fructose vs glucose on

regional cerebral blood flow in brain regions involved with appetite and reward pathways. Jama 309, 63-70.

Page, K.A., Seo, D., Belfort-DeAguiar, R., Lacadie, C., Dzuira, J., Naik, S., Amarnath, S., Constable, R.T., Sherwin, R.S., Sinha, R., 2011. Circulating glucose levels modulate neural control of desire for high-calorie foods in humans. J Clin Invest 121, 4161-4169.

Pallebage-Gamarallage, M., Lam, V., Takechi, R., Galloway, S., Clark, K., Mamo, J., 2012. Restoration of dietary-fat induced blood-brain barrier dysfunction by anti-inflammatory lipid-modulating agents. Lipids in health and disease 11, 117.

Palou, M., Sanchez, J., Rodriguez, A.M., Priego, T., Pico, C., Palou, A., 2009. Induction of NPY/AgRP orexigenic peptide expression in rat hypothalamus is an early event in fasting: relationship with circulating leptin, insulin and glucose. Cell Physiol Biochem 23, 115-124.

Pansuria, M., Xi, H., Li, L., Yang, X.F., Wang, H., 2012. Insulin resistance, metabolic stress, and atherosclerosis. Front Biosci (Schol Ed) 4, 916-931.

Paoletti, P., Bellone, C., Zhou, Q., 2013. NMDA receptor subunit diversity: impact on receptor properties, synaptic plasticity and disease. Nat Rev Neurosci 14, 383-400.

Parent, M.B., Darling, J.N., Henderson, Y.O., 2014. Remembering to eat: hippocampal regulation of meal onset. American journal of physiology. Regulatory, integrative and comparative physiology 306, R701-713.

Park, C.R., Seeley, R.J., Craft, S., Woods, S.C., 2000. Intracerebroventricular insulin enhances memory in a passive-avoidance task. Physiology & behavior 68, 509-514.

Park, H.R., Park, M., Choi, J., Park, K.Y., Chung, H.Y., Lee, J., 2010. A high-fat diet impairs neurogenesis: involvement of lipid peroxidation and brain-derived neurotrophic factor. Neuroscience letters 482, 235-239.

Pearce, K.L., Noakes, M., Wilson, C., Clifton, P.M., 2012. Continuous glucose monitoring and cognitive performance in type 2 diabetes. Diabetes Technol Ther 14, 1126-1133.

Pelchat, M.L., Johnson, A., Chan, R., Valdez, J., Ragland, J.D., 2004. Images of desire: food-craving activation during fMRI. Neuroimage 23, 1486-1493.

Petersen, K.F., Shulman, G.I., 2006. Etiology of insulin resistance. The American journal of medicine 119, S10-16.

Pintana, H., Apaijai, N., Pratchayasakul, W., Chattipakorn, N., Chattipakorn, S.C., 2012. Effects of metformin on learning and memory behaviors and brain mitochondrial functions in high fat diet induced insulin resistant rats. Life sciences 91, 409-414.

Pipatpiboon, N., Pintana, H., Pratchayasakul, W., Chattipakorn, N., Chattipakorn, S.C., 2013. DPP4-inhibitor improves neuronal insulin receptor function, brain mitochondrial function and cognitive function in rats with insulin resistance induced by high-fat diet consumption. The European journal of neuroscience 37, 839-849.

Pipatpiboon, N., Pratchayasakul, W., Chattipakorn, N., Chattipakorn, S.C., 2012. PPARgamma agonist improves neuronal insulin receptor function in hippocampus and brain mitochondria function in rats with insulin resistance induced by long term high-fat diets. Endocrinology 153, 329-338.

Piroli, G.G., Grillo, C.A., Reznikov, L.R., Adams, S., McEwen, B.S., Charron, M.J., Reagan, L.P., 2007. Corticosterone impairs insulin-stimulated translocation of GLUT4 in the rat hippocampus. Neuroendocrinology 85, 71-80.

Plum, L., Schubert, M., Bruning, J.C., 2005. The role of insulin receptor signaling in the brain. Trends in endocrinology and metabolism: TEM 16, 59-65.

Portella, A.K., Silveira, P.P., Laureano, D.P., Cardoso, S., Bittencourt, V., Noschang, C., Werlang, I., Fontella, F.U., Dalmaz, C., Goldani, M.Z., 2015. Litter size reduction alters insulin signaling in the ventral tegmental area and influences dopamine-related behaviors in adult rats. Behavioural brain research 278, 66-73.

Pratchayasakul, W., Kerdphoo, S., Petsophonsakul, P., Pongchaidecha, A., Chattipakorn, N., Chattipakorn, S.C., 2011. Effects of high-fat diet on insulin receptor function in rat hippocampus and the level of neuronal corticosterone. Life sciences 88, 619-627.

Puig, J., Blasco, G., Daunis, I.E.J., Molina, X., Xifra, G., Ricart, W., Pedraza, S., Fernandez-Aranda, F., Fernandez-Real, J.M., 2015. Hypothalamic damage is associated with inflammatory markers and worse cognitive performance in obese subjects. The Journal of clinical endocrinology and metabolism 100, E276-281.

Qiu, X., Zhang, Y., Feng, H., Jiang, D., 2016. Positron Emission Tomography Reveals Abnormal Topological Organization in Functional Brain Network in Diabetic Patients. Frontiers in neuroscience 10, 235.

Rangel, A., 2013. Regulation of dietary choice by the decision-making circuitry. Nat Neurosci 16, 1717-1724.

Rani, V., Deshmukh, R., Jaswal, P., Kumar, P., Bariwal, J., 2016. Alzheimer's disease: Is this a brain specific diabetic condition? Physiology & behavior 164, 259-267.

Rasgon, N.L., Kenna, H.A., Wroolie, T.E., Kelley, R., Silverman, D., Brooks, J., Williams, K.E., Powers, B.N., Hallmayer, J., Reiss, A., 2011. Insulin resistance and hippocampal volume in women at risk for Alzheimer's disease. Neurobiol Aging 32, 1942-1948.

Reid, K.B., Grant, P.T., Youngson, A., 1968. The sequence of amino acids in insulin isolated from islet tissue of the cod (Gadus callarias). The Biochemical journal 110, 289-296.

Robinson, E., Aveyard, P., Daley, A., Jolly, K., Lewis, A., Lycett, D., Higgs, S., 2013. Eating attentively: a systematic review and meta-analysis of the effect of food intake memory and awareness on eating. Am J Clin Nutr 97, 728-742.

Rodin, J., Wack, J., Ferrannini, E., DeFronzo, R.A., 1985. Effect of insulin and glucose on feeding behavior. Metabolism: clinical and experimental 34, 826-831.

Rolls, E.T., 2004. The functions of the orbitofrontal cortex. Brain and cognition 55, 11-29.

Rozin, P., Dow, S., Moscovitch, M., Rajaram, S., 1998. What Causes Humans to Begin and End a Meal? A Role for Memory for What Has Been Eaten, as Evidenced by a Study of Multiple Meal Eating in Amnesic Patients. Psychol Sci 9, 392-396.

Sadeghi, A., Hami, J., Razavi, S., Esfandiary, E., Hejazi, Z., 2016. The Effect of Diabetes Mellitus on Apoptosis in Hippocampus: Cellular and Molecular Aspects. Int J Prev Med 7, 57.

Saltiel, A.R., Kahn, C.R., 2001. Insulin signalling and the regulation of glucose and lipid metabolism. Nature 414, 799-806.

Sartorius, T., Peter, A., Heni, M., Maetzler, W., Fritsche, A., Haring, H.U., Hennige, A.M., 2015. The brain response to peripheral insulin declines with age: a contribution of the blood-brain barrier? PloS one 10, e0126804.

Savigner, A., Duchamp-Viret, P., Grosmaitre, X., Chaput, M., Garcia, S., Ma, M., Palouzier-Paulignan, B., 2009. Modulation of spontaneous and odorant-evoked activity of rat olfactory sensory neurons by two anorectic peptides, insulin and leptin. Journal of neurophysiology 101, 2898-2906.

Schulingkamp, R.J., Pagano, T.C., Hung, D., Raffa, R.B., 2000. Insulin receptors and insulin action in the brain: review and clinical implications. Neurosci Biobehav Rev 24, 855-872.

Schwartz, M.W., Woods, S.C., Porte, D., Jr., Seeley, R.J., Baskin, D.G., 2000. Central nervous system control of food intake. Nature 404, 661-671.

Sethi, J.K., Vidal-Puig, A.J., 2007. Thematic review series: adipocyte biology. Adipose tissue function and plasticity orchestrate nutritional adaptation. Journal of lipid research 48, 1253-1262.

Shah, G.N., Mooradian, A.D., 1997. Age-related changes in the blood-brain barrier. Exp Gerontol 32, 501-519.

Silveira, P.P., Gaudreau, H., Atkinson, L., Fleming, A.S., Sokolowski, M.B., Steiner, M., Kennedy, J.L., Meaney, M.J., Levitan, R.D., Dubé, L., 2016. Genetic Differential Susceptibility to Socioeconomic Status and Childhood Obesogenic Behavior. JAMA Pediatrics.

Skeberdis, V.A., Lan, J., Zheng, X., Zukin, R.S., Bennett, M.V., 2001. Insulin promotes rapid delivery of N-methyl-D- aspartate receptors to the cell surface by exocytosis. Proc Natl Acad Sci U S A 98, 3561-3566.

Soetens, B., Braet, C., 2007. Information processing of food cues in overweight and normal weight adolescents. Br J Health Psychol 12, 285-304.

Steculorum, S.M., Solas, M., Bruning, J.C., 2014. The paradox of neuronal insulin action and resistance in the development of aging-associated diseases. Alzheimer's & dementia : the journal of the Alzheimer's Association 10, S3-11.

Stern, S.A., Chen, D.Y., Alberini, C.M., 2014. The effect of insulin and insulin-like growth factors on hippocampus- and amygdala-dependent long-term memory formation. Learning & memory 21, 556-563.

Stockhorst, U., de Fries, D., Steingrueber, H.J., Scherbaum, W.A., 2004. Insulin and the CNS: effects on food intake, memory, and endocrine parameters and the role of intranasal insulin administration in humans. Physiology & behavior 83, 47-54.

Stoeckel, L.E., Arvanitakis, Z., Gandy, S., Small, D., Kahn, C.R., Pascual-Leone, A., Pawlyk, A., Sherwin, R., Smith, P., 2016. Complex mechanisms linking neurocognitive dysfunction to insulin resistance and other metabolic dysfunction. F1000Res 5, 353.

Stranahan, A.M., Norman, E.D., Lee, K., Cutler, R.G., Telljohann, R.S., Egan, J.M., Mattson, M.P., 2008. Diet-induced insulin resistance impairs hippocampal synaptic plasticity and cognition in middle-aged rats. Hippocampus 18, 1085-1088.

Taylor, A.M., Bus, T., Sprengel, R., Seeburg, P.H., Rawlins, J.N., Bannerman, D.M., 2014. Hippocampal NMDA receptors are important for behavioural inhibition but not for encoding associative spatial memories. Philosophical transactions of the Royal Society of London. Series B, Biological sciences 369, 20130149.

Thaler, J.P., Yi, C.X., Schur, E.A., Guyenet, S.J., Hwang, B.H., Dietrich, M.O., Zhao, X., Sarruf, D.A., Izgur, V., Maravilla, K.R., Nguyen, H.T., Fischer, J.D., Matsen, M.E., Wisse, B.E., Morton, G.J., Horvath, T.L., Baskin, D.G., Tschop, M.H., Schwartz, M.W., 2012. Obesity is associated with hypothalamic injury in rodents and humans. J Clin Invest 122, 153-162.

Tozuka, Y., Wada, E., Wada, K., 2009. Diet-induced obesity in female mice leads to peroxidized lipid accumulations and impairment of hippocampal neurogenesis during the

early life of their offspring. FASEB journal : official publication of the Federation of American Societies for Experimental Biology 23, 1920-1934.

Tschritter, O., Preissl, H., Hennige, A.M., Stumvoll, M., Porubska, K., Frost, R., Marx, H., Klosel, B., Lutzenberger, W., Birbaumer, N., Haring, H.U., Fritsche, A., 2006. The cerebrocortical response to hyperinsulinemia is reduced in overweight humans: a magnetoencephalographic study. Proc Natl Acad Sci U S A 103, 12103-12108.

Tucsek, Z., Toth, P., Sosnowska, D., Gautam, T., Mitschelen, M., Koller, A., Szalai, G., Sonntag, W.E., Ungvari, Z., Csiszar, A., 2014. Obesity in aging exacerbates blood-brain barrier disruption, neuroinflammation, and oxidative stress in the mouse hippocampus: effects on expression of genes involved in beta-amyloid generation and Alzheimer's disease. J Gerontol A Biol Sci Med Sci 69, 1212-1226.

Ursache, A., Wedin, W., Tirsi, A., Convit, A., 2012. Preliminary evidence for obesity and elevations in fasting insulin mediating associations between cortisol awakening response and hippocampal volumes and frontal atrophy. Psychoneuroendocrino 37, 1270-1276.

van der Laan, L.N., de Ridder, D.T., Viergever, M.A., Smeets, P.A., 2011. The first taste is always with the eyes: a meta-analysis on the neural correlates of processing visual food cues. Neuroimage 55, 296-303.

Verdile, G., Fuller, S.J., Martins, R.N., 2015. The role of type 2 diabetes in neurodegeneration. Neurobiol Dis 84, 22-38.

Volkow, N.D., Wang, G.J., Baler, R.D., 2011. Reward, dopamine and the control of food intake: implications for obesity. Trends in cognitive sciences 15, 37-46.

Wallner-Liebmann, S., Koschutnig, K., Reishofer, G., Sorantin, E., Blaschitz, B., Kruschitz, R., Unterrainer, H.F., Gasser, R., Freytag, F., Bauer-Denk, C., Schienle, A., Schafer, A., Mangge, H., 2010. Insulin and hippocampus activation in response to images of high-calorie food in normal weight and obese adolescents. Obesity (Silver Spring) 18, 1552-1557.

Wang, G.J., Yang, J., Volkow, N.D., Telang, F., Ma, Y., Zhu, W., Wong, C.T., Tomasi, D., Thanos, P.K., Fowler, J.S., 2006. Gastric stimulation in obese subjects activates the hippocampus and other regions involved in brain reward circuitry. Proc Natl Acad Sci U S A 103, 15641-15645.

Wansink, B., Payne, C.R., 2007. Counting bones: environmental cues that decrease food intake. Percept Mot Skills 104, 273-276.

Whitmer, R.A., Gunderson, E.P., Barrett-Connor, E., Quesenberry, C.P., Jr., Yaffe, K., 2005. Obesity in middle age and future risk of dementia: a 27 year longitudinal population based study. Bmj 330, 1360.

WHO, 2016. Obesity and overweight. World Health Organization.

Wilcox, G., 2005. Insulin and insulin resistance. Clin Biochem Rev 26, 19-39.

Wimmer, G.E., Shohamy, D., 2012. Preference by association: how memory mechanisms in the hippocampus bias decisions. Science 338, 270-273.

Winocur, G., Greenwood, C.E., 1999. The effects of high fat diets and environmental influences on cognitive performance in rats. Behavioural brain research 101, 153-161.

Winocur, G., Greenwood, C.E., 2005. Studies of the effects of high fat diets on cognitive function in a rat model. Neurobiology of Aging 26 Suppl 1, 46-49.

Wolf, P.A., Beiser, A., Elias, M.F., Au, R., Vasan, R.S., Seshadri, S., 2007. Relation of obesity to cognitive function: importance of central obesity and synergistic influence of concomitant hypertension. The Framingham Heart Study. Current Alzheimer research 4, 111-116.

Woods, C.A., Guttman, Z.R., Huang, D., Kolaric, R.A., Rabinowitsch, A.I., Jones, K.T., Cabeza de Vaca, S., Sclafani, A., Carr, K.D., 2016. Insulin receptor activation in the nucleus accumbens reflects nutritive value of a recently ingested meal. Physiology & behavior 159, 52-63.

Woods, S.C., Seeley, R.J., Porte, D., Jr., Schwartz, M.W., 1998. Signals that regulate food intake and energy homeostasis. Science 280, 1378-1383.

Wylie-Rosett, J., 2004. Paradigm shifts in obesity research and treatment: introduction. Obes Res 12 Suppl 2, 85S-87S.

Xu, Q.G., Li, X.Q., Kotecha, S.A., Cheng, C., Sun, H.S., Zochodne, D.W., 2004. Insulin as an in vivo growth factor. Exp Neurol 188, 43-51.

Yau, P.L., Javier, D.C., Ryan, C.M., Tsui, W.H., Ardekani, B.A., Ten, S., Convit, A., 2010. Preliminary evidence for brain complications in obese adolescents with type 2 diabetes mellitus. Diabetologia 53, 2298-2306.

Ye, J., 2013. Mechanisms of insulin resistance in obesity. Front Med 7, 14-24.

Zeyda, M., Stulnig, T.M., 2009. Obesity, inflammation, and insulin resistance--a mini-review. Gerontology 55, 379-386.

Zhang, H., Hao, Y., Manor, B., Novak, P., Milberg, W., Zhang, J., Fang, J., Novak, V., 2015. Intranasal insulin enhanced resting-state functional connectivity of hippocampal regions in type 2 diabetes. Diabetes 64, 1025-1034.

Zhang, W., Thompson, B.J., Hietakangas, V., Cohen, S.M., 2011. MAPK/ERK signaling regulates insulin sensitivity to control glucose metabolism in Drosophila. PLoS genetics 7, e1002429.

Zhang, Y., Lu, S., Liu, C., Zhang, H., Zhou, X., Ni, C., Qin, W., Zhang, Q., 2016. Altered brain activation and functional connectivity in working memory related networks in patients with type 2 diabetes: An ICA-based analysis. Sci Rep 6, 23767.

Zhao, W., Chen, H., Xu, H., Moore, E., Meiri, N., Quon, M.J., Alkon, D.L., 1999. Brain insulin receptors and spatial memory. Correlated changes in gene expression, tyrosine phosphorylation, and signaling molecules in the hippocampus of water maze trained rats. The Journal of biological chemistry 274, 34893-34902.

Zhao, W.Q., De Felice, F.G., Fernandez, S., Chen, H., Lambert, M.P., Quon, M.J., Krafft, G.A., Klein, W.L., 2008. Amyloid beta oligomers induce impairment of neuronal insulin receptors.

FASEB journal : official publication of the Federation of American Societies for Experimental Biology 22, 246-260.

Zonta, M., Angulo, M.C., Gobbo, S., Rosengarten, B., Hossmann, K.A., Pozzan, T., Carmignoto, G., 2003. Neuron-to-astrocyte signaling is central to the dynamic control of brain microcirculation. Nat Neurosci 6, 43-50.

4.3. ARTIGO CLÍNICO

Artigo na versão pré-submissão.

Title: The vicious cycle of obesity: insulin sensitivity and cognitive processes involved in eating behavior of individuals born small for gestational age

Or: Diminished insulin sensitivity is associated with altered brain activation to hyperpalatable food images and with risky feeding behavior for obesity in individuals born small for gestational age

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Abstract: Impairments in fetal growth are associated with a greater risk for developing obesity-related diseases in adulthood, preceded by a preference for eating hyperpalatable foods. As proposed in the “vicious cycle of obesity” framework, excessive intake of hyperpalatable foods leads to insulin resistance, disruption in cognition and hippocampal function, and further altered feeding behavior. We hypothesized that variations in insulin sensitivity would be correlated with differential brain activation facing hyperpalatable food cues in healthy adolescents, as well as associated with variations in implicit memory for food choices. Moreover, we sought to explore the presence of this vicious cycle in a sample of adolescents classified according with the presence or absence of impaired fetal growth. Fetal growth was based on birth weight ratio and those in the lower tertile of the distribution were considered small for gestational age. After blood sample collection, all participants could choose foods as a snack offered in the research center cafeteria. Implicit, non-declarative food memory was tested 6 months later through the evaluation of a series of photos of snacks. Feeding behavior was also assessed by the nutritional composition of the snack chosen, 24h Dietary Recall, Food Frequency and Dutch Eating Behavior questionnaires. Furthermore, brain responses to hyperpalatable foods were investigated using a functional magnetic resonance imaging task showing hyperpalatable versus healthy foods or versus non-food objects images. Brain structural MRI volumetry was also analyzed. HOMA-IR index correlated positively with activation in the cuneus, and negatively with activation in the left middle frontal lobe, superior frontal gyrus and precuneus when facing hyperpalatable foods versus non-food objects images. In addition, HOMA-IR index and insulinemia were higher in participants who did not choose their original snack compared to those who chose their own snack. Subjects who were born with impaired fetal growth had higher snack caloric density, greater chance of not choosing their own snack and bilateral reduction in the hippocampal subiculum. In addition, there is an interaction between HOMA-IR and birth weight ratio for

external eating behavior. We suggest that diminished insulin sensitivity correlated with activation in areas of visual attention and inactivation of areas associated with inhibitory control in healthy adolescents. Insulin sensitivity also associated with less consistency in implicit memory for a consumed meal, which may suggest lower ability to establish a dietary pattern, and can contribute to the development of obesity. Besides that, insulin sensitivity and hippocampal alterations are associated with differences in feeding behavior described for low birth weight individuals, suggesting that cognition and hormone regulation are important components involved in food intake modifications in this vulnerable population.

Key-words: Poor fetal growth; Intrauterine growth restriction; Gestational nutritional deprivation; Feeding behavior; External eating; Food memory; MRI; Subiculum; HOMA-IR index; Metabolic syndrome.

Introduction

There was a drastic reduction in neonatal mortality associated to birth weight (1) before the increase of chronic non-communicable diseases worldwide (2). Nowadays, the prevalence rates of intrauterine growth restriction (IUGR) varies between 10-15% (3), and these individuals are at high risk for developing excessive adiposity-related diseases such as insulin resistance in adulthood (4–9). Moreover, they present greater preference for eating hyperpalatable foods (foods high in energy, fats, free sugars or salt/sodium) (10–21) as compared to those without IUGR. The increased risk for metabolic disorders throughout life of these individuals is a consequence of their early feeding behavior programming and subsequent exposure to hyperpalatable foods.

Poor growth *in utero* also has significant implications for the neurodevelopment of the fetus, with long-term neurological consequences. Many studies have evidenced that individuals who suffered low intrauterine growth have a higher incidence of cognitive deviations when compared to the general population (22–33). It is known that the hippocampus is a brain region vulnerable to neonatal adverse conditions (34–39) and its volume reduction has been involved with these cognitive impairments exhibited by subjects

born with low weight (40–46). Classically associated with memory, the hippocampus is also recognized as a feeding behavior modulator via multiple interconnected pathways and its physiology is sensitive to signals of hunger and satiety, helping to inhibit the ability of food cues to evoke appetite and eating (47,48). This food inhibitory control system seems to be impaired when there is hippocampal damage, possibly leading to increased food intake and chance of developing obesity (49–51). In addition, there is evidence that memory plays a role in the control of hunger and food intake, as the representation of food consumed is used to process subsequent decisions about what, when and how much to eat (47,52). Memory, even without conscious awareness, decreases the impact of recent reward and environmental cues on choices, with enhanced connectivity between hippocampus and prefrontal cortex, contributing to reward decision-making (53).

Among the obesity-related diseases that subjects small for gestational age are most vulnerable is type II diabetes, that is developed as a consequence of inadequate insulin secretion since birth, followed by progressive decreasing insulin sensitivity (7,9,54–58). Interestingly, insulin has been linked to brain functions such as eating control (59) and pre-diabetic insulin resistance is associated with subtle cognitive changes that may occur during the lifespan, from adolescence to old age (60). In this study, we tested (a) if variations in insulin sensitivity correlate with the brain activation in response to hyperpalatable food images (rich on sugar, fat, and/or salt)(61), as well as if they associate with the ability to retrieve implicitly learned food choices in adolescents (62). These would be evidence that poor insulin sensitivity could contribute to intake imbalance and obesogenic behavior (63). Considering that excessive intake of hyperpalatable foods leads to insulin resistance, which disrupts hippocampal function and hence the ability to control the response to food cues, and, most importantly, that all these elements are especially observed in poor intrauterine growth individuals, this study also sought to find the possible associations between them. So, we also tested (b) whether low birth weight would be associated with hippocampal structural differences and changes in obesogenic feeding behaviors according to variations in insulin sensitivity in order to better understand the neurobiology involved in the risky eating behavior demonstrated by these individuals.

Material and Methods

Sample

To test our hypotheses, 52 individuals (31 female, 17.58 ±2.36 years) were evaluated. The subjects were followed in a prospective cohort, which details can be found elsewhere(64). These participants were recruited from six schools around the area of a family health unit of Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil. In 2008, children and adolescents from these schools were invited to participate in the study, which included psychiatric and nutritional assessments. A total of 242 individuals completed the assessment in 2008 and, from this initial group, 75 participated in a more in-depth re-evaluation that included psychiatric diagnosis, nutritional assessment, DNA extraction and a MRI exam in 2013/2014. The study was approved by Institutional Ethics Committee of Hospital de Clínicas de Porto Alegre and Research Ethics Committee of Pontifícia Universidade Católica do Rio Grande do Sul. It followed guidelines for research involving humans, including the Resolution 196/96 from the National Health Council. Local ethical committee approval and written informed consent (either from subjects or from their guardians) were obtained from participants before entering the study. Confidentiality with respect to identity, privacy and confidentiality of data was guaranteed.

Measurements

Fetal growth was based on the birth weight ratio (BWR), which is the ratio between the infant birth weight and the mean birth weight, sex- and gestational age-specific for the local population (59). BWR was used either as a continuous variable or categorized into adequate for gestational age (“AGA”, two superior tertiles of the BWR distribution) or small for gestational age (“SGA”, those in the lower tertile). All the participants were fasting when anthropometric assessment was performed at the research center during the morning by trained researchers. Weight and height were measured in duplicate (the average value was adopted) using accurate and calibrated equipments (digital platform balance Toledo, São Paulo, Brazil and vertical stadiometer Harpenden, Holtain Limited, Crymych, UK). Body mass index (BMI) was calculated as weight (kg) divided by height (m2). Percentage of body fat was

evaluated by bioelectrical impedance analysis (Biodynamics-310, Seattle, WA, USA) and following the recommendations of Kyle et al, 2004.

For biochemical analysis, blood sample was collected in the morning after fasting for 12 h and centrifuged at 4000 r.p.m. for 10 min. Glucose, total and HDL cholesterol, and triglycerides levels were determined by the enzymatic colorimetric method and insulin levels by chemiluminescence using ADVIA 1800 and ADVIA Centaur insulin assay (Siemens Healthcare Diagnostics Inc., Tarrytown, NY, USA). LDL was estimated using the Friedewald equation. Homeostasis Assessment Model-Insulin Resistance (HOMA-IR) index was calculated using fasting serum insulin (mU/mL) × fasting serum glucose (mmol/L))/22.5.

Socioeconomic status was based on level of education and presence of household items and level of household head education according to Brazilian Research Companies Association score points. Intelligence quotient (IQ) was calculated using the Wescheler Abreviated Scale of Inteligence (WASI) (60) and phonemic and semantic verbal fluency (number of valid words), using the Child Brief Neuropsychological Assessment Battery (NEUPSILIN-INF) (61).

Feeding intake and behavior

After anthropometric measures and blood collection, participants received a voucher to purchase a snack of their choice at research center cafeteria (Figure 1A). The chosen foods were displayed in a tray and photographed. In a subsequent visit, performed 6 months later, also on a fasted state, photos of four different snacks, including the one from their own previous choice, were showed to them with a question: "If you could eat now, which one of the following snacks would you choose?”. Choices for both composition (Figure 1B) as well as spatial arrangement (Figure 1C) of the snack were investigated. Our intention in this snack choice test was to evaluate implicit, non-declarative food memory, which is known as a category of mnemonic processes involved in automatic behavior (53), that is linked to decision-making to food choices, modulating eating behavior (65,66). Food preferences choices are one of the best examples of implicit memory because this behavior is not consciously and intentionally learned, and it is resistant to change (67). Food intake

estimates were made using the nutritional composition of the selected snack. The quantitative analysis of macro- and micronutrients consumed was calculated using the USDA National Nutrient Database (68). The Dutch Eating Behaviour Questionnaire (DEBQ) (69,70) classified eating behavior in restrained, emotional, and external according to its subscales and was assessed after subjects ate the snack of their choice at research center cafeteria.

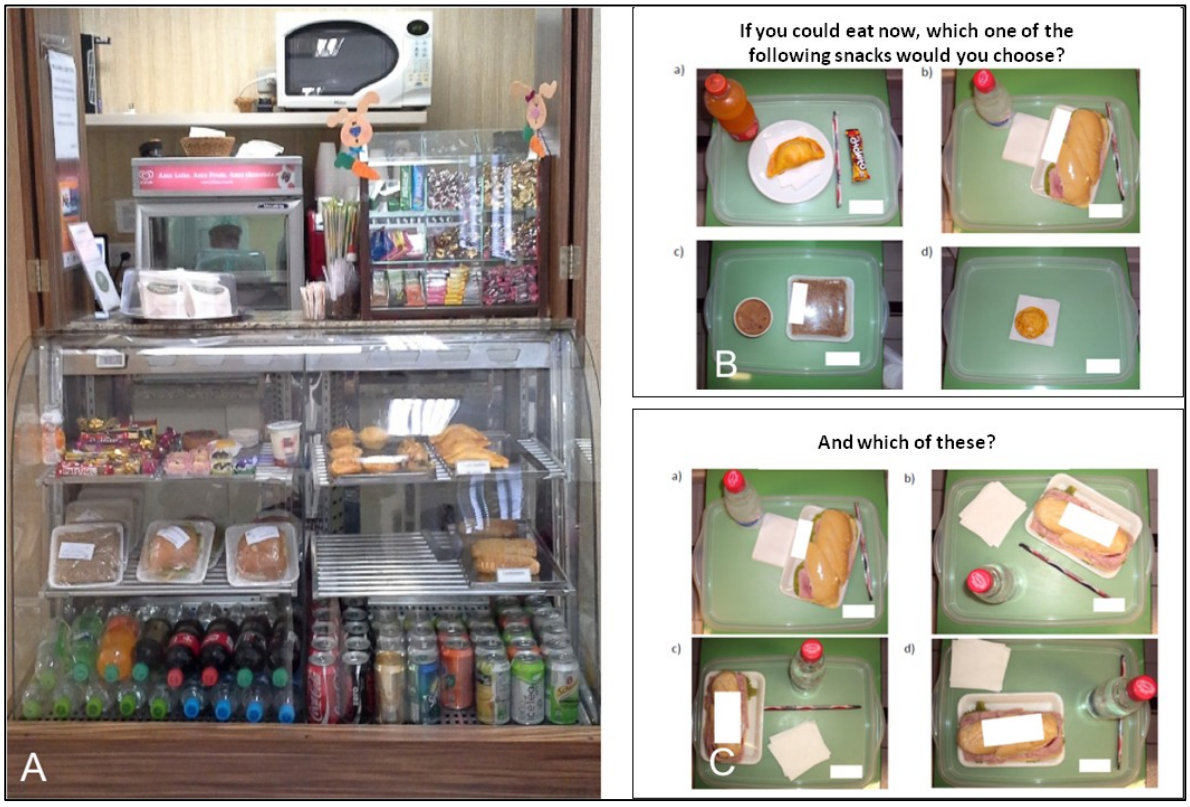

Figure 1. Research centre cafeteria. Individuals received an equal sum of money to buy a snack of their choice (A). The snack was photographed and in the subsequent visit the participants were asked which snack they would choose at that moment. Choices for both composition (B) as well spatial arrangement (C) were investigated. In both cases, one of the pictures was the original snack eaten by the participant. Adapted from Mucellini *et al* (152).

Structural and functional MRI acquisition, paradigm, preprocessing and analysis

Of the 52 participants, 40 were eligible for structural and functional Magnetic Resonance Imaging (fMRI) acquisition (no bracers, pregnancy or other exclusion criteria). Participants were fasted for at least 4h and, 30min before acquisition, they received a standard snack comprised by a cereal bar and a box of juice, total of 174kcal, 39g

carbohydrate (90% of total calories), 0.9g protein (2% of total calories) and 1.6g of lipids (8% of total calories.

MRI data were acquired using echo planar imaging sequences with a GE 3-Tesla scanner (GE Healthcare Signa HDxT, Waukesha, WI, USA) equipped with an eight channels head coil. The following parameters were used for structural images: T1 with voxels in isotropic spatial resolution of $1mm^3$, 170 contiguous slices and matrix image of 256*256 Images were inversion recovery type with TE = 2.18 ms and TR = −6.1 ms, and for functional images: 26 axial slices interspersed with a slice thickness of 4.0 mm and gap of 0.4 mm, FOV of 240 mm X 240 mm and matrix size of 80 X 64, TE = 30 ms, TR= 2.000 ms, flip angle of 90°. Data were pre-processed and analyzed with SPM8 (SPM8, http://www.fil.ion.ucl.ac.uk/spm) implemented in MATLAB (MathWorks, Inc., Natick, MA, United States). For each participant, pre-processing analyses included: slice timing correction, realignment of functional time series, co-registration of functional and anatomical images, spatial normalization in Montreal Neurological Institute space, spatial smoothing with an 8mm full-width half-maximum Gaussian smoothing kernel, and high- and low-pass filtering. Data from four participants who moved over 4mm in any plane were excluded from analyses.

Structural MRI analysis volumetry was performed using multiple automatically generated templates (MAGeT-Brain)(71). The fMRI paradigm, adapted from Page et al.(72), was set to investigate brain activation in response to hyperpalatable and healthy food and non-food objects images (such as a chair). Figures were selected from a database of images (73,74). A pilot study including adolescents from the same age range of the current study population was performed to establish which food images were perceived as hyperpalatable and healthy. Paradigm was created and presented using E-Prime software (version 2, Psychological Software Tools, Pittsburgh, PA, USA), with 3 blocks of approximately 7min each. Each block included 21 randomized images (seven hyperpalatable foods, seven healthy foods and seven non-food objects).

For subject level analyses, a general linear model (GLM) was used to estimate changes in brain regions responses using four regressors: hyperpalatable food, healthy food, and non-food objects images and baseline periods (convolved with an ideal homodynamic response curve). A two-level hierarchical model was conducted using multiple regression

model analyses in which HOMA-IR index was used as predictor. Whole-brain analysis was conducted to identify the response areas to main effects of hyperpalatable food, healthy food, and non-food objects images. Correlations between HOMA-IR index and brain activation were performed with a family-wise error (FEW) correction for multiple comparisons (pFWEcorr<0.05), using HOMA-IR index as a continuous variable. All t-maps were calculated for entire cortical volume. XJVIEW 8.14 software (http://www.alivelearn.net/xjview/) was used to display anatomical locations.

Statistical analysis

Levene's test was used to test homogeneity of variances. Statistical significance level was set at $p<0.05$. To compare individuals according to their implicit memory for the consumed meal, we used either Pearson chi-squared's and Student's T tests (baseline characteristics) or analysis of variance (ANOVA) adjusted for age, time between visits and verbal fluency (metabolic outcomes). Statistical significance level was set at $p<0.05$.

In order to compare baseline characteristics between groups according to intrauterine growth, we used for the Pearson Chi-squared's and Student's T tests. We used analysis of variance (ANOVA) adjusted for BMI z-score (for analyzing feeding behavior) and for total brain volume (for analyzing MRI volumetry). A correlation between external eating behavior and HOMA-IR in each group and a multiple regression to predict external eating behavior from HOMA-IR and BWR were run.

Results

Demographic, anthropometric, and biochemical

From the 52 individuals, 51 performed the snack choice test completely (one participant did not answer the question about spatial arrangement of the snack). There were no statistically significant differences on baseline characteristics such as time between visits, age, sex, ethnicity, socioeconomic status, verbal fluency and intelligence quotient when categorizing the sample between subjects that selected their original snack *versus* those that

did not in relation to the composition of the snack (Table 1). However, participants who did not choose their first original snack had increased plasma insulin [own snack 13.03+6.18 uU/mL, other snack 16.89+7,54, ANOVA adjusted for age, time between visits and verbal fluency, F (1, 46) = 4.237, p=0.045] and HOMA-IR index [own snack 2.70+1,36, other snack 3,54+1,57, F (1, 46) = 4.309, p=0.044] (Figure 2) as compared to those who choose their own snack. The two groups did not differ in other variables such as BMI [own snack 22.54+4.54 kg/m2, other snack 24.59+4.20, F (1, 46) = 1.087, p=0.303] or glycemia [own snack 83.06+6.66 mg/dl, other snack 84.87+7.61, F (1,46) = 0.873, p=0.355].

Table 1. Baseline characteristics based in the choice of snack.

Sample characteristics	**Own snack (n=37)**	**Other snack (n=15)**	***P***
Sex (females)[a]	21 (67.7%)	10 (32.3%)	0.551
Ethnicity (white)[a]	25 (75.8%)	8 (24.2%)	0.341
Age (years)[b]	17.34 (±2.34)	18.16 (±2.43)	0.266
Time between evaluations (days)[b]	197.86 (±75.96)	203.00 (±64.18)	0.819
Verbal fluency (number of valid words)[b]	41.50 (±10.84)	44.20 (±10.48)	0.417
IQ (total WASI)[b]	122.79 (±25.49)	123.80 (±25.57)	0.940
Socioeconomic status (%)[b]	16.49 (±5.21)	17.85 (±4.89)	0.439

[a]Pearson χ^2 test (data expressed as absolut and relative frequencies). [b]Student's t-test (data expressed as mean and ± standard deviation).

From these 51 subjects, 34 (66.7%) were AGA, 15 (29.4%) were SGA and 2 (3.9%) had no birth weight data. There were no statistically significant differences on baseline characteristics such as sex, age, verbal fluency, intelligence quotient, ethnicity, maternal education and socioeconomic status between these two groups (Table 2). They also did not differ in BMI, BMI z-score, waist circumference size, body fat percentage, total, HDL, and LDL cholesterol, triglycerides, glucose, and insulin levels and HOMA-IR index, but, as expected, individuals born with SGA had significant lower weight at birth than AGA (Table 1).

Table 2. Baseline characteristics in subjects with adequate (AGA) or small for gestational age (SGA).

Sample characteristics	AGA (n=34)	SGA (n=15)	χ^2 or t	*P*
Sex (females)[a]	20 (58.8%)	8 (53.3%)	0.128	0.762
Age (years)[b]	17.58 (2.31)	17.32 (2.52)	-0.363	0.718
Weight at birth (g)[b]	3350.00 (458.91)	2750.33 (201.83)	-4.837	<0.001
BMI (kg/m^2)[b]	23.15 (4.05)	22.00 (4.56)	-0.884	0.381
BMI z-score[b]	0.51 (1.04)	0.10 (1.33)	-1.176	0.246
Waist circunference (cm)[b]	74.58 (9.40)	73.88 (11.69)	-0.224	0.824
Body fat (%)[b]	27.09 (19.89)	21.94 (7.91)	-0.965	0.339
Total cholesterol (mg/dL)[b]	148.59 (30.61)	148.07 (24.93)	-0.58	0.954
HDL cholesterol (mg/dL)[b]	44.88 (11.95)	42.00 (10.06)	-0.814	0.420
LDL cholesterol (mg/dL)[b]	88.13 (21.27)	90.47 (18.10)	-0.370	0.713
Triglycerides (mg/dL)[b]	77.88 (35.81)	78.00 (41.86)	0.010	0.992
Glucose (mg/dL)[b]	82.91 (7.18)	85.00 (6.76)	0.955	0.345
Insulin (uU/mL)[b]	14.24 (7.32)	14.58 (5.13)	0.162	0.872
HOMA-IR[b]	2.94 (1.54)	3.08 (1.22)	0.317	0.752
Verbal fluency (number of valid words)[b]	42.35 (10.78)	41.07 (10.26)	-0.390	0.698
IQ (total WASI)[b]	129.38 (20.84)	113.00 (30.82)	-1.312	0.208
Ethnicity (white)[a]	23 (67.6%)	8 (57.1%)	0.478	0.522
Maternal education (>8 years)[a]	13 (56.5%)	9 (90%)	3.515	0.109
Socioeconomic status (score points)[b]	17.55 (4.89)	16.40 (4.48)	-0.739	0.464

[a]Pearson χ^2 test (data expressed as absolut and relative frequencies). [b]Student's t-test (data expressed as mean and ± standard deviation).

Feeding behavior

No difference was found between AGA and SGA individuals in caloric intake and in percentage of calories derived from carbohydrates, lipids and proteins of the consumed snack of their choice (Table 3). Snack caloric density was greater on the SGA group (Student's t-test, t(47)=2.165, p=0.035), but it was not statistically significant when adjusted for BMI z-score.

Both SGA and AGA groups chose with same frequency their own snack based in food composition. However, SGA subjects chose with less frequency their own snack based in spatial arrangement in comparison to AGA (Table 3). There was no difference in DEBQ restrained, emotional and external eating behavior scales between groups. The correlation between external eating behavior and HOMA-IR index seems to be stronger for the SGA

group (R=0.469, p=0.078) as compared to AGA group (R=-0.293, P=0.093), although the simple slope does not reach statistical significance in SGA group. HOMA-IR index and BWR did not predict external eating (F(3,45) = 2.482, p<0.073, R2=0.142). However, there is a statistically significant interaction effect between HOMA-IR index and BWR (p<0.019), and a significant isolated effect of the HOMA-IR index (p=0.032), but not BWR (p=0.069), in external eating behavior.

Table 3. Feeding behavior in subjects with adequate (AGA) or small for gestational age (SGA).

Measure		AGA (n=34)	SGA (n=15)	F or χ^2	Df	*P*
Chosen snack[a]	Total energy (kcal)	553.55 (199.34)	492.52 (258.06)	0.912	1, 46	0.344
	Energy from protein (%kcal)	12.38 (4.91)	10.82 (4.61)	0.844	1, 46	0.363
	Energy from carbohydrate (%kcal)	51.57 (10.63)	55.99 (12.12)	1.441	1, 46	0.236
	Energy from lipid (%kcal)	36.77 (8.22)	33.82 (8.75)	1.153	1, 46	0.288
	Snack caloric density (kcal/g)	0.87 (0.35)	1.15 (0.55)	3.593	1, 46	0.064
Snack choice test[b]	Choice based in food composition (own snack)	22 (64.7%)	12 (80.0%)	1.146	1	0.336
	Choice based in spatial arrangement (own snack)	27 (79.4%)	6 (40%)	1.051	1	0.010
Dutch eating behaviour questionnaire (DEBQ)[a]	Restrained eating (score points)	22.06 (10.41)	25.73 (11.97)	3.451	1, 46	0.070
	Emotional eating (score points)	31.09 (13.22)	29.93 (9.68)	0.056	1, 46	0.814
	External eating (score points)	29.62 (6.30)	31.47 (6.28)	1.237	1, 46	0.272

[a]One-way ANOVA adjusted for BMI z-score (data expressed as mean and ± standard deviation). [b]Pearson χ^2 test (data expressed as absolut and relative frequencies). Df: degrees of freedom interval (between, within).

Structural and functional MRI

When analyzing eligible participants for MRI acquisition, we found a negative correlation between the HOMA-IR index and the activation on left superior frontal gyrus (-60, -46, -2 mm, peak pFWEcorr<0.0006) and left middle frontal lobe (-22, 18, 40 mm, peak pFWEcorr<0.0008), as well as right precuneus (40, -76, 36 mm, peak pFWEcorr<0.004, Figure 2) using the contrast “hyperpalatable foods *versus* non-food objects images”. In addition, we observed a positive correlation between HOMA-IR index and activation of right cuneus (18, -96, 14 mm, cluster pFWEcorr<0.006). When we evaluated the contrast “hyperpalatable *versus* healthy foods images”, there was a significant negative correlation between HOMA-IR

index and activation on right precentral gyrus (38, -20, 50 mm, peak pFWEcorr<0.009), right frontal superior gyrus (28, -12, 56 mm, peak pFWEcorr<0.02) and postcentral gyrus (48, -20, 54 mm, peak pFWEcorr<0.03). Moreover, we could show a positive correlation between HOMA-IR index and activation on right cuneus (20, -96, 16 mm, peak pFWEcorr<0.0004).

Smaller right and left subiculum were found in SGA group in comparison to AGA group (Table 4). No differences were found between groups in the volume of whole hippocampus and its other subfields (cornu ammonis (CA) 1, CA2 and CA3, CA4 and dentate gyrus and strata radiatum, lacunosum, and moleculare).

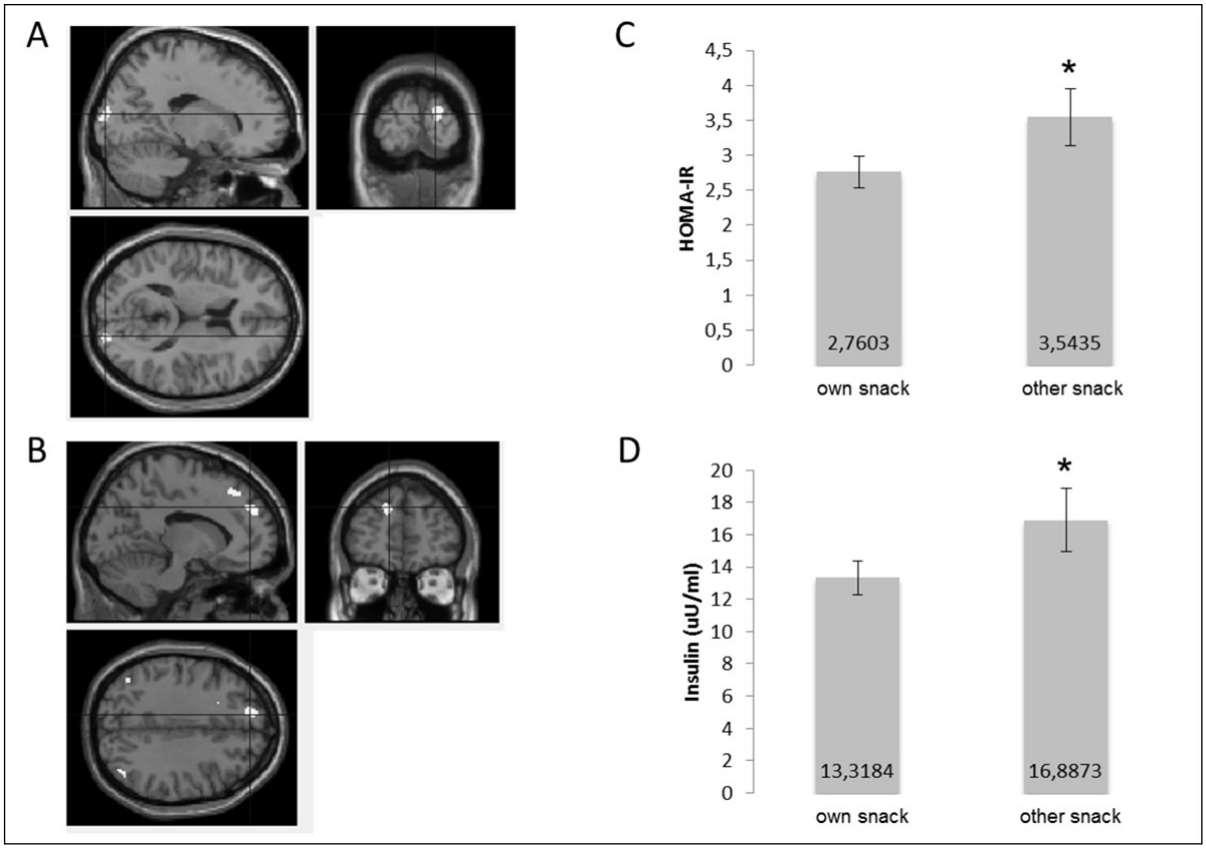

Figure 2. Main results of whole sample. (A) Positive correlation between HOMA-IR index and right cuneus activation in the contrast "palatable *versus* healthy foods images" (SPM multiple regression analyses using HOMA-IR as regressor, $p_{FWR\ corr}$<0.0004); (B) negative correlation between HOMA-IR index and left middle frontal lobe activation in the contrast "palatable foods *versus* non-food objects images" ($p_{FDR\ corr}$<0.0008); (C) participants who chose other snack have increased HOMA-IR index (ANOVA, p=0.044) (D) and plasma insulin (p=0.045) when compared to those who chose their own snack.

Table 4. Volume of hippocampus and its subfields (mm^3) in subjects with adequate (AGA) or small for gestational age (SGA).

Brain structure	AGA (n=29)	SGA (n=10)	F	Df	*P*
Right hippocampus	2352.85 (272.70)	2277.46 (196.55)	0.519	1, 36	0.476
Left hippocampus	2350.18 (280.62)	2241.97 (209.48)	1.234	1, 36	0.274
Right CA4 and DG	601.69 (69.26)	597.18 (46.11)	0.0001	1, 36	0.991
Left CA4 and DG	628.08 (78.38)	585.89 (59.36)	2.853	1, 36	0.100
Right CA2 and CA3	150.36 (26.83)	157.71 (17.69)	0.887	1, 36	0.352
Left CA2 and CA3	139.60 (30.13)	143.82 (25.63)	0.181	1, 36	0.673
Right CA1	761.91 (92.62)	733.68 (72.04)	0.629	1, 36	0.433
Left CA1	710.84 (93.65)	693.33 (69.59)	0.168	1, 36	0.685
Right str. rad. l-m.	515.51 (73.73)	505.52 (60.03)	0.058	1, 36	0.811
Left str. rad. l-m.	541.44 (76.17)	520.64 (58.27)	0.476	1, 36	0.495
Right subiculum	323.37 (43.74)	283.37 (32.77)	11.907	1, 36	0.001
Left subiculum	330.23 (44.47)	298.29 (31.47)	6.767	1, 36	0.013

One-way ANOVA adjusted for total brain volume (data expressed as mean and ± standard deviation. Df: degrees of freedom interval (between, within); DG: dentate gyrus; Str. rad. l-m: *strata radiatum*, *lacunosum* and *moleculare*.

Discussion

In this study, as hypothesized, (a) diminished insulin sensitivity correlated with activation in areas of visual attention and inactivation of areas associated with inhibitory control in healthy adolescents, and is associated with less consistency in implicit memory for a consumed meal. Besides that, (b) subjects who had poor fetal growth showed implicit food memory inconsistency, reduced volume of the hippocampal subiculum, and their external eating behavior was directly related to a measure of insulin sensitivity.

When facing hyperpalatable food contrasted with non-food objects images, the higher was the insulin resistance index, the lower was the activation of brain regions involved in inhibitory control, stimulus-driven attentional control and self-regulation (75–77). Furthermore, as insulin resistance index increases, the higher was the activation of cuneus, implicated in visual processing, valuation, and saliency during decision-making (78), suggesting that subjects with increased HOMA-IR index were more susceptible to tempting food cues (77) and to identify hyperpalatable food cues as visually valuable and salient (79). When facing hyperpalatable food compared to healthy food images, the participants with higher insulin resistance index showed lower activation in the sensorimotor areas related to

the saliency of food cues and eating behavior(78), and they also demonstrated higher activation of cuneus, reinforcing the hypothesis that subjects with increased HOMA-IR index had altered value and saliency to food.

Interestingly, individuals who did not choose their own snack had diminished insulin sensitivity and insulinemia. These behavioral outcomes are compatible with the imaging data, as poor insulin sensitivity led to altered brain activation facing hyperpalatable food images and modified attention control to food cues. This altered implicit learned food preference is interpreted as impaired food habituation, which is a memory phenomenon, and may be implicated in obesity development (80,81). Altered stability of feeding patterns is associated with poor choice of foods, increased energy intake and greater weight gain (82,83), probably because food choices are taken based on external cues, without attention to current satiety state. Therefore, implicit food memory impairment seems to be an early behavioral sign associated with alteration in insulin sensitivity and, most important, precedes obesity (84). This specific behavioral feature may contribute to increased food intake (47,85), leading to overeating, obesity and higher insulin resistance in long the term, as a “vicious cycle” model proposed by Martin & Davidson (86).

Anthropometric and biochemical parameters of poor fetal growth subjects were not altered in comparison to adequate fetal growth subjects, probably because the studied sample is still too young to have metabolic alterations. It was possible to observe, however, that the SGA individuals chose a snack with higher caloric density, reflecting a greater chance to develop increased adiposity over time. Beyond that, it seems that the higher the HOMA index in these individuals, the higher the external eating behavior. External eaters have an increased sensitivity to reward cues and poor ability to regulate cognitive responses to food, showing a tendency to exhibit impulsive behavior facing food motivational stimuli (87). These results are in agreement with humans and animal models studies in which restricted subjects eat more and are more impulsive to eat, especially high-carbohydrate or high-fat foods (11–16,20,88–90). Insulin has traditionally been considered an important signaling molecule in regulating energy homeostasis and feeding behavior, being associated with overeating and impairment in inhibitory food control. Interestingly, binge eating, besides psychological reasons, can result from rises and falls in blood glucose levels from eating food

with high carbohydrate content (91). Our findings are in accordance to the “thrifty phenotype” hypothesis that low birth weight and associated long-term insulin resistance are adaptive if food supplies are scarce, but, when they are abundant, this becomes a risk factor for metabolic syndrome (9,20)

Furthermore, individuals born with low birth weight had a greater chance of not choosing their own snack consumed months earlier based in spatial arrangement, which was considered an impaired memory related to a visual food cue and may be a signal of an altered eating behavior. Food variety, including visual variety, affects palatability and energy intake (92–95) and not having a pattern in food plating may be one of the reasons for increased consumption in restricted individuals. The relevance of food arrangement has been demonstrated by a growing body of studies, attesting that individuals "eat first with their eyes", being willing to pay more, to like more and to intent to eat more depending on visual attractiveness of the food elements (96–98). Meal layout planning also helps to decide on the kind and quantity of food to be eaten and is an adequate dietary intervention to reduce metabolic risk factors, including glycemic index (99–101). Besides that, implicit learned food preferences can contribute to metabolic susceptibility if valenced attitudes toward foods are developed (66). Displaying healthy foods in a more varied and attractive way or helping in the formation of a more rigid pattern of plating using implicit valenced cues, especially for hyperpalatable foods, could be viable strategies to promote healthier eating habits in poor fetal growth subjects.

In addition, the subiculum was reduced bilaterally in fetal growth restricted individuals. This finding corroborates the evidence that immature neurons in this region of hippocampal formation are selectively vulnerable to some insults such as ischemia, hypoglycemia, and hypoxia (102,103), as well as protein deprivation (104,105). Moreover, the “pontosubicular necrosis”, a specific form of prenatal or perinatal brain injury that led to neuronal apoptosis in the basal pons and hippocampal subiculum, is strongly associated with intrauterine growth restriction and uteroplacental insufficiency (106). The subiculum is involved in cognitive functions, as memory and spatial representation, and also participates in the temporal control of emotional and motivated behaviors (107). Its anatomy suggests that subiculum mediate the interactions between the hippocampal formation and mesocortical

areas, including afferent projections to nucleus accumbens, possibly acting in behavioral reinforcement (108–111) and mediating food intake (112,113). Hippocampal connectivity with striatum and neocortex can induce an unconscious bias in valuations and better memory performance for environmental cues preceding reward reduces reward strength in subsequent decision-making, suggesting a competitive relationship between the striatum and the hippocampus (114,115). Hippocampus is suggested to be a discriminatory retention region for food cues and memory related to eating affects how much attention is paid to food cues (49,116). Furthermore, the inhibitory control of food intake and appetitive behavior depends on hippocampal structural and functional integrity, influencing what, when and how much to eat (117,118). As subiculum may play a role in memory and spatial representation and motivated behavior regulation, thus its reduced volume found in subjects with low intrauterine growth may explain the altered feeding habits found in this study – impaired food memory (no platting pattern) and inhibitory control (higher intake and external eating related to insulin resistance).

It is important to consider that impaired fetal growth is known to alter other neurobiological mechanisms involved in appetite, satiety, reward, impulsiveness and interpretation of food cues. There is evidence of imbalance in homeostatic and hedonic control of food behavior in individuals with poor intrauterine growth, with alterations in nucleus of the solitary tract(119), in the internal signs of satiety and appetite, as insulin, leptin, ghrelin, serotonin, NPY and AgRP in hypothalamus (120–129), and in dopaminergic and opioid signaling in the mesocorticolimbic system (90,130–134). Hypothalamic-pituitary-adrenal axis dysfunction (135–138) may also influence the stress-related eating of subjects with intrauterine restriction (139,140). Insulin may also modulate feeding behavior of low birth weight subjects through different brain circuitries. Insulin sensitivity correlates with activity of dopaminergic neurons (141) and modulates feeding preferences in mesocorticolimbic pathways (142). Insulin signaling also has been found to regulate dopamine neurotransmission, working together to orchestrate both the motivation to engage in consummatory behavior and to calibrate the associated level of reward (143). Neuroinflammation and blood-brain barrier injury are associated factors to insulin resistance and intrauterine restriction (144) and may be a possible link between cognitive impairment and feeding behavior (145,146). Therefore, these studies indicate that imbalance in other

neuroendocrine systems may be associated with excessive food consumption, especially for hyperpalatable foods, of individuals who were born small for gestational age. It is also known that hippocampus is involved in explicit food-related memory acquisition and recall, internal perception of satiety, time and meal length estimating, cue-food associations learning and control of stress-related eating (48). Additionally, the difference in time (6 months) (147,148) and type of presentation (real and photo food) (149) between visits should be taken into account in interpreting our results.

Our main limitation is the small sample size, which may limit our ability to detect between group differences. Future investigation with a larger sample and considering others neuro-endocrine-behavior aspects are necessary to strength the evidence of this work. One of our strengths is to introduce a behavioral measure that could distinguish variations in HOMA-IR and insulinemia. Besides that, previous eating behavior studies investigated hindbrain and midbrain circuits involved in homeostatic and hedonic control of food intake of subjects with low birth weight (150,151). Our study evidenced an altered mechanism that controls a cognitive related aspect of food intake, still little studied in this vulnerable population.

In conclusion, our work has contributed to point out a mechanism involved in a risk feeding behavior for obesity and related metabolic disturbances, with insulin sensitivity and implicit food memory being of interest for target prevention and counseling programs to promote the development of healthy individuals. Our findings also suggest a possible role of insulin sensitivity and hippocampal integrity in the altered feeding behavior of individuals who were born small for gestational age. Considering the significant prevalence of individuals with low birth weight in world population, the understanding of neurobiology involved in risky eating behavior to develop chronic metabolic diseases can assist both in their prevention through early interventions and in their most appropriate management.

Acknowledgements: We thank the participants for their time and support. The authors report no conflicts of interest in this work. The current study was supported by the National Council for Technological and Scientific Development (CNPq) (PPS, 478820/2010),

Research and Event Incentive Fund of Hospital de Clínicas de Porto Alegre (FIPE/HCPA) (12-0254), Foundation for the Coordination of Higher Education and Graduate Training (CAPES) and Toxic Stress Research network of the JPB Foundation. The financial backers played no role in the design and analysis of the study or in the writing of this manuscript.

References

1. David RJ, Siegel E. Decline in neonatal mortality, 1968 to 1977: better babies or better care? Pediatrics. 1983 Apr;71(4):531–40.

2. World Health Organization. Obesity and overweight Fact sheet 311. World Health Organization; 2017;

3. Romo A, Carceller R, Tobajas J. Intrauterine growth retardation (IUGR): epidemiology and etiology. Pediatr Endocrinol Rev. 2009 Feb;6 Suppl 3:332–6.

4. Baird J, Osmond C, MacGregor A, Snieder H, Hales CN, Phillips DIW. Testing the fetal origins hypothesis in twins: the Birmingham twin study. Diabetologia. 2001 Jan 10;44(1):33–9.

5. Barnett AH, Eff C, Leslie RD, Pyke DA. Diabetes in identical twins. A study of 200 pairs. Diabetologia. 1981 Feb;20(2):87–93.

6. Bo S, Cavallo-Perin P, Scaglione L, Ciccone G, Pagano G. Low birthweight and metabolic abnormalities in twins with increased susceptibility to Type 2 diabetes mellitus. Diabet Med. 2000 May;17(5):365–70.

7. Barker DJ, Hales CN, Fall CH, Osmond C, Phipps K, Clark PM. Type 2 (non-insulin-dependent) diabetes mellitus, hypertension and hyperlipidaemia (syndrome X): relation to reduced fetal growth. Diabetologia. 1993 Jan;36(1):62–7.

8. Barker DJP. The developmental origins of chronic adult disease. Acta Paediatr Suppl. Norway; 2004 Dec;93(446):26–33.

9. Hales CN, Barker DJ. Type 2 (non-insulin-dependent) diabetes mellitus: the thrifty phenotype hypothesis. Diabetologia. 1992 Jul;35(7):595–601.

10. Portella AK, Kajantie E, Hovi P, Desai M, Ross MG, Goldani MZ, et al. Effects of in utero conditions on adult feeding preferences. J Dev Orig Health Dis. 2012 Jun 6;3(3):140–52.

11. Crume TL, Scherzinger A, Stamm E, McDuffie R, Bischoff KJ, Hamman RF, et al. The long-term impact of intrauterine growth restriction in a diverse U.S. cohort of children: the EPOCH study. Obesity (Silver Spring). NIH Public Access; 2014 Feb;22(2):608–15.

12. Kaseva N, Wehkalampi K, Hemio K, Hovi P, Jarvenpaa A-L, Andersson S, et al. Diet and nutrient intake in young adults born preterm at very low birth weight. J Pediatr. United States; 2013 Jul;163(1):43–8.

13. Barbieri MA, Portella AK, Silveira PP, Bettiol H, Agranonik M, Silva AA, et al. Severe intrauterine growth restriction is associated with higher spontaneous carbohydrate intake in young women. Pediatr Res. United States; 2009 Feb;65(2):215–20.

14. Lussana F, Painter RC, Ocke MC, Buller HR, Bossuyt PM, Roseboom TJ. Prenatal exposure to the Dutch famine is associated with a preference for fatty foods and a more atherogenic lipid profile. Am J Clin Nutr. United States; 2008 Dec;88(6):1648–52.

15. Stein AD, Rundle A, Wada N, Goldbohm RA, Lumey LH. Associations of gestational exposure to famine with energy balance and macronutrient density of the diet at age 58 years differ according to the reference population used. J Nutr. United States; 2009 Aug;139(8):1555–61.

16. Perala M-M, Mannisto S, Kaartinen NE, Kajantie E, Osmond C, Barker DJP, et al. Body size at birth is associated with food and nutrient intake in adulthood. PLoS One. United States; 2012;7(9):e46139.

17. Ayres C, Agranonik M, Portella AK, Filion F, Johnston CC, Silveira PP. Intrauterine growth restriction and the fetal programming of the hedonic response to sweet taste

in newborn infants. Int J Pediatr. Egypt; 2012;2012:657379.

18. Rotstein M, Stolar O, Uliel S, Mandel D, Mani A, Dollberg S, et al. Facial Expression in Response to Smell and Taste Stimuli in Small and Appropriate for Gestational Age Newborns. J Child Neurol. 2015 Oct 18;30(11):1466–71.

19. Laureano DP, Molle RD, Portella AK, Silveira PP. Facial Expressions in Small for Gestational Age Newborns. J Child Neurol. 2016 Mar 30;31(3):398–9.

20. Silveira PP, Agranonik M, Faras H, Portella AK, Meaney MJ, Levitan RD. Preliminary evidence for an impulsivity-based thrifty eating phenotype. Pediatr Res. United States; 2012 Mar;71(3):293–8.

21. Dalle Molle R, Silveira PP. Small for gestational age children have specific food preferences. J Pediatr. 2015 Jun;166(6):1547.

22. Starčević M, Predojević M, Butorac D, Tumbri J, Konjevoda P, Kadić AS. Early functional and morphological brain disturbances in late-onset intrauterine growth restriction. Early Hum Dev. 2016 Feb;93:33–8.

23. El Ayoubi M, Patkai J, Bordarier C, Desfrere L, Moriette G, Jarreau P-H, et al. Impact of fetal growth restriction on neurodevelopmental outcome at 2 years for extremely preterm infants: a single institution study. Dev Med Child Neurol. 2016 Dec;58(12):1249–56.

24. Allen MC. Developmental outcome and followup of the small for gestational age infant. Semin Perinatol. 1984 Apr;8(2):123–56.

25. Guellec I, Lapillonne A, Renolleau S, Charlaluk M-L, Roze J-C, Marret S, et al. Neurologic Outcomes at School Age in Very Preterm Infants Born With Severe or Mild Growth Restriction. Pediatrics. 2011 Apr 1;127(4):e883–91.

26. Morsing E, Asard M, Ley D, Stjernqvist K, Marsal K. Cognitive Function After Intrauterine Growth Restriction and Very Preterm Birth. Pediatrics. 2011 Apr 1;127(4):e874–82.

27. Kutschera J, Urlesberger B, Maurer U, Müller W. [Small for gestational age - Somatic, neurological and cognitive development until adulthood]. Z Geburtshilfe Neonatol. 2002 Apr;206(2):65–71.

28. Grantham-McGregor SM. Small for gestational age, term babies, in the first six years of life. Eur J Clin Nutr. 1998 Jan;52 Suppl 1:S59-64.

29. Martorell R, Ramakrishnan U, Schroeder DG, Melgar P, Neufeld L. Intrauterine growth retardation, body size, body composition and physical performance in adolescence. Eur J Clin Nutr. 1998 Jan;52 Suppl 1:S43-52-3.

30. Bickle Graz M, Tolsa J-F, Fischer Fumeaux CJ. Being Small for Gestational Age: Does it Matter for the Neurodevelopment of Premature Infants? A Cohort Study. PLoS One. Public Library of Science; 2015;10(5):e0125769.

31. Chaudhari S, Otiv M, Khairnar B, Pandit A, Hoge M, Sayyad M. Pune low birth weight study - birth to adulthood - cognitive development. Indian Pediatr. 2013 Sep;50(9):853–7.

32. Geva R, Eshel R, Leitner Y, Valevski AF, Harel S. Neuropsychological Outcome of Children With Intrauterine Growth Restriction: A 9-Year Prospective Study. Pediatrics. 2006 Jul 1;118(1):91–100.

33. Geva R, Eshel R, Leitner Y, Fattal-Valevski A, Harel S. Memory functions of children born with asymmetric intrauterine growth restriction. Brain Res. 2006 Oct 30;1117(1):186–94.

34. Cintra L, Díaz-Cintra S, Galván A, Kemper T, Morgane PJ. Effects of protein undernutrition on the dentate gyrus in rats of three age groups. Brain Res. 1990 Nov 5;532(1–2):271–7.

35. Debassio WA, Kemper TL, Galler JR, Tonkiss J. Prenatal malnutrition effect on pyramidal and granule cell generation in the hippocampal formation. Brain Res Bull. 1994;35(1):57–61.

36. Sizonenko S V., Borradori-Tolsa C, Vauthay DM, Lodygensky G, Lazeyras F, Hüppi PS. Impact of intrauterine growth restriction and glucocorticoids on brain development: Insights using advanced magnetic resonance imaging. Mol Cell Endocrinol. 2006 Jul 25;254–255:163–71.

37. Lodygensky GA, Seghier ML, Warfield SK, Tolsa CB, Sizonenko S, Lazeyras F, et al. Intrauterine Growth Restriction Affects the Preterm Infant's Hippocampus. Pediatr Res. 2008 Apr;63(4):438–43.

38. Kuchna I. Quantitative studies of human newborns' hippocampal pyramidal cells after perinatal hypoxia. Folia Neuropathol. 1994;32(1):9–16.

39. Schmidt-Kastner R, Freund TF. Selective vulnerability of the hippocampus in brain ischemia. Neuroscience. 1991;40(3):599–636.

40. Leitner Y, Heldman D, Harel S, Pick CG. Deficits in spatial orientation of children with intrauterine growth retardation. Brain Res Bull. 2005 Sep 30;67(1–2):13–8.

41. de Bie HMA, de Ruiter MB, Ouwendijk M, Oostrom KJ, Wilke M, Boersma M, et al. Using fMRI to Investigate Memory in Young Children Born Small for Gestational Age. Xie Z, editor. PLoS One. 2015 Jul 1;10(7):e0129721.

42. Camprubí Camprubí M, Balada Caballé R, Ortega Cano JA, Ortega de la Torre M de LA, Duran Fernández-Feijoo C, Girabent-Farrés M, et al. Learning and memory disabilities in IUGR babies: Functional and molecular analysis in a rat model. Brain Behav. 2017 Mar;7(3):e00631.

43. Giménez M, Junqué C, Narberhaus A, Caldú X, Salgado-Pineda P, Bargalló N, et al. Hippocampal gray matter reduction associates with memory deficits in adolescents with history of prematurity. Neuroimage. 2004 Nov;23(3):869–77.

44. Abernethy LJ, Klafkowski G, Foulder-Hughes L, Cooke RWI. Magnetic Resonance Imaging and T2 Relaxometry of Cerebral White Matter and Hippocampus in Children Born Preterm. Pediatr Res. 2003 Dec;54(6):868–74.

45. Isaacs EB, Edmonds CJ, Chong WK, Lucas A, Morley R, Gadian DG. Brain morphometry and IQ measurements in preterm children. Brain. 2004 Nov 10;127(12):2595–607.

46. Isaacs EB, Lucas A, Chong WK, Wood SJ, Johnson CL, Marshall C, et al. Hippocampal volume and everyday memory in children of very low birth weight. Pediatr Res. 2000 Jun;47(6):713–20.

47. Parent MB, Darling JN, Henderson YO. Remembering to eat: hippocampal regulation of meal onset. Am J Physiol Regul Integr Comp Physiol. 2014/02/28. Neuroscience Institute, Georgia State University, Atlanta, Georgia and Department of Psychology, Georgia State University, Atlanta, Georgia mbparent@gsu.edu. Neuroscience Institute, Georgia State University, Atlanta, Georgia and.; 2014;306(10):R701-13.

48. Stevenson RJ, Francis HM. The hippocampus and the regulation of human food intake. Psychol Bull. 2017 Oct;143(10):1011–32.

49. Davidson TL, Kanoski SE, Schier LA, Clegg DJ, Benoit SC. A Potential Role for the Hippocampus in Energy Intake and Body Weight Regulation. Curr Opin Pharmacol. 2007 Dec 26;7(6):613–6.

50. Kanoski SE, Grill HJ. Hippocampus Contributions to Food Intake Control: Mnemonic, Neuroanatomical, and Endocrine Mechanisms. Biol Psychiatry. 2015 Sep;

51. Davidson TL, Kanoski SE, Walls EK, Jarrard LE. Memory inhibition and energy regulation. Physiol Behav. United States; 2005 Dec;86(5):731–46.

52. Brunstrom JM, Burn JF, Sell NR, Collingwood JM, Rogers PJ, Wilkinson LL, et al. Episodic Memory and Appetite Regulation in Humans. PLoS One. Public Library of Science; 2012 Dec 5;7(12):e50707.

53. Wang JX, Cohen NJ, Voss JL. Covert rapid action-memory simulation (CRAMS): A hypothesis of hippocampal–prefrontal interactions for adaptive behavior. Neurobiol Learn Mem. 2015;117:22–33.

54. Barker DJ. The fetal origins of type 2 diabetes mellitus. Annals of internal medicine.

United States; 1999. p. 322–4.

55. Barker DJP. The developmental origins of insulin resistance. Horm Res. Switzerland; 2005;64 Suppl 3:2–7.

56. Boehmer BH, Limesand SW, Rozance PJ. The impact of IUGR on pancreatic islet development and β-cell function. J Endocrinol. 2017 Nov;235(2):R63–76.

57. GATFORD KL, SIMMONS RA. Prenatal Programming of Insulin Secretion in Intrauterine Growth Restriction. Clin Obstet Gynecol. 2013 Sep;56(3):520–8.

58. Gatford KL, Simmons RA, De Blasio MJ, Robinson JS, Owens JA. Review: Placental Programming of Postnatal Diabetes and Impaired Insulin Action after IUGR. Placenta. 2010 Mar;31:S60–5.

59. Biessels GJ, Reagan LP. Hippocampal insulin resistance and cognitive dysfunction. Nat Rev Neurosci. 2015;16(11):660–71.

60. Koekkoek PS, Kappelle LJ, van den Berg E, Rutten GEHM, Biessels GJ. Cognitive function in patients with diabetes mellitus: guidance for daily care. Lancet Neurol. England; 2015 Mar;14(3):329–40.

61. Wallner-Liebmann S, Koschutnig K, Reishofer G, Sorantin E, Blaschitz B, Kruschitz R, et al. Insulin and Hippocampus Activation in Response to Images of High-Calorie Food in Normal Weight and Obese Adolescents Obesity Volume 18, Issue 8. Obesity. 2010. p. 1552–7.

62. Docteur A, Urdapilleta I, Defrance C, Raison J. Implicit and Explicit Memory Bias for Words Related To Food, Shape and Body Parts in Obese and Normal Weight Females. Curr Psychol Lett. 2008;24(2):52–62.

63. Mucellini AB, Fonseca NK de O da, Manfro GG, Silveira PP. Hippocampal insulin resistance and altered food decision-making as players on obesity risk. Neurosci Biobehav Rev. United States; 2017 Mar;77:165–76.

64. Salum GA, Isolan LR, Bosa VL, Tocchetto AG, Teche SP, Schuch I, et al. The

multidimensional evaluation and treatment of anxiety in children and adolescents: rationale, design, methods and preliminary findings. Rev Bras Psiquiatr. 2011 Jun;33(2):181–95.

65. Parma V, Castiello U, Köster EP, Mojet J. Selecting food. The contribution of memory, liking, and action. Appetite. 2014 May;76:186–96.

66. Legget KT, Cornier M-A, Rojas DC, Lawful B, Tregellas JR. Harnessing the power of disgust: a randomized trial to reduce high-calorie food appeal through implicit priming. Am J Clin Nutr. 2015 Aug 1;102(2):249–55.

67. Köster EP. Diversity in the determinants of food choice: A psychological perspective. Food Qual Prefer. 2009 Mar;20(2):70–82.

68. USDA. USDA National Nutrient Database for Standard Reference [Internet]. 2013. Available from: http://www.ars.usda.gov/ba/bhnrc/ndl 2013.

69. van Strien T, Frijters JER, Bergers GPA, Defares PB. The Dutch Eating Behavior Questionnaire (DEBQ) for assessment of restrained, emotional, and external eating behavior. Int J Eat Disord. Wiley Subscription Services, Inc., A Wiley Company; 1986 Feb 1;5(2):295–315.

70. Viana V, Lourenço S. Estilo alimentar: adaptação e validação do questionário holandês do comportamento alimentar. Psicol Teor Investig e Prática,. 2003;XXVI(1):59–71.

71. Pipitone J, Park MTM, Winterburn J, Lett TA, Lerch JP, Pruessner JC, et al. Multi-atlas segmentation of the whole hippocampus and subfields using multiple automatically generated templates. Neuroimage. 2014 Nov 1;101:494–512.

72. Page KA, Seo D, Belfort-DeAguiar R, Lacadie C, Dzuira J, Naik S, et al. Circulating glucose levels modulate neural control of desire for high-calorie foods in humans. J Clin Invest. United States; 2011 Oct;121(10):4161–9.

73. Deluchi M, Costa FS, Friedman R, Goncalves R, Bizarro L. Attentional bias to unhealthy food in individuals with severe obesity and binge eating. Appetite. England; 2017

Jan;108:471–6.

74. Lang P, Bradley M, Cuthbert B. International affective picture system (IAPS): Affective ratings of pictures and instruction manual. Technical Report A-8. 1997.

75. McCaffery JM, Haley AP, Sweet LH, Phelan S, Raynor HA, Del Parigi A, et al. Differential functional magnetic resonance imaging response to food pictures in successful weight-loss maintainers relative to normal-weight and obese controls. Am J Clin Nutr . 2009 Oct 1;90(4):928–34.

76. Behary P, Miras AD. Brain responses to food and weight loss. Exp Physiol. 2014 Sep 1;99(9):1121–7.

77. van Meer F, van der Laan LN, Charbonnier L, Viergever MA, Adan RA, Smeets PA. Developmental differences in the brain response to unhealthy food cues: an fMRI study of children and adults. Am J Clin Nutr. United States; 2016 Dec;104(6):1515–22.

78. Litt A, Plassmann H, Shiv B, Rangel A. Dissociating Valuation and Saliency Signals during Decision-Making. Cereb Cortex. 2011 Jan 1;21(1):95–102.

79. Rodrigues DM, Reis RS, Dalle Molle R, Machado TD, Mucellini AB, Bortoluzzi A, et al. Decreased comfort food intake and allostatic load in adolescents carrying the A3669G variant of the glucocorticoid receptor gene. Appetite. England; 2017 Apr;116:21–8.

80. Epstein LH, Salvy SJ, Carr K a, Dearing KK, Bickel WK. Food reinforcement, delay discounting and obesity. Physiol Behav. Elsevier Inc.; 2010 Jul;100(5):438–45.

81. Raynor HA, Jeffery RW, Phelan S, Hill JO, Wing RR. Amount of Food Group Variety Consumed in the Diet and Long-Term Weight Loss Maintenance. Obes Res. 2005 May;13(5):883–90.

82. McCrory MA, Fuss PJ, McCallum JE, Yao M, Vinken AG, Hays NP, et al. Dietary variety within food groups: association with energy intake and body fatness in men and women. Am J Clin Nutr. 1999 Mar;69(3):440–7.

83. Raynor HA, Epstein LH. Dietary variety, energy regulation, and obesity. Psychol Bull.

2001 May;127(3):325–41.

84. Kullmann S, Heni M, Veit R, Ketterer C, Schick F, Haring H-U, et al. The obese brain: association of body mass index and insulin sensitivity with resting state network functional connectivity. Hum Brain Mapp. United States; 2012 May;33(5):1052–61.

85. Davidson TL, Hargrave SL, Swithers SE, Sample CH, Fu X, Kinzig KP, et al. Inter-relationships among diet, obesity and hippocampal-dependent cognitive function. Neuroscience. 2013/09/04. Center for Behavioral Neuroscience, American University, Washington, DC, United States. Electronic address: terryd@american.edu.; 2013;253:110–22.

86. Martin A, Davidson TL. Human cognitive function and the obesogenic environment. Physiol Behav. 2014;Sep; 136:185–93.

87. Hou R, Mogg K, Bradley BP, Moss-Morris R, Peveler R, Roefs A. External eating, impulsivity and attentional bias to food cues. Appetite. 2011 Jan;56:424–7.

88. Reis RS, Dalle Molle R, Machado TD, Mucellini AB, Rodrigues DM, Bortoluzzi A, et al. Impulsivity-based thrifty eating phenotype and the protective role of n-3 PUFAs intake in adolescents. Transl Psychiatry. 2016;6.

89. Reis RS, Bernardi JR, Steiner M, Meaney MJ, Levitan RD, Silveira PP. Poor infant inhibitory control predicts food fussiness in childhood - A possible protective role of n-3 PUFAs for vulnerable children. Prostaglandins Leukot Essent Fatty Acids. Scotland; 2015 Jun;97:21–5.

90. Dalle Molle R, Laureano DP, Alves MB, Reis TM, Desai M, Ross MG, et al. Intrauterine growth restriction increases the preference for palatable foods and affects sensitivity to food rewards in male and female adult rats. Brain Res. Netherlands; 2015 Aug;1618:41–9.

91. Herpertz S, Albus C, Lichtblau K, K  hle K, Mann K, Senf W. Relationship of weight and eating disorders in type 2 diabetic patients: A multicenter study. Int J Eat Disord. John Wiley & Sons, Inc.; 2000 Jul 1;28(1):68–77.

92. Wadhera D, Capaldi-Phillips ED. A review of visual cues associated with food on food acceptance and consumption. Eat Behav. 2014 Jan;15(1):132–43.

93. Friis R, Skov LR, Olsen A, Appleton KM, Saulais L, Dinnella C, et al. Comparison of three nudge interventions (priming, default option, and perceived variety) to promote vegetable consumption in a self-service buffet setting. Kunze G, editor. PLoS One. 2017 May 31;12(5):e0176028.

94. Kongsbak I, Skov LR, Nielsen BK, Ahlmann KF, Schaldemose, Hanna Atkinson L, Wichmanna M, et al. Increasing fruit and vegetable intake among male university students in an ad libitum buffet setting: A choice architectural nudge intervention. Food Qual Prefer. Elsevier; 2016 Apr 1;49:183–8.

95. Zampollo F, Kniffin KM, Wansink B, Shimizu M. Food plating preferences of children: the importance of presentation on desire for diversity. Acta Paediatr. 2012 Jan;101(1):61–6.

96. Zellner DA, Siemers E, Teran V, Conroy R, Lankford M, Agrafiotis A, et al. Neatness counts. How plating affects liking for the taste of food. Appetite. 2011 Dec;57(3):642–8.

97. Zellner DA, Loss CR, Zearfoss J, Remolina S. It tastes as good as it looks! The effect of food presentation on liking for the flavor of food☆. Appetite. 2014 Jun;77:31–5.

98. Cavazza N, Guidetti M, Butera F. Ingredients of gender-based stereotypes about food. Indirect influence of food type, portion size and presentation on gendered intentions to eat. Appetite. 2015 Aug;91:266–72.

99. Raidl M, Spain K, Lanting R, Lockard M, Johnson S, Spencer M, et al. The healthy diabetes plate. Prev Chronic Dis. 2007 Jan;4(1):A12.

100. Camelon KM, Hådell K, Jämsén PT, Ketonen KJ, Kohtamäki HM, Mäkimatilla S, et al. The Plate Model: a visual method of teaching meal planning. DAIS Project Group. Diabetes Atherosclerosis Intervention Study. J Am Diet Assoc. 1998 Oct;98(10):1155–8.

101. Jayawardena R, Fernando P, Lokunarangoda N, Pathirana AK. Effects of the “plate model” as part of dietary intervention on modification of selected cardiometabolic risk factors in post-myocardial infarction patients: study protocol for a randomized controlled trial. Trials. 2017 Dec 10;18(1):314.

102. Isumi H, Uchida Y, Hayashi T, Furukawa S, Takashima S. Neuron death and glial response in pontosubicular necrosis. The role of the growth inhibition factor. Clin Neuropathol. 2000;19(2):77–84.

103. Mito T, Kamei A, Takashima S, Becker L. Clinicopathological Study of Pontosubicular Necrosis. Neuropediatrics. 1993 Aug 19;24(4):204–7.

104. Andrade JP, Madeira MD, Paula-Barbosa MM. Differential vulnerability of the subiculum and entorhinal cortex of the adult rat to prolonged protein deprivation. Hippocampus. John Wiley & Sons, Inc.; 1998 Jan 1;8(1):33–47.

105. Lister JP, Blatt GJ, DeBassio WA, Kemper TL, Tonkiss J, Galler JR, et al. Effect of prenatal protein malnutrition on numbers of neurons in the principal cell layers of the adult rat hippocampal formation. Hippocampus. Wiley Subscription Services, Inc., A Wiley Company; 2005 Jan 1;15(3):393–403.

106. Burke C, Gobe G. Pontosubicular apoptosis (“necrosis”) in human neonates with intrauterine growth retardation and placental infarction. Virchows Arch. 2005 Jun 19;446(6):640–5.

107. O’Mara SM, Sanchez-Vives M V., Brotons-Mas JR, O’Hare E. Roles for the subiculum in spatial information processing, memory, motivation and the temporal control of behaviour. Prog Neuro-Psychopharmacology Biol Psychiatry. 2009 Aug 1;33(5):782–90.

108. French SJ, Totterdell S. Individual nucleus accumbens-projection neurons receive both basolateral amygdala and ventral subicular afferents in rats. Neuroscience. 2003;119(1):19–31.

109. Britt JP, Benaliouad F, McDevitt RA, Stuber GD, Wise RA, Bonci A. Synaptic and

Behavioral Profile of Multiple Glutamatergic Inputs to the Nucleus Accumbens. Neuron. 2012 Nov 21;76(4):790–803.

110. Groenewegen HJ, Vermeulen-Van der Zee E, te Kortschot A, Witter MP. Organization of the projections from the subiculum to the ventral striatum in the rat. A study using anterograde transport of Phaseolus vulgaris leucoagglutinin. Neuroscience. 1987 Oct;23(1):103–20.

111. Kahn I, Shohamy D. Intrinsic connectivity between the hippocampus, nucleus accumbens, and ventral tegmental area in humans. Hippocampus. NIH Public Access; 2013 Mar;23(3):187–92.

112. Kirkham TC, Cooper SJ. Appetite and body weight : integrative systems and the development of anti-obesity drugs. Elsevier Academic Press; 2007. 371 p.

113. Sweeney P, Yang Y. An excitatory ventral hippocampus to lateral septum circuit that suppresses feeding. Nat Commun. 2015 Dec 15;6:10188.

114. Wimmer GE, Shohamy D. Preference by association: how memory mechanisms in the hippocampus bias decisions. Science. United States; 2012 Oct;338(6104):270–3.

115. Wimmer GE, Braun EK, Daw ND, Shohamy D. Episodic memory encoding interferes with reward learning and decreases striatal prediction errors. J Neurosci. United States; 2014 Nov;34(45):14901–12.

116. Higgs S. Cognitive processing of food rewards. Appetite. 2016 Sep;104:10–7.

117. Hebben N, Corkin S, Eichenbaum H, Shedlack K. Diminished ability to interpret and report internal states after bilateral medial temporal resection: Case H.M. Behav Neurosci. 1985;Vol 99(6):1031–9.

118. Rozin P, Dow S, Moscovitch M, Rajaram S. What Causes Humans to Begin and End a Meal? A Role for Memory for What Has Been Eaten, as Evidenced by a Study of Multiple Meal Eating in Amnesic Patients. Psychol Sci. 1998 Sep;9(5):392–6.

119. Lira LA, Almeida LCA, da Silva AAM, Cavalcante TCF, de Melo DDCB, de Souza JA, et al.

Perinatal undernutrition increases meal size and neuronal activation of the nucleus of the solitary tract in response to feeding stimulation in adult rats. Int J Dev Neurosci. 2014 Nov;38:23–9.

120. Delahaye F, Breton C, Risold P-Y, Enache M, Dutriez-Casteloot I, Laborie C, et al. Maternal Perinatal Undernutrition Drastically Reduces Postnatal Leptin Surge and Affects the Development of Arcuate Nucleus Proopiomelanocortin Neurons in Neonatal Male Rat Pups. Endocrinology. 2008 Feb;149(2):470–5.

121. Desai M, Gayle D, Han G, Ross MG. Programmed Hyperphagia Due to Reduced Anorexigenic Mechanisms in Intrauterine Growth-Restricted Offspring. Reprod Sci. 2007 May 6;14(4):329–37.

122. Shin B-C, Dai Y, Thamotharan M, Gibson LC, Devaskar SU. Pre- and postnatal calorie restriction perturbs early hypothalamic neuropeptide and energy balance. J Neurosci Res. 2012 Jun;90(6):1169–82.

123. Yousheng Jia Y, Nguyen T, Desai M, Ross MG. Programmed Alterations in Hypothalamic Neuronal Orexigenic Responses to Ghrelin Following Gestational Nutrient Restriction. Reprod Sci. SAGE PublicationsSage CA: Los Angeles, CA; 2008 Sep 18;15(7):702–9.

124. Fukami T, Sun X, Li T, Desai M, Ross MG. Mechanism of Programmed Obesity in Intrauterine Fetal Growth Restricted Offspring: Paradoxically Enhanced Appetite Stimulation in Fed and Fasting States. Reprod Sci. 2012 Apr 16;19(4):423–30.

125. Orozco-Solís R, Matos RJB, Lopes de Souza S, Grit I, Kaeffer B, Manhães de Castro R, et al. Perinatal nutrient restriction induces long-lasting alterations in the circadian expression pattern of genes regulating food intake and energy metabolism. Int J Obes. Nature Publishing Group; 2011 Jul 9;35(7):990–1000.

126. Remmers F, Verhagen LAW, Adan RAH, Delemarre-van de Waal HA. Hypothalamic Neuropeptide Expression of Juvenile and Middle-Aged Rats after Early Postnatal Food Restriction. Endocrinology. 2008 Jul;149(7):3617–25.

127. Manuel-Apolinar L, ROCHA L, DAMASIO L, TESORO-CRUZ E, ZARATE A. Role of prenatal undernutrition in the expression of serotonin, dopamine and leptin receptors in adult mice: Implications of food intake. Mol Med Rep. 2014 Feb;9(2):407–12.

128. Desai M, Li T, Ross MG. Fetal Hypothalamic Neuroprogenitor Cell Culture: Preferential Differentiation Paths Induced by Leptin and Insulin. Endocrinology. 2011 Aug;152(8):3192–201.

129. Lopes de Souza S, Orozco-Solis R, Grit I, Manhães de Castro R, Bolaños-Jiménez F. Perinatal protein restriction reduces the inhibitory action of serotonin on food intake. Eur J Neurosci. 2008 Mar;27(6):1400–8.

130. Vucetic Z, Totoki K, Schoch H, Whitaker KW, Hill-Smith T, Lucki I, et al. Early life protein restriction alters dopamine circuitry. Neuroscience. 2010 Jun 30;168(2):359–70.

131. Alves MB, Dalle Molle R, Desai M, Ross MG, Silveira PP. Increased palatable food intake and response to food cues in intrauterine growth-restricted rats are related to tyrosine hydroxylase content in the orbitofrontal cortex and nucleus accumbens. Behav Brain Res. Netherlands; 2015;287:73–81.

132. Laureano DP, Dalle Molle R, Alves MB, Luft C, Desai M, Ross MG, et al. Intrauterine growth restriction modifies the hedonic response to sweet taste in newborn pups - Role of the accumbal mu-opioid receptors. Neuroscience. United States; 2016 May;322:500–8.

133. Peciña S, Smith KS, Berridge KC. Hedonic Hot Spots in the Brain. Neurosci. 2006 Dec 29;12(6):500–11.

134. Silveira PP, Pokhvisneva I, Gaudreau H, Atkinson L, Fleming AS, Sokolowski MB, et al. Fetal growth interacts with multilocus genetic score reflecting dopamine signaling capacity to predict spontaneous sugar intake in children. Appetite. 2017 Oct;

135. Dellschaft NS, Alexandre-Gouabau M-C, Gardner DS, Antignac J-P, Keisler DH, Budge H, et al. Effect of pre- and postnatal growth and post-weaning activity on glucose

metabolism in the offspring. J Endocrinol. 2015 Jan 12;224(2):171–82.

136. Óvilo C, González-Bulnes A, Benítez R, Ayuso M, Barbero A, Pérez-Solana ML, et al. Prenatal programming in an obese swine model: sex-related effects of maternal energy restriction on morphology, metabolism and hypothalamic gene expression. Br J Nutr. 2014 Feb 5;111(4):735–46.

137. Vieau D, Sebaai N, Léonhardt M, Dutriez-Casteloot I, Molendi-Coste O, Laborie C, et al. HPA axis programming by maternal undernutrition in the male rat offspring. Psychoneuroendocrinology. 2007 Aug;32:S16–20.

138. Lesage J, Blondeau B, Grino M, Bréant B, Dupouy JP. Maternal Undernutrition during Late Gestation Induces Fetal Overexposure to Glucocorticoids and Intrauterine Growth Retardation, and Disturbs the Hypothalamo-Pituitary Adrenal Axis in the Newborn Rat [1]. Endocrinology. 2001 May;142(5):1692–702.

139. Dallman MF, Pecoraro N, Akana SF, Fleur SE la, Gomez F, Houshyar H, et al. Chronic stress and obesity: A new view of “comfort food.” PNAS. 2003;100(20).

140. Dallman MF, Pecoraro NC, Fleur SE la. Chronic stress and comfort foods: Self-medication and abdominal obesity. Brain Behav Immun. 2005;19:275–80.

141. Heni M, Kullmann S, Ketterer C, Guthoff M, Linder K, Wagner R, et al. Nasal insulin changes peripheral insulin sensitivity simultaneously with altered activity in homeostatic and reward-related human brain regions. Diabetologia. 2012;55:1773–82.

142. Portella AK, Silveira PP, Laureano DP, Cardoso S, Bittencourt V, Noschang C, et al. Litter size reduction alters insulin signaling in the ventral tegmental area and influences dopamine-related behaviors in adult rats. Behav Brain Res. 2015 Feb;278:66–73.

143. Daws LC, Avison MJ, Robertson SD, Niswender KD, Galli A, Saunders C. Insulin signaling and addiction. Neuropharmacology. Elsevier Ltd; 2011 Mar;

144. Wixey JA, Chand KK, Colditz PB, Bjorkman ST. Review: Neuroinflammation in intrauterine growth restriction. Placenta. 2017 Jun;54:117–24.

145. Kullmann S, Heni M, Hallschmid M, Fritsche A, Preissl H, Häring H-U. Brain Insulin Resistance at the Crossroads of Metabolic and Cognitive Disorders in Humans. Physiol Rev. 2016;96(4).

146. Davidson TL, Monnot A, Neal AU, Martin AA, Horton JJ, Zheng W. The effects of a high-energy diet on hippocampal-dependent discrimination performance and blood-brain barrier integrity differ for diet-induced obese and diet-resistant rats. Physiol Behav. 2012;107(1):26–33.

147. Thrailkill EA, Epstein LH, Bouton ME. Effects of inter-food interval on the variety effect in an instrumental food-seeking task. Clarifying the role of habituation. Appetite. 2015 Jan;84:43–53.

148. Epstein LH, Carr KA, Cavanaugh MD, Paluch RA, Bouton ME. Long-term habituation to food in obese and nonobese women. Am J Clin Nutr. 2011 Aug 1;94(2):371–6.

149. Spence C, Okajima K, Cheok AD, Petit O, Michel C. Eating with our eyes: From visual hunger to digital satiation. Brain Cogn. Academic Press; 2016 Dec 1;110:53–63.

150. Dalle Molle R, Bischoff AR, Portella AK, Silveira PP. The fetal programming of food preferences: current clinical and experimental evidence. J Dev Orig Health Dis. 2016 Jun 28;7(3):222–30.

151. Bischoff AR, DalleMolle R, Silveira PP. Fetal Programming of Food Preferences and Feeding Behavior. In: Diet, Nutrition, and Fetal Programming. Cham: Springer International Publishing; 2017. p. 453–70.

152. Mucellini AB, Dalle Molle R, Rodrigues DM, Machado TD, Reis RS, Fonseca NK de O da, et al. Insulin sensitivity associated with brain activation in response to palatable food images and to implicit learned food preferences in non-obese adolescents. Manuscr Submitt Publ. 2017;

4.4. ARTIGO EXPERIMENTAL

Artigo na versão pré-submissão.

Title: Hippocampal insulin sensitivity and behavioral reactivity to food cues in adult rats exposed to poor fetal growth

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Abstract: Despite the known impact of poor fetal growth on metabolism and cognitive function, little is known about the molecular mechanisms that link the altered feeding behavior to metabolic syndrome. This study investigated whether exposure to poor fetal growth followed by chronic palatable food availability in rats affects (1) insulin-dependent hippocampal function and (2) food memory and feeding predictability, as well as if it is associated with the development of metabolic alterations. On 10th day of pregnancy, rats were divided into control group (Adlib), which continued with standard chow ad libitum, and experimental group (FR), which received 50% of the chow intake of Adlib. At birth, male pups were adopted by Adlib mothers and, at 60 days, half of offspring from each group received high-fat and sugar (HFS) diet and half continued with standard (CON) diet. At 140 days, behavioral tasks started, and, at 200 days of age, tissues were collected. When restricted animals were chronically fed with hyperpalatable diet, they were capable of recognizing food novelty, an ability that was associated with hyperinsulinemia and higher body weight gain during experiment. Poor intrauterine growth also reduced eating and feeding entropy when predictability of food reward was changed, suggesting functional alterations in the hippocampus. Rats with poor fetal growth had pre-insulin resistant state, with altered hippocampal signaling and increased glutamatergic receptor subunit phosphorylation induced by insulin systemic injection. These findings indicate that poor fetal growth together with chronic hyperpalatable food exposure induces changes in hippocampal insulin sensitivity, and this may be reflected in risky eating behaviors favoring body weight gain.

Key-words: Intrauterine growth restriction; Small for gestational age; Feeding behavior; Food memory; Metabolic syndrome; Palatable food; Animal model

Introduction

Exposure to fetal adversity, evidenced by poor fetal growth, increases the propensity to develop health conditions associated with metabolic syndrome (1), such as type II diabetes (2–5), dyslipidemia (6,7), abdominal adiposity (8,9), and cardiovascular diseases (10,11). Another common feature is that fetal growth restricted subjects tend to have higher

intake of carbohydrate and fats from early life (12,13) until adulthood (14–18) in humans. As eating habits may be linked to the development of metabolic disorders mentioned above (19–22), the continuous feeding unbalance over the lifetime may be a reason for the increased risk of developing these conditions in this population (23).

This differential feeding behavior of low birth weight individuals indicates that they have alterations in brain mechanisms involved in food decision making (24,25), probably associated with changes in the functioning of the homeostatic and hedonic systems (26–31). However, other brain regions responsible for eating regulation as the hippocampus are still poorly studied in this population. The hippocampus is involved in many memory processes, including those used to evaluate what, where, when, and how much to eat, in satiety perception, in inhibitory control, and in many other eating functions (32). These abilities may be impaired when there is hippocampal damage, generally leading to excessive consumption (33–35). Moreover, alterations in insulin function in this brain area have been described (36,37). The excessive intake of hyperpalatable foods can generate a vicious cycle, impairing peripheral and hippocampal insulin sensitivity and, thus, impairing eating regulation (33,38). The hippocampus appears to be particularly susceptible to malnutrition and chronic placental insufficiency, both related to poor fetal growth (39–46), which may be linked to a dysfunction in insulin regulation of the synaptic activity (47).

The hypothesis of this study is that poor fetal growth leads to insulin resistance and altered glutamatergic activation in hippocampus, and changes food memory, leading to a higher intake of hyperpalatable foods and compromised metabolic state. As both humans and rodents exposed to fetal growth restriction tend to be resistant to insulin (48,49) and to have decreased hippocampal function (50,51), this study sought to investigate, using an animal model, whether poor fetal growth induces alterations in (a) eating memory and feeding behavior predictability through behavioral tasks, (b) hippocampal expression of proteins that are essential to synaptic function, memory formation and behavioral inhibition, through the quantification of GluN2A and GluN2B subunits of glutamatergic N-Methyl-D-Aspartate (NMDA) receptor and GluN2B phosphorylated and (c) hippocampal insulin signaling cascade, through the quantification of kinase B (Akt) and suppressor of cytokine signaling 3 (SOCS3). Considering that the interaction between fetal life events and

subsequent environmental factors may also change the risk for the metabolic and cognitive disorders (52,53), half of the animals were also chronically exposed to a high-fat and sugar diet.

Materials and methods

Experimental conditions

All procedures contributing to this work were approved by the Animal Research Ethics Committee of Hospital de Clínicas de Porto Alegre (protocol number 13-0544). Twelve virgin female Sprague-Dawley rats of approximately 60 days of age from Multidisciplinary Center for Biological Research of University of Campinas, Brazil were housed in Plexiglas home cages (49 x 34 x 16 cm), maintained in controlled 12h standard dark/light cycle and 22 ±2ºC temperature, and with control chow (CON diet; 3.06kcal/g, 28.76% protein, 11.76% fat, 59.48% carbohydrate; no sucrose; NUVILAB®, Colombo, Brazil) and water provided ad libitum. Vaginal cytology was evaluated daily to determine estrous cycle regularity. Females were placed with males when they were in proestrous phase and sexually receptive. Pregnancy was confirmed by the presence of sperm on vaginal smear on the day after mating and, then, considered gestational day 0.

At 10th gestational day, mothers were randomly allocated to two groups: (a) control rats with ad libitum CON diet (Adlib group) and (b) undernourished females which received 50% of Adlib group daily weight consumption of CON diet (food restricted or FR group). Chow was offered for both groups always in the morning and food restriction was held until offspring birth. Within 24h of birth, litters were standardized to a maximum of 8 pups/litter, with 4 females and 4 males. Cross-fostering was performed and all litters were adopted by Adlib mothers. Then, the following groups were formed: (a) Adlib offspring adopted by Adlib dams and (b) FR offspring adopted by Adlib dams. Only male offspring were studied in this study and remaining animals were used in other projects also approved by the institution's ethics committee. On postnatal day (PND) 21, male pups were weaned and received ad libitum CON diet. On PND 60, half of pups of each group were exposed to an ad libitum hyperpalatable high-fat and sugar chow (HFS diet; 4.82kcal/g, 11.62% protein, 63.49% fat,

24.90% carbohydrate, being 20% from sucrose; Prag Soluções®, Jaú, Brazil). Thus, the following four groups of male pups were formed: a) offspring from Adlib dams fed with CON diet (Adlib-CON, n=12); b) offspring from Adlib dams fed with HFS diet (Adlib-HFS, n=12); c) offspring from FR dams fed with CON diet (FR-CON, n=12); d) offspring from FR dams fed with HFS diet (FR-HFS, n=12), as shown in Figure 1. Body weight was measured weekly from weaning to the end of experiment. Behavioral tasks started on PND 140 and euthanasia occurred on PND 200.

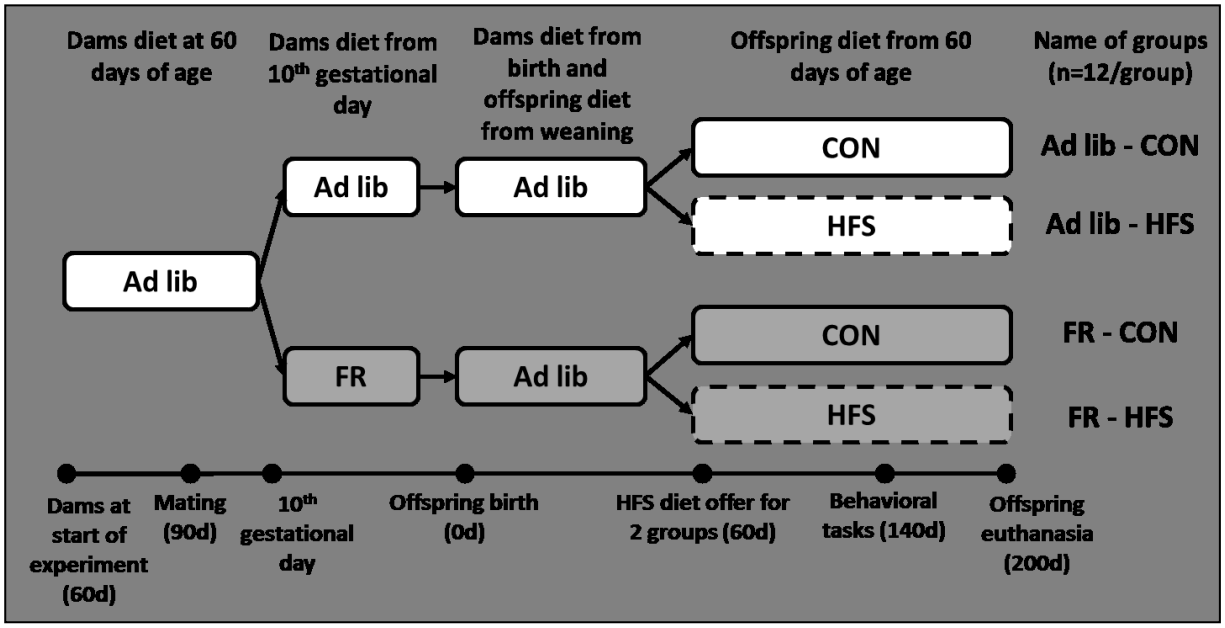

Figure 1: Experimental design. Adlib: *ad libitum* control chow feeding; FR: restricted control chow feeding during gestation; CON: control diet; HFS: high-fat and sugar diet; Adlib-CON: offspring from Adlib dams fed with CON; Adlib-HFS: offspring from Adlib dams fed with HFS; FR-CON: offspring from FR dams fed with CON; FR-HFS: offspring from FR dams fed with HFS.

Behavioral tasks

The sequence of tasks was established following an increasing order of complexity and exposure to environmental interventions. The aim was to assess the effect of the dietary manipulations on long-term memory related to type, place, time, and quantity of eating (32,54), as well as the role of hippocampal function in these effects (55,56). Before each animal was placed in the task apparatus, it was cleaned with 70% alcohol. All tasks were performed in an observation room illuminated with white light during light cycle and taped.

After, an observer that was blinded to the animal's experimental groups scored the task throughout videotapes.

Open field task

First, rats performed the Open Field task, in order to evaluate the anxiety and motor activity. It was performed in a wooden box measuring 45x40x60cm with a front glass wall. Box floor was demarcated by three vertical lines and two horizontal lines, forming 12 quadrants, being 10 peripheral and 2 central. Animals were placed in floor center, with their body and head facing the glass wall, and they explored the area for 5 minutes. Taping occurred during the entire exposure time. To assess levels of anxiety and motor activity, the percentage of time that animal stayed in peripheral quadrants and the number of crossings in floor lines were calculated. After 24h, animals were replaced in the box under same environmental conditions, in order to evaluate the habituation memory, by the number of crossings, in this previously explored environment.

Object and Food Recognition tasks

Object Recognition task was performed in the same apparatus, 24h after the Open Field habituation task. Training session consisted in placing two identical objects (two glass bottles or two big Lego blocks) on the box floor, equidistant in relation to the walls, and animals could explore them individually for 5min. After 24h, test session occurred: animals were placed back in the same box, but one of the familiar objects used in the training session was replaced by a new object, different from the familiar (bottle or Lego block). Objects were counterbalanced between animals. Animals remained in the box for 5min. Exploration of object was considered as to smell or to touch object with vibrissae (rearing or climbing on the object was not defined as exploration). OpenFLD 1.0 software (designed by Stéfano Pupe Johann, Porto Alegre, Brazil) was used for videos analysis. A preference ratio, which is ratio between the time spent exploring new object on the total time spent exploring both objects in test session, was used as measurement of recognition memory. This data was compared with the fixed value of 0.5, which means no difference in exploration of new or old objects

(55,57). Twenty-four hours after performing Object Recognition task, Food Recognition task took place. It was similar to the task described above, but using portions of hyperpalatable foods (Moça Flakes Nestlè® e o Cheetos PepsiCo®) in place of bottles and blocks of Lego®. These foods have strong odor of condensed milk and cheese, respectively, and animals could exploit them with their nose, being a way to evaluate the capacity to distinguish the type (smell) of food. In a pilot experiment, it was shown that rats prefer Flakes Nestlè® and Cheetos PepsiCo® equally to standard ration (data not shown).

Search for Food task

Five days after performing Food Recognition task, animals underwent Search for Food task (58) in an acrylic box with 42x67x46cm. The box floor had nine holes, measuring 4cm in diameter and 1cm deep, covered with wood shavings. The task consisted of 3 phases: (1) on the first day (habituation day), the animals explored the box for ten minutes and received a small piece of chocolate (1.5 g/rat) upon returning to the housing cage; (2) from the second to fourth day (training days), animals had restricted feeding during the previous night (about 80% of habitual intake), explored the box for ten minutes, and received a small piece of chocolate (1.5 g/rat) upon returning to the housing cage; (3) on the fifth day (testing day), the animals were fasted overnight and explored the box for ten minutes. On this day, however, two holes of the box floor contained a piece of chocolate (1.5 g) hidden under wood shavings. The latency to find chocolates was analyzed.

Food intake monitoring

Approximately 35 days after Search for Food task, the animals had their food consumption computed through an episodic measurement system (BioDAQ® Food intake monitoring system, Research Diets) as previously described (59). Rats remained individually in transparent cages for 5 days and the task consisted of 3 phases: (1) on the first day (habituation day), they received the respective diet of their group (CON or HFS); (2) from the second to the fourth day (training days), rats went through a 3-hour fast in the afternoon. After the fasting period, all rats received HFS diet for 10 minutes, so that rats from CON

group could become accustomed to HFS chow. After 10 minutes, each rat received the respective diet of their group again; (3) on fifth day (test day), all rats were fasted again for 3h, but, after the fasting period, all animals received HFS diet until the following day (and not only for 10 minutes), including rats of CON group. Analysis of the results was performed only from the first ingestion after fifth day fasting period. The purposes of this task were twofold: analyze eating behavior based on Henderson et al study (60), as intake increase and/or anticipation of a new meal is considered food memory impairment, and to calculate the entropy or predictability of the feeding pattern, feeding behavior entropy was measured in two different ways: (a) Data from the first meal after fasting of 5th day and over the following 3 hours were used to access food memory. This test period was divided in 180 1 minute beans and the animal behavior was classified into two possible states: resting or eating hyperpalatable chow. Then, entropy was measured by Shannon entropy, calculating the probabilities to be in each of the two states for all rats together and producing a measure known as the entropy rate (66), and (b) the tolerance, r, (0.3 times standard deviation of the consumption) was calculated for each subject using the continuous measure as described in (b); there were defined that two sequences xi and xj will match if they are within a tolerance r, i.e. the distance between xi and xj is less than or equal r. For each subject, two probabilities were calculated: that two sequences of two consecutive periods will match and that two sequences of three consecutive periods will match. Further, for each subject, sample entropy was calculated as a negative logarithm of conditional probability that two sequences within a tolerance r for two consecutive periods will remain within tolerance r for the next period (67). All BioDAQ data were adjusted per 100g body weight.

Biochemical analysis

Five days after the end of behavioral tasks, rats were killed by decapitation with 4h of fasting. Fifteen minutes before death, each animal received saline 0.9% (1mL/Kg) or regular human insulin (1UI/Kg) IP in order to activate the insulin signaling cascade (68). Serum triglycerides, and glucose in saline injected rats were determined by enzymatic colorimetric methods and serum insulin by ELISA techniques using commercial kits (Rat/Mouse Insulin ELISA Kits, Millipore®, USA). The Homeostasis Assessment Model-Insulin Resistance (HOMA-

IR) was calculated using the following formula: insulin (ng/mL) × glucose (mg/dL)/22.5. Retroperitoneal and perigonadal adipose tissue were identified by direct inspection, dissected, placed in a Petri dish and weighed using a scale accurate to 0.01g (Marte®, Canoas, Brazil) immediately after decapitation.

Akt, phospho-Akt, SOCS-3, GluN2A, GluN2B and phospho-GluN2B quantification occurred through Western blotting technique in hippocampus punches (69). SOCS-3 had also been quantified in the hypothalamus to confirm if insulin resistance has reached other brain areas, considering that this region is abundant in insulin receptors and more susceptible to variations of this hormone (70). Membranes of cytosolic (6000rpm at 4ºC for 90 seconds) and membrane (13000rpm at 4ºC for 300seconds) extractions were incubated overnight at 4°C with primary antibody (anti-rabbit Akt, phospho-Ser473-Akt or SOCS3, Cell Signaling® in samples of hippocampal and hypothalamic cytosol extracts; anti-rabbit NR2B, NR2A, Millipore® or phospho-Tyr1472-NR2B Sigma-Aldrich® in samples of hippocampal membrane extracts). The next day, membranes were incubated for 2h with secondary antibody (anti-rabbit IgG-HRP, Cell Signaling®). To obtain the quantification of a standard protein, membranes were subsequently incubated overnight at 4°C with anti-α-tubulin antibody (Sigma-Aldrich®), and the next day they were incubated with respective secondary antibody (anti-mouse IgG-HRP, Cell Signaling®). Revelation was carried out using ImageQuant TL software (Image Quant TL, GE Heathcare®). Protein quantification from images was calculated using ImageJ 1.50i software (Wayne Rasband, National Institutes of Health, USA, http://imagej.nih.gov/ij).

Statistical analysis

Data were expressed as mean ±standard deviation (SD). Student's T-test was used for birth and weaning weight analysis, and protein quantification comparing groups with saline or insulin injection. We used Analysis of Variance test (ANOVA) for repeated measures (RM) with Tukey post-hoc test for the body weight evolution and memory of habituation on Open Field task or Two-way ANOVA test with Bonferroni post-hoc test for adipose tissue index, Open Field, Object and Food Recognition, Search for Food tasks, BioDAQ measures, and all biochemical analysis. At last, Object and Food Recognition tasks were after analyzed by using

a One-sample Student's T-test, by comparing group's means with the fixed value of 0.5, and Sample entropy consumption on BioDAQ, by One-way ANOVA test with Sheffe post-hoc test. In all cases, statistical level of significance was set as $p<0.05$.

Results

Behavioral results

There was no interaction between fetal growth and diet, neither any isolated effect of fetal growth nor diet in the time spent on the periphery and in the number of total crossings in the Open Field task (Figure 2). On the second day of exposure to the Open Field task, there was a significant effect of time in reducing the number of crossings (RM ANOVA, $F(1, 36) = 36.18$, $p<0.0001$), but no isolated effect of fetal growth and diet, neither interaction between fetal growth, diet and time. In addition, there was no isolated effect of fetal growth and diet, neither interaction in the preference ratio for objects or for foods presented on the test day on Object and Food Recognition tasks (Figure 3). All groups had preference higher than 0.5 for the new object presented on the test day of Object Recognition task, but only FR-HFS group did it for the new food on the test day of Food Recognition task (One-sample Student's T-test, $p<0.05$).

In the Search for Food task, there were no isolated effects of fetal growth and diet, nor any interaction in the latency for finding the chocolate (Figure 4). The same happened with post-meal interval and satiety of first meal of the BioDAQ® test (Table 1), with no isolated effects of fetal growth and diet, nor interaction between them. However, there was an isolated effect of diet, with Adlib-CON and FR-CON groups ingesting more hyperpalatable chow on first meal (in grams and in calories) (Two-way ANOVA, $F(1,30)= 13.21$, $p=0.001$ and $F(1,30)= 5.58$, $p=0.0249$, respectively), second meal (in grams) ($F(1,24)= 4.56$, $p=0.0431$) and during all the time of the test (in grams and tended in calories) ($F(1,44)= 28.96$, $p<0.0001$ and $F(1,44)= 3.20$, $p=0.0804$, respectively) than Adlib-HFS and FR-HFS groups. The CON groups also had longer first meal and Shannon and Sample entropy than HFS groups ($F(1,30)= 18.15$, $p=0.0002$, $F(1,43)= 14.30$, $p=0.0005$ and $F(1,43)=19.70$, $p<0.0001$, respectively). When analyzing the four groups (One-way ANOVA, $F(1,43)= 6.807$, $p=0.001$),

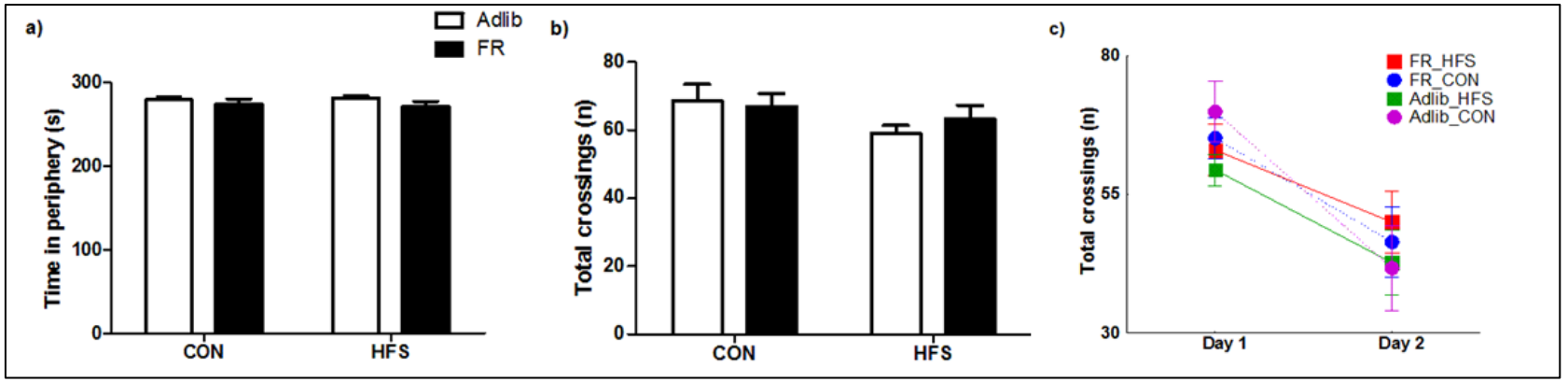

Figure 2: Anxiety-like and locomotion behaviors on Open Field task. There was no isolated effect of fetal growth and diet, neither interaction between them in time spent on periphery (a) and in total crossings on flor (b) of the box (Two-way ANOVA, $p>0.05$). On the second day of exposure to the Open Field task (c), there was only the effect of time on the reduction of crossings (RM ANOVA, $p<0.0001$). Adlib: *ad libitum* control chow feeding during gestation; FR: restricted control chow feeding during gestation; CON: control diet; HFS: high-fat and sugar diet.

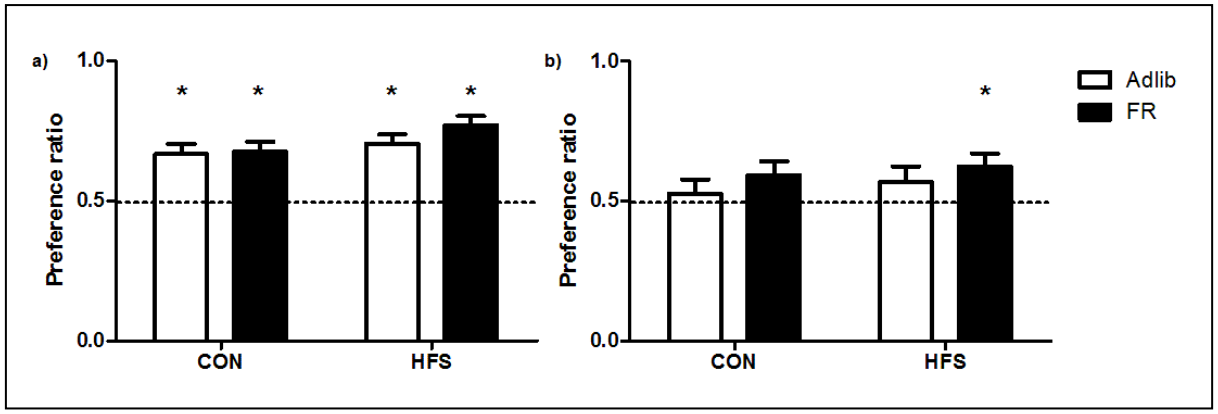

Figure 3: Behavior on Object and Food Recognition tasks. There was no isolated effect of fetal growth and diet, neither interaction between them in the preference ratio for objects (a) or for foods (b) presented on test day (Two-way ANOVA, $p>0.05$). All groups presented a preference significantly higher than 0.5 for the new object presented on the test day of Object Recognition task, but only FR-HFS group did it for the new food on Food Recognition task (*One-sample Student's T-test, $p<0.05$). Adlib: *ad libitum* control chow feeding during gestation; FR: restricted control chow feeding during gestation; CON: control diet; HFS: high-fat and sugar diet.

Sample Entropy in Adlib-HFS and FR-HFS groups was found significantly lower than that of Adlib-CON group (Scheff post-hoc test, p=0.006 and p=0.004, respectively), with FR-CON being in between, similar to all groups. Furthermore, there was an isolated effect of fetal growth on the consumption of the second meal (tendency in grams and in calories) (Two-way ANOVA, F(1,24)= 3.33, p=0.0806 and F(1,24)= 3.43, p=0.0764, respectively) and of total time of the test (in grams and in calories) (F(1,44)= 10.64, p=0.0021 and F(1,44)= 14.22, p=0.0005, respectively), with poor fetal growth reducing intake. The FR-CON and FR-HFS group had lower intake than Adlib-CON (in grams and calories) and Adlib-HFS (in calories), respectively, in total time of the test (Bonferroni post-hoc test, p<0.05). No interaction between fetal growth and diet was detected in any feeding measure on BioDAQ®.

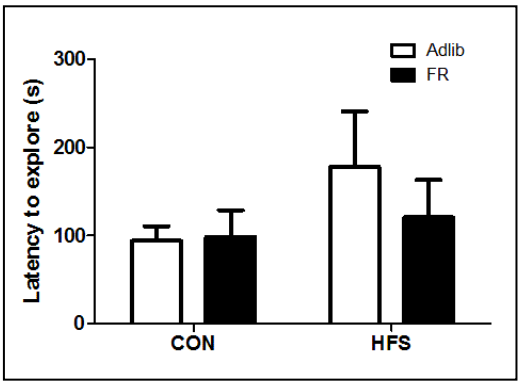

Figure 4: Behavior on Search for Food task. The four groups took the same time to find chocolate (Two-way ANOVA, p<0.05). Adlib: *ad libitum* control chow feeding during gestation; FR: restricted control chow feeding during gestation; CON: control diet; HFS: high-fat and sugar diet.

Metabolic and biochemical results

Offspring of food restricted mothers were born with smaller body weight (5.5 ± 0.8 g) than the offspring of Adlib ones (Student's T-test, 6.6 ± 0.3 g, p=0.009). At 21 days of age, male pups of both groups had equivalent body weight (FR group 56.29 ± 7.13 g and Adlib group 57.52 ± 4.0 g, p=0.3). For body weight gain, a significant interaction between fetal growth, diet and time of treatment was found (RM ANOVA, F (26,1112) = 1,73, p= 0.01), with FR-HFS group gaining more weight than the other groups, as well as between fetal growth and time of treatment (F(26,1112) = 1.84, p= 0.006), and between diet and time (F(26,1112) = 41.52, p<0.001), with poor fetal growth and HFS diet fed groups being heavier throughout the experiment (Figure 5). There were isolated effects of time (F(26,1112) = 2728.30, p< 0.001) and diet (F(1,44) = 30.21, p< 0.001), in which body weight increased throughout time in all groups, and those who were fed with HFS diet had higher body weight. No interaction

Table 1. Feeding pattern on BioDAQ®.

Measures	Adlib-CON			Ad lib-HFS			FR-CON			FR-HFS			*P*		
	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD	n	Inter.	Fetal growth	Diet
1st meal of test†															
Consumption (g)	0.528	0.415	8	0.188	0.105	7	0.612	0.338	11	0.212	0.145	8	0.769	0.601	0.001
Consumption (kcal)	1.615	1.271	8	0.908	0.504	7	1.872	1.035	11	1.022	0.697	8	0.830	0.578	0.025
Duration (s)	488.0	346.7	8	194.5	114.2	7	563.6	244.8	11	177.8	90.84	8	0.567	0.715	<0.001
Post-meal interval (s)	946.6	1,853.0	8	707.4	587.2	7	1,646.00	4,345.0	11	1,046.0	1,079.0	8	0.850	0.588	0.661
Satiety	932.4	2501	8	174.0	185.7	7	136.5	293.4	11	206.5	213.7	8	0.339	0.378	0.426
2st meal of test†															
Consumption (g)	0.330	0.251	7	0.114	0.118	6	0.134	0.153	10	0.073	0.046	5	0.246	0.081	0.043
Consumption (kcal)	1.012	0.769	7	0.549	0.570	6	0.411	0.468	10	0.350	0.223	5	0.362	0.076	0.238
3h of test†															
Shannon entropy	0.100	0.049	12	0.074	0.019	12	0.111	0.039	12	0.060	0.021	11	0.219	0.865	<0.001
Sample entropy	0.122	0.084	12	0.036	0.025	12	0.102	0.074	12	0.031	0.033	11	0.660	0.463	<0.001
Total time of the test															
Consumption (g)	2.962	1.469	12	1.312	0.562	12	1.856*	0.759	12	0.744	0.327	12	0.300	0.002	<0.001
Consumption (kcal)	8.923	4.359	12	6.323	2.711	12	5.679*	2.324	12	3.588*	1.577	12	0.698	<0.001	0.080

Mean values with their standard deviations and number of rats. All measures were adjusted for body weight. SD: standard deviation; Inter.: interaction between fetal growth and diet; Adlib: ad libitum control chow feeding during gestation; FR: restricted control chow feeding during gestation; CON: control diet; HFS: high-fat and sugar diet; Adlib-CON: offspring from Adlib dams fed with CON; Adlib-HFS: offspring from Adlib dams fed with HFS; FR-CON: offspring from FR dams fed with CON; FR-HFS: offspring from FR dams fed with HFS; Satiety: post meal interval divided per consumption (kcal). *Significantly different from Adlib-CON; **Significantly different from Adlib-HFS (Bonferroni post-hoc test, $p<0.05$). †Some animals were excluded because did not started to eat immediately after the end of fasting and/or they took more than 3h to have the second meal.

between fetal growth and diet and isolated fetal growth effect were observed in body weight gain. Tukey post-hoc test revealed that Adlib-HFS group showed greater body weight as compared to Adlib-CON group from week 20 of intervention onwards (Tukey test, $p<0.05$) and FR-CON group from week 21 onwards ($p<0.05$), except on 23. FR-HFS group showed higher weight than Adlib-CON and FR-CON groups from weeks 14 and 16 onwards, respectively ($p<0.05$).

Adipose tissue weight and biochemical data are presented in Table 2. It was observed an isolated effect of diet on all parameters analyzed: perigonadal and retroperitoneal adipose tissue weight (Two-way ANOVA, $F(1,43)= 81.72$, $p<0.001$ and $F(1,42)=128.3$, $p<0.001$, respectively), triglycerides ($F(1,20)= 5.76$, $p=0.03$), and glucose ($F(1,20)= 15.28$, $p<0.001$), insulin ($F(1,16)= 17.46$, $p=0.004$), HOMA-IR ($F(1,16)= 20.5$, $p<0.001$), with HFS diet raising all of them. There was no isolated fetal growth effect, nor interaction between fetal growth and diet, and post-hoc test showed no statistical difference between groups in any of these measures (Bonferroni post-hoc test, $p>0.05$).

Regarding hippocampal protein concentrations, there was a significant isolated effect of diet on pAkt/Akt ratio, with HFS diet reducing it (Two-way ANOVA, $F(1,19) = 12.86$, $p=0.0020$) (Table 3). Post-hoc analysis showed that FR-CON has higher pAkt/Akt ratio than Adlib-CON group ($p<0.05$). On hippocampal SOCS-3 concentration, there was significant interaction between fetal growth and diet ($F(1,19) = 4.64$, $p=0.0443$) and significant isolated effect of fetal growth ($F(1,19) = 64.21$, $p<0.0001$), with poor fetal growth increasing SOCS-3. Post-hoc analysis showed that FR-CON and FR-HFS groups have higher hippocampal SOCS-3 concentration than Adlib-CON and Adlib-HFS groups, respectively ($p<0.05$). SOCS3 concentration had a similar pattern in hypothalamic extracts, although the interaction between fetal growth and diet does not reach statistical significance ($F(1, 19) = 3.99$, $p=0.0603$) as well as the effect of fetal growth ($F(1, 19) = 3.56$, $p=0.0745$). Post-hoc showed that FR-CON group has higher hypothalamic SOCS-3 concentration than Adlib-CON group ($p<0.05$). There was no interaction between fetal growth and diet, or isolated effects of them in pGluN2B/GluN2B ration and GluN2A concentration. Insulin injection raised the hippocampal pGluN2B/GluN2B ratio (Student's T- test, 0.37 ± 0.22, $p<0.05$), compared to saline injection, in FR-CON group (0.17 ± 0.05) (Table 4).

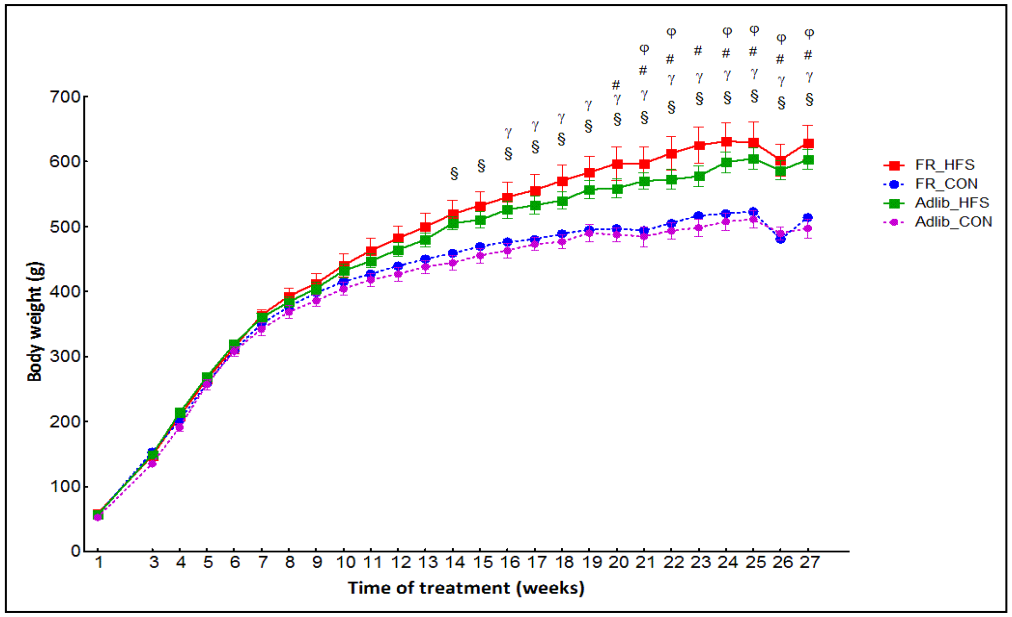

Figure 5: Evolution of body gain in male pups. Interaction was observed between fetal growth, diet and time of treatment (RM ANOVA with Tukey post-hoc test). Adlib: ad libitum control chow feeding during gestation; FR: restricted control chow feeding during gestation; CON: control diet; HFS: high-fat and sugar diet; Adlib-CON: offspring from Adlib dams fed with CON; Adlib-HFS: offspring from Adlib dams fed with HFS; FR-CON: offspring from FR dams fed with CON; FR-HFS: offspring from FR dams fed with HFS. φ: FR-CON versus Adlib-HFS; #: Adlib-CON versus Adlib-HFS; ɣ: FR-CON versus FR-HFS; §: Adlib-CON versus FR-HFS.

Table 2. Metabolic profile.

Measures	Adlib-COM			Adlib-HFS			FR-CON			FR-HFS			*P*		
	Mean	SD	N	Mean	SD	n	Mean	SD	n	Mean	SD	n	Inter.	Fetal growth	Diet
Perigonadal adipose tissue weight (%)	1.18	0.35	12	2.71	0.81	12	1.28	0.24	11	3.0	0.81	12	0.62	0.29	<0.01
Retroperitoneal adipose tissue weight (%)	1.30	0.34	12	2.71	0.81	12	1.12	0.31	10	4.03	1.24	12	0.21	0.65	<0.01
Triglycerides (mmol/L)	1.51	0.64	6	1.68	0.40	6	1.13	0.19	6	2.29	1.12	6	0.09	0.69	0.03
Glucose (mmol/L)	6.46	0.99	6	8.20	1.02	6	6.17	0.86	6	7.88	1.38	6	0.97	0.49	<0.01
Insulin (pmol/L)	366.45	130.99	6	655.72	147.49	6	407.75	199.85	6	779.1	335.55	6	0.68	0.41	<0.01
HOMA-IR	2.89	1.24	6	6.63	0.67	6	3.25	1.74	6	7.83	3.35	6	0.65	0.41	<0.01

Mean values with their standard deviations and number of rats. Adipose tissue weights were adjusted for body weight. SD: standard deviation; Inter.: interaction between fetal growth and diet; HOMA-IR: Homeostasis Assessment Model-Insulin Resistance; Adlib: *ad libitum* control chow feeding during gestation; FR: restricted control chow feeding during gestation; CON: control diet; HFS: high-fat and sugar diet; Adlib-CON: offspring from Adlib dams fed with CON; Adlib-HFS: offspring from Adlib dams fed with HFS; FR-CON: offspring from FR dams fed with CON; FR-HFS: offspring from FR dams fed with HFS. Two-way ANOVA showed only effect of diet on these measures.

Table 3. Hippocampal proteins.

Proteins	Adlib-COM			Adlib-HFS			FR-CON			FR-HFS			*P*		
	Mean	SD	N	Mean	SD	n	Mean	SD	n	Mean	SD	n	Inter.	Fetal growth	Diet
pAkt/Akt ratio	45.62	40.77	6	0.66	0.20	5	135.7*	109.4	6	0.92	0.15	6	0.09	0.09	<0.01
SOCS3	0.09	0.04	6	0.15	0.05	6	0.39*	0.12	6	0.32**	0.05	6	0.04	<0.01	0.93
SOCS3 (HT)	1.98	1.56	6	5.09	4.00	6	48.10*	55.13	6	3.78	2.21	5	0.06	0.07	0.10
pGluN2B/GluN2B ratio	1.43	1.58	6	1.43	1.97	6	0.65	0.27	6	1.06	0.53	6	0.71	0.29	0.70
GluN2A	0.76	0.69	6	0.36	0.16	6	0.66	0.46	6	0.51	0.32	6	0.49	0.89	0.15

Mean values with their standard deviations and number of rats. SD: standard deviation; Inter.: interaction between fetal growth and diet; HT: SOCS3 from hypothalamus; Adlib: *ad libitum* control chow feeding during gestation; FR: restricted control chow feeding during gestation; CON: control diet; HFS: high-fat and sugar diet; Adlib-CON: offspring from Adlib dams fed with CON; Adlib-HFS: offspring from Adlib dams fed with HFS; FR-CON: offspring from FR dams fed with CON; FR-HFS: offspring from FR dams fed with HFS. *Significantly different from Adlib-CON; **Significantly different from Adlib-HFS (Bonferroni post-hoc test, $p<0.05$).

Table 4. Hippocampal proteins after intraperitoneal injection of saline or insulin.

Proteins	Adlib-COM						Adlib-HFS						FR-CON						FR-HFS					
	Saline			Insulin			Saline			Insulin			Saline			Insulin			Saline			Insulin		
	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD	n
pAkt/Akt ratio	1.12	0.26	6	0.88	0.10	5	0.23	0.15	5	0.37	0.27	5	0.90	0.27	6	1.30	0.42	6	1.94	0.98	6	3.62	1.90	4
SOCS3	0.71	0.45	6	0.46	0.08	5	0.86	0.26	5	0.75	0.23	5	0.84	0.23	6	0.70	0.07	6	0.39	0.08	6	0.30	0.17	4
pGluN2B/GluN2B ratio	0.55	0.15	6	0.65	0.28	5	0.25	0.09	6	0.21	0.10	6	0.17	0.05	6	0.37*	0.22	5	0.29	0.09	6	0.26	0.10	6
GluN2A	0.24	0.12	6	0.20	0.04	6	0.59	0.08	6	0.56	0.56	6	0.48	0.20	6	1.13	0.74	5	0.35	0.18	6	0.45	0.31	6

Mean values with their standard deviations and number of rats. SD: standard deviation; Adlib: *ad libitum* control chow feeding during gestation; FR: restricted control chow feeding during gestation; CON: control diet; HFS: high-fat and sugar diet; Adlib-CON: offspring from Adlib dams fed with CON; Adlib-HFS: offspring from Adlib dams fed with HFS; FR-CON: offspring from FR dams fed with CON; FR-HFS: offspring from FR dams fed with HFS. *Significantly different from correspondent saline group (Student's T test, $p<0.05$).

Discussion

In this study, rats exposed to poor fetal growth showed pre-resistant insulin signaling and increased hippocampal glutamatergic receptor subunit phosphorylation induced by insulin systemic injection. When restricted animals were chronically fed with hyperpalatable diet, they were capable of recognizing food novelty, a behavioral feature that was associated with hyperinsulinemia and higher body weight gain during the experiment. Intrauterine undernutrition also reduced feeding behavior entropy when the predictability of food reward was changed, suggesting a differential hippocampal activation by these food cues. These findings indicate that poor fetal growth followed by chronic high-fat and sugar intake induces altered hippocampal insulin sensitivity, and this may be reflected in risky eating behaviors favoring body weight gain and metabolic changes.

The animal model used was effective to reduce body weight of the offspring at birth, and restricted animals could catch-up their growth at weaning, as previously reported in others studies that used the same animal model (26,27,59). Restricted animals that consumed high-fat and sugar diet had greater weight gain throughout the experiment. In disagreement to our study that found an interaction between fetal growth and diet only in body weight, previous studies have shown that fetal food restricted animals had a metabolic profile that was more compromised than the control group, and when these animals were fed with high-fat diet, the differences between the groups were accentuated (71–73). Animals who consumed hyperpalatable diet, regardless intrauterine environment, had the poorer peripheral metabolic outcomes since they showed higher abdominal adiposity, triglycerides, glucose, leptin, and insulin levels and HOMA-IR index compared to the groups that were fed with a control diet. One hypothesis for this finding may be that the diet used in the study was rich in sugar as well as fat, being similarly detrimental for both control and restricted groups, since, in studies that showed a compromised metabolic profile, the hyperpalatable diet exceeded only lipids (71–73). In addition, the long treatment can be an explanation for reaching ceiling effects equally in both groups.

Intrauterine environment and diet intake interacted in hippocampal SOCS-3 concentration, suggesting that hyperpalatable diet associated with poor fetal growth

compromised hippocampal insulin function, as this molecule has a recognized role in tissue inflammation and insulin signaling (74). SOCS-3 level was also altered in hypothalamus, as well as in the nucleus accumbens and in the ventral tegmental area in a study that used the same animal model as ours (75), showing that insulin sensitivity is also altered in other brain regions. High-fat and sugar diet ingestion reduced pAkt/Akt ratio, indicating that the chronic hyperpalatable diet intake induced changes compatible to hippocampal insulin resistance. Fetal food restriction raised pAkt/Akt ratio and SOCS-3 concentration, which probably indicates a pre-insulin resistance stage, characterized for increased glucose sensitivity in the brain, with enhancement of the insulin receptor activation (69). Akt phosphorylation is one of the consequences of insulin signaling in the cell, being a molecular mechanism that contributes to the modulation of synaptic function in the hippocampal area (76). This meets the higher pGluN2B/GluN2B ratio in restricted animals that received systemic insulin injection. Possibly, insulin injection increased synaptic availability (68,76) in animals that suffered nutritional deficiency during gestation, as they present an up-regulation of NMDA receptor subunits expression in response to increased circulating levels of glucocorticoids, leading to hippocampal hyperexcitability and excitotoxic injury (77,78).

Precisely restricted rats that ingested high-fat and sugar diet were the only group to recognize the novel type of food exposed on the food recognition task, and among other metabolic modifications, they had higher body weight. It is reasonable to suggest that hyperinsulinemia in this group modulated a long-term change in hippocampal function, being reflected in the altered food memory. Recognition of novel palatable odor cues, which was already evidenced in another study with fetal restricted rats (27), suggests that poor fetal growth associated with hyperpalatable food ingestion exposes the subjects to new hedonic signals of food and palatable variability, being associated with overconsumption and overweight (79–86). The relationship of food variability with hyperinsulinemia is also intriguing, as it is known that when a new meal is offered, satiety is delayed due to peaks of insulin secretion, and the higher the food palatability, the higher insulin peak, which may progressively lead to hyperphagia and increasing body weight (87–89). Therefore, it was observed that fetal growth impairment alters insulin-dependent hippocampal function and,

when chronically exposed to hyperpalatable food, food cues recognition changes, which may be related to a long-term overconsumption and with excessive body weight gain.

Besides that, restricted rats showed decreased consumption of the hyperpalatable diet at the second meal and during the total time after fasting on the test day of food intake monitoring. This suggests a perseverance of the behavior following the conditioning situation, since rats were trained to have access to the palatable diet only for ten minutes in the days that preceded the test. On the other hand, rats that routinely ate control diet, regardless of the fetal environment, consumed more hyperpalatable diet at the first and second meals. These animals also consumed more during the whole period of food intake monitoring after fasting, but did not show change in satiety of the first meal. It suggests that the training time was not enough to get them habituated to the hyperpalatable food, which increased the hedonic/reward-related, not homeostatic-related, intake in these animals. In addition, the first meal of these animals lasted longer, and also they had higher entropy of feeding behavior compared to rats that routinely ate hyperpalatable diet. However, when the groups were analyzed independently, the restricted rats that routinely ate control diet and were exposed to the hyperpalatable diet only during food monitoring (FR-CON group) had intermediate sample entropy values, being comparable both to control animals (Adlib-CON group) and to those that ate hyperpalatable diet chronically (Adlib-HFS and FR-HFS groups). At baseline (in other words, in situations that do not involve conditioning), we recently observed that poor fetal growth increases feeding behavior entropy, suggesting a less organized and predictable behavior (75), which is in line with our other recent findings in humans showing that low birth weight individuals do not have a food platting pattern (90). However, in the current study, we evaluated feeding behavior entropy after conditioning the animals to receive hyperpalatable diet for 10 minutes after three hours of fasting, inducing a predictable hippocampal-dependent learning (62). There was a change on the day of test, since hyperpalatable diet was then available until the next day for all groups; the hippocampus is sensitive to improbable events evoking mismatch like this change in the duration of offering hyperpalatable diet and augments the response to surprising events (61,91,92). As hippocampal lesions are associated with behavioral perseveration (for instance, perseveration of conditioned responding in the absence of reward, or in the face of

changes in reward magnitude) (61–65), therefore higher feeding behavior entropy after a food conditioning may signal higher hippocampal activity. Considering that Adlib-CON group had appropriate hippocampal function, higher entropy in the feeding pattern would be expected, as indeed we observed in this experiment. In addition, if both fetal adversity and chronic high-fat and sugar diet induce hippocampal damage, this may explain the behavioral perseverance or reduction in entropy of restricted animals, and even more so in those who chronically ate the hyperpalatable diet, as hippocampal lesions lead to more predictable conditioned anticipatory stereotypies in situations predictive of food reward (62,63).

Diet and intrauterine environment did not have effects on motor activity, anxiety behavior, place habituation, and object recognition, what may indicate that food memory findings were not affected by these parameters. All groups spent the same time to find the hidden chocolate, suggesting that recognition memory related to location of an already known food is not altered by intrauterine restriction and hyperpalatable diet. On the other hand, this also may indicate that the task used was not capable to highlight this featured food memory – as it used a food known by smell and taste, not only by odor, other regions beyond the hippocampus may have been required, as amygdala and insular cortex, which may not be susceptible to the experimental conditions (93). It is also important to consider that imbalance in other neuroendocrine systems may be associated with excessive food consumption, especially hyperpalatable foods, of individuals who have suffered poor fetal growth (26–30,42,59,94–102), and that hippocampus may be altering feeding behavior through modulation of other cognitive functions (48). Further studies are needed to strength the evidence of this work considering these neuro-endocrine-behavior aspects, exploring other proteins involved in the insulin mechanism of action and in hippocampal function, besides investigating other brain regions and behavioral tasks involved in food memory regulation

In conclusion, gestational nutritional restriction with chronic ingestion of hyperpalatable diet was associated with alteration in insulin-dependent hippocampal function, food novelty recognition and feeding behavior predictability and higher body weight gain. This study contributed to point out a hormone-brain mechanism involved in a risky eating behaviors that may facilitate body weight gain and metabolic consequences in

restricted individuals, and it may help in the search for tools capable for preventing diseases in this vulnerable population.

Acknowledgements: The authors appreciate the collaboration of DOHaD group, Prof. Carla Dalmaz lab, and Experimental Research Center of Hospital de Clínicas de Porto Alegre (HCPA) members during the experimental procedures. The authors also thank the financial support by the National Council for Scientific and Technological Development and Research and Event Incentive Fund (FIPE) of HCPA. The financial backers played no role in the design and analysis of the study or in the writing of this article. The authors' contributions are as follows: A. B. M. was involved in all stages of the study design, experimental procedures, data analysis and manuscript writing; M. B. B., A. P. A. S., D. P. L. and M. A. B. were involved in experimental procedures; G. G. M. and P. P. S. contributed to the study design, data analysis and manuscript writing. The authors have no conflicts of interest to declare.

References

1. Barker DJP. Obesity and early life. Obes Rev. 2007;8(1):45–9.

2. Barker DJ. The fetal origins of type 2 diabetes mellitus. Annals of internal medicine. United States; 1999. p. 322–4.

3. Eriksson JG, Forsen T, Tuomilehto J, Jaddoe VW V, Osmond C, Barker DJP. Effects of size at birth and childhood growth on the insulin resistance syndrome in elderly individuals. Diabetologia. Germany; 2002 Mar;45(3):342–8.

4. Vaag A, Jensen CB, Poulsen P, Brons C, Pilgaard K, Grunnet L, et al. Metabolic aspects of insulin resistance in individuals born small for gestational age. Horm Res. Switzerland; 2006;65 Suppl 3:137–43.

5. Whincup PH, Kaye SJ, Owen CG, Huxley R, Cook DG, Anazawa S, et al. Birth weight and risk of type 2 diabetes: a systematic review. JAMA. United States; 2008 Dec;300(24):2886–97.

6. Lauren L, Jarvelin M-R, Elliott P, Sovio U, Spellman A, McCarthy M, et al. Relationship between birthweight and blood lipid concentrations in later life: evidence from the existing literature. Int J Epidemiol. England; 2003 Oct;32(5):862–76.

7. Davies AA, Smith GD, Ben-Shlomo Y, Litchfield P. Low birth weight is associated with higher adult total cholesterol concentration in men: findings from an occupational cohort of 25,843 employees. Circulation. United States; 2004 Sep;110(10):1258–62.

8. Pilgaard K, Hammershaimb Mosbech T, Grunnet L, Eiberg H, Van Hall G, Fallentin E, et al. Differential nongenetic impact of birth weight versus third-trimester growth velocity on glucose metabolism and magnetic resonance imaging abdominal obesity in young healthy twins. J Clin Endocrinol Metab. United States; 2011 Sep;96(9):2835–43.

9. Ravelli AC, van Der Meulen JH, Osmond C, Barker DJ, Bleker OP. Obesity at the age of 50 y in men and women exposed to famine prenatally. Am J Clin Nutr. United States; 1999 Nov;70(5):811–6.

10. Barker DJP, Osmond C, Forsen TJ, Kajantie E, Eriksson JG. Trajectories of growth among children who have coronary events as adults. N Engl J Med. United States; 2005 Oct;353(17):1802–9.

11. Law CM, Shiell AW, Newsome CA, Syddall HE, Shinebourne EA, Fayers PM, et al. Fetal, infant, and childhood growth and adult blood pressure: a longitudinal study from birth to 22 years of age. Circulation. United States; 2002 Mar;105(9):1088–92.

12. Ayres C, Agranonik M, Portella AK, Filion F, Johnston CC, Silveira PP. Intrauterine growth restriction and the fetal programming of the hedonic response to sweet taste in newborn infants. Int J Pediatr. Egypt; 2012;2012:657379.

13. Silveira PP, Agranonik M, Faras H, Portella AK, Meaney MJ, Levitan RD. Preliminary evidence for an impulsivity-based thrifty eating phenotype. Pediatr Res. United States; 2012 Mar;71(3):293–8.

14. Barbieri MA, Portella AK, Silveira PP, Bettiol H, Agranonik M, Silva AA, et al. Severe intrauterine growth restriction is associated with higher spontaneous carbohydrate intake in young women. Pediatr Res. United States; 2009 Feb;65(2):215–20.

15. Stein AD, Rundle A, Wada N, Goldbohm RA, Lumey LH. Associations of gestational exposure to famine with energy balance and macronutrient density of the diet at age 58 years differ according to the reference population used. J Nutr. United States; 2009 Aug;139(8):1555–61.

16. Kaseva N, Wehkalampi K, Hemio K, Hovi P, Jarvenpaa A-L, Andersson S, et al. Diet and nutrient intake in young adults born preterm at very low birth weight. J Pediatr. United States; 2013 Jul;163(1):43–8.

17. Lussana F, Painter RC, Ocke MC, Buller HR, Bossuyt PM, Roseboom TJ. Prenatal exposure to the Dutch famine is associated with a preference for fatty foods and a more atherogenic lipid profile. Am J Clin Nutr. United States; 2008 Dec;88(6):1648–52.

18. Perala M-M, Mannisto S, Kaartinen NE, Kajantie E, Osmond C, Barker DJP, et al. Body size at birth is associated with food and nutrient intake in adulthood. PLoS One. United States; 2012;7(9):e46139.

19. Gross LS, Li L, Ford ES, Liu S. Increased consumption of refined carbohydrates and the epidemic of type 2 diabetes in the United States: an ecologic assessment. Am J Clin Nutr. United States; 2004 May;79(5):774–9.

20. Oh K, Hu FB, Cho E, Rexrode KM, Stampfer MJ, Manson JE, et al. Carbohydrate intake, glycemic index, glycemic load, and dietary fiber in relation to risk of stroke in women. Am J Epidemiol. United States; 2005 Jan;161(2):161–9.

21. Liu S, Willett WC, Stampfer MJ, Hu FB, Franz M, Sampson L, et al. A prospective study of dietary glycemic load, carbohydrate intake, and risk of coronary heart disease in US women. Am J Clin Nutr. United States; 2000 Jun;71(6):1455–61.

22. Layman DK, Boileau RA, Erickson DJ, Painter JE, Shiue H, Sather C, et al. A reduced ratio of dietary carbohydrate to protein improves body composition and blood lipid profiles during weight loss in adult women. J Nutr. United States; 2003 Feb;133(2):411–7.

23. Portella AK, Silveira PP. Neurobehavioral determinants of nutritional security in fetal growth-restricted individuals. Ann N Y Acad Sci. United States; 2014 Dec;1331:15–33.

24. Portella AK, Silveira PP. Neurobehavioral determinants of nutritional security in fetal growth-restricted individuals. Ann N Y Acad Sci. 2014 Dec;1331(1):15–33.

25. Dalle Molle R, Bischoff AR, Portella AK, Silveira PP. The fetal programming of food preferences: current clinical and experimental evidence. J Dev Orig Health Dis. 2016 Jun 28;7(3):222–30.

26. Laureano DP, Dalle Molle R, Alves MB, Luft C, Desai M, Ross MG, et al. Intrauterine growth restriction modifies the hedonic response to sweet taste in newborn pups - Role of the accumbal mu-opioid receptors. Neuroscience. United States; 2016 May;322:500–8.

27. Alves MB, Dalle Molle R, Desai M, Ross MG, Silveira PP. Increased palatable food intake and response to food cues in intrauterine growth-restricted rats are related to

tyrosine hydroxylase content in the orbitofrontal cortex and nucleus accumbens. Behav Brain Res. Netherlands; 2015;287:73–81.

28. Desai M, Gayle D, Han G, Ross MG. Programmed Hyperphagia Due to Reduced Anorexigenic Mechanisms in Intrauterine Growth-Restricted Offspring. Reprod Sci. 2007 May 6;14(4):329–37.

29. Fukami T, Sun X, Li T, Desai M, Ross MG. Mechanism of Programmed Obesity in Intrauterine Fetal Growth Restricted Offspring: Paradoxically Enhanced Appetite Stimulation in Fed and Fasting States. Reprod Sci. 2012 Apr 16;19(4):423–30.

30. Manuel-Apolinar L, ROCHA L, DAMASIO L, TESORO-CRUZ E, ZARATE A. Role of prenatal undernutrition in the expression of serotonin, dopamine and leptin receptors in adult mice: Implications of food intake. Mol Med Rep. 2014 Feb;9(2):407–12.

31. Martimiano PH de M, da Silva GR, Coimbra VF da SA, Matos RJB, de Souza BFP, da Silva AAM, et al. Perinatal malnutrition stimulates motivation through reward and enhances drd1a receptor expression in the ventral striatum of adult mice. Pharmacol Biochem Behav. Elsevier; 2015 Jul 1;134:106–14.

32. Stevenson RJ, Francis HM. The hippocampus and the regulation of human food intake. Psychol Bull. 2017 Oct;143(10):1011–32.

33. Davidson TL, Kanoski SE, Schier LA, Clegg DJ, Benoit SC. A Potential Role for the Hippocampus in Energy Intake and Body Weight Regulation. Curr Opin Pharmacol. 2007 Dec 26;7(6):613–6.

34. Kanoski SE, Grill HJ. Hippocampus Contributions to Food Intake Control: Mnemonic, Neuroanatomical, and Endocrine Mechanisms. Biol Psychiatry. 2015 Sep;

35. Higgs S. Cognitive processing of food rewards. Appetite. 2016 Sep;104:10–7.

36. Mucellini AB, Fonseca NK de O da, Manfro GG, Silveira PP. Hippocampal insulin resistance and altered food decision-making as players on obesity risk. Neurosci Biobehav Rev. United States; 2017 Mar;77:165–76.

37. Cheke LG, Bonnici HM, Clayton NS, Simons JS. Obesity and insulin resistance are associated with reduced activity in core memory regions of the brain. Neuropsychologia. 2017;96.

38. Davidson TL, Hargrave SL, Swithers SE, Sample CH, Fu X, Kinzig KP, et al. Inter-relationships among diet, obesity and hippocampal-dependent cognitive function. Neuroscience. 2013/09/04. Center for Behavioral Neuroscience, American University,

Washington, DC, United States. Electronic address: terryd@american.edu.; 2013;253:110–22.

39. Camprubí Camprubí M, Balada Caballé R, Ortega Cano JA, Ortega de la Torre M de los A, Duran Fernández-Feijoo C, Girabent-Farrés M, et al. Learning and memory disabilities in IUGR babies: Functional and molecular analysis in a rat model. Brain Behav. 2017 Mar;7(3):e00631.

40. Lodygensky GA, Seghier ML, Warfield SK, Tolsa CB, Sizonenko S, Lazeyras F, et al. Intrauterine Growth Restriction Affects the Preterm Infant's Hippocampus. Pediatr Res. 2008 Apr;63(4):438–43.

41. Simões R V., Muñoz-Moreno E, Carbajo RJ, González-Tendero A, Illa M, Sanz-Cortés M, et al. In Vivo Detection of Perinatal Brain Metabolite Changes in a Rabbit Model of Intrauterine Growth Restriction (IUGR). Chavatte-Palmer P, editor. PLoS One. 2015 Jul 24;10(7):e0131310.

42. Lesage J, Blondeau B, Grino M, Bréant B, Dupouy JP. Maternal Undernutrition during Late Gestation Induces Fetal Overexposure to Glucocorticoids and Intrauterine Growth Retardation, and Disturbs the Hypothalamo-Pituitary Adrenal Axis in the Newborn Rat 1. Endocrinology. 2001 May;142(5):1692–702.

43. Ruff CA, Faulkner SD, Rumajogee P, Beldick S, Foltz W, Corrigan J, et al. The extent of intrauterine growth restriction determines the severity of cerebral injury and neurobehavioural deficits in rodents. Baud O, editor. PLoS One. 2017 Sep 21;12(9):e0184653.

44. Zhang Y, Wei J, Yang Z. Perinatal undernutrition attenuates field excitatory postsynaptic potentials and influences dendritic spine density and morphology in hippocampus of male rat offspring. Neuroscience. 2013 Aug 6;244:31–41.

45. Dieni S, Rees S. Dendritic morphology is altered in hippocampal neurons following prenatal compromise. J Neurobiol. 2003 Apr;55(1):41–52.

46. Kuchna I. Quantitative studies of human newborns' hippocampal pyramidal cells after perinatal hypoxia. Folia Neuropathol. 1994;32(1):9–16.

47. Duran Fernandez-Feijoo C, Carrasco Carrasco C, Villalmazo Francisco N, Cebria Romero J, Fernandez Lorenzo JR, Jimenez-Chillaron JC, et al. Influence of catch up growth on spatial learning and memory in a mouse model of intrauterine growth restriction. PLoS One. United States; 2017;12(5):e0177468.

48. Hales CN, Barker DJ. Type 2 (non-insulin-dependent) diabetes mellitus: the thrifty phenotype hypothesis. Diabetologia. 1992 Jul;35(7):595–601.

49. Simmons RA, Templeton LJ, Gertz SJ. Intrauterine growth retardation leads to the development of type 2 diabetes in the rat. Diabetes. 2001 Oct;50(10):2279–86.

50. Isaacs EB, Lucas A, Chong WK, Wood SJ, Johnson CL, Marshall C, et al. Hippocampal volume and everyday memory in children of very low birth weight. Pediatr Res. 2000 Jun;47(6):713–20.

51. Camprubí Camprubí M, Balada Caballé R, Ortega Cano JA, Ortega de la Torre M de LA, Duran Fernández-Feijoo C, Girabent-Farrés M, et al. Learning and memory disabilities in IUGR babies: Functional and molecular analysis in a rat model. Brain Behav. 2017 Mar;7(3):e00631.

52. Barker DJP. The developmental origins of chronic adult disease. Acta Paediatr Suppl. Norway; 2004 Dec;93(446):26–33.

53. Mucellini AB, Goularte JF, da Cunha AC de A, Caceres RC, Noschang C, Benetti C da S, et al. Effects of exposure to cafeteria diet during gestation and after weaning on metabolism and body weight of adult male offspring in rats (vol 111, pg 1499, 2014). Br J Nutr. 2014;112(1):142–3.

54. Parent MB, Darling JN, Henderson YO. Remembering to eat: hippocampal regulation of meal onset. Am J Physiol Regul Integr Comp Physiol. 2014/02/28. Neuroscience Institute, Georgia State University, Atlanta, Georgia and Department of Psychology, Georgia State University, Atlanta, Georgia mbparent@gsu.edu. Neuroscience Institute, Georgia State University, Atlanta, Georgia and.; 2014;306(10):R701-13.

55. Hammond RS, Tull LE, Stackman RW. On the delay-dependent involvement of the hippocampus in object recognition memory. Neurobiol Learn Mem. 2004/06/09. Department of Behavioral Neuroscience, Oregon Health and Science University, Portland, OR 97239, USA.; 2004;82(1):26–34.

56. Tran DMD, Westbrook RF. Rats Fed a Diet Rich in Fats and Sugars Are Impaired in the Use of Spatial Geometry. Psychol Sci. SAGE PublicationsSage CA: Los Angeles, CA; 2015 Dec 2;26(12):1947–57.

57. Clarke JR, Cammarota M, Gruart A, Izquierdo I, Delgado-García JM. Plastic modifications induced by object recognition memory processing. Proc Natl Acad Sci . 2010 Feb 9;107(6):2652–7.

58. Noschang C, Krolow R, Arcego DM, Laureano D, Fitarelli LD, Huffell AP, et al. The influence of early life interventions on olfactory memory related to palatable food, and on oxidative stress parameters and Na+/K+-ATPase activity in the hippocampus and olfactory bulb of female adult rats. Neurochem Res. United States; 2012 Aug;37(8):1801–10.

59. Dalle Molle R, Laureano DP, Alves MB, Reis TM, Desai M, Ross MG, et al. Intrauterine growth restriction increases the preference for palatable foods and affects sensitivity to food rewards in male and female adult rats. Brain Res. Netherlands; 2015 Aug;1618:41–9.

60. Henderson YO, Smith GP, Parent MB. Hippocampal neurons inhibit meal onset. Hippocampus. United States; 2013 Jan;23(1):100–7.

61. Strange BA, Duggins A, Penny W, Dolan RJ, Friston KJ. Information theory, novelty and hippocampal responses: unpredicted or unpredictable? Neural Networks. 2005 Apr;18(3):225–30.

62. White NM, Naeem M. Learning not to respond: Role of the hippocampus in withholding responses during omission training. Behav Brain Res. 2017 Feb 1;318:61–70.

63. Ito R, Everitt BJ, Robbins TW. The hippocampus and appetitive Pavlovian conditioning: Effects of excitotoxic hippocampal lesions on conditioned locomotor activity and autoshaping. Hippocampus. 2005;15(6):713–21.

64. Jarrard LE, Isaacson RL. Runway response preservation in the hippocampectomized rat: determined by extinction variables. Nature. 1965;207:109–10.

65. Flaherty CF, Coppotelli C, Hsu D, Otto T. Excitotoxic lesions of the hippocampus disrupt runway but not consummatory contrast. Behav Brain Res. 1998 Jun;93(1–2):1–9.

66. Molet J, Heins K, Zhuo X, Mei YT, Regev L, Baram TZ, et al. Fragmentation and high entropy of neonatal experience predict adolescent emotional outcome. Transl Psychiatry. Nature Publishing Group; 2016 Jan 5;6(1):e702.

67. Richman JS, Moorman JR. Physiological time-series analysis using approximate entropy and sample entropy. Am J Physiol Heart Circ Physiol. 2000 Jun;278(6):H2039-49.

68. Muller AP, Gnoatto J, Moreira JD, Zimmer ER, Haas CB, Lulhier F, et al. Exercise increases insulin signaling in the hippocampus: physiological effects and pharmacological impact of intracerebroventricular insulin administration in mice. Hippocampus. United States; 2011 Oct;21(10):1082–92.

69. Paxinos G, Watson C. The rat brain in stereotaxic coordinates. 6th ed. Elsevier; 2007.

70. Steculorum SM, Solas M, Bruning JC. The paradox of neuronal insulin action and resistance in the development of aging-associated diseases. Alzheimers Dement TA - Alzheimers, Dement. Department of Mouse Genetics and Metabolism, Institute for Genetics, University of Cologne, Koln, Germany Center for Endocrinology, Diabetes and Preventive Medicine, University Hospital Cologne, Koln, Germany Center for Molecular Medicine Cologne, Koln, G; 2014;(1552–5279 (Electronic)).

71. Rueda-Clausen CF, Dolinsky VW, Morton JS, Proctor SD, Dyck JRB, Davidge ST. Hypoxia-induced intrauterine growth restriction increases the susceptibility of rats to high-fat diet-induced metabolic syndrome. Diabetes. United States; 2011 Feb;60(2):507–16.

72. Zinkhan EK, Chin JR, Zalla JM, Yu B, Numpang B, Yu X, et al. Combination of intrauterine growth restriction and a high-fat diet impairs cholesterol elimination in rats. Pediatr Res. United States; 2014 Nov;76(5):432–40.

73. Yan H, Zheng P, Yu B, Yu J, Mao X, He J, et al. Postnatal high-fat diet enhances ectopic fat deposition in pigs with intrauterine growth retardation. Eur J Nutr. Germany; 2017 Mar;56(2):483–90.

74. Torisu T, Sato N, Yoshiga D, Kobayashi T, Yoshioka T, Mori H, et al. The dual function of hepatic SOCS3 in insulin resistance in vivo. Genes Cells. England; 2007 Feb;12(2):143–54.

75. Laureano DP, Alves MB, Miguel P, Machado TD, Reis AR, Mucellini AB, et al. Intrauterine growth restriction modifies the accumbal dopaminergic response to palatable food intake. Manuscr Submitt Publ. 2017;

76. Lee C-C, Huang C-C, Wu M-Y, Hsu K-S. Insulin stimulates postsynaptic density-95 protein translation via the phosphoinositide 3-kinase-Akt-mammalian target of rapamycin signaling pathway. J Biol Chem. United States; 2005 May;280(18):18543–50.

77. Schober ME, McKnight RA, Yu X, Callaway CW, Ke X, Lane RH. Intrauterine growth restriction due to uteroplacental insufficiency decreased white matter and altered NMDAR subunit composition in juvenile rat hippocampi. Am J Physiol Regul Integr Comp Physiol. American Physiological Society; 2009 Mar 1;296(3):R681-92.

78. Schober ME, McKnight RA, Yu X, Callaway CW, Ke X, Lane RH. Intrauterine growth restriction affects postnatal cerebral N-methyl-D=aspartate receptor subtype expression. J Investig Med. BMJ Publishing Group Limited; 2006 Jan 1;54(1):S161.2-S161.

79. Raynor HA, Jeffery RW, Phelan S, Hill JO, Wing RR. Amount of Food Group Variety Consumed in the Diet and Long-Term Weight Loss Maintenance. Obes Res. 2005 May;13(5):883–90.

80. McCrory MA, Fuss PJ, McCallum JE, Yao M, Vinken AG, Hays NP, et al. Dietary variety within food groups: association with energy intake and body fatness in men and women. Am J Clin Nutr. 1999 Mar;69(3):440–7.

81. Raynor HA, Epstein LH. Dietary variety, energy regulation, and obesity. Psychol Bull. 2001 May;127(3):325–41.

82. Thrailkill EA, Epstein LH, Bouton ME. Effects of inter-food interval on the variety effect in an instrumental food-seeking task. Clarifying the role of habituation. Appetite. 2015 Jan;84:43–53.

83. Wilkinson LL, Hinton EC, Fay SH, Rogers PJ, Brunstrom JM. The “variety effect” is anticipated in meal planning. Appetite. 2013 Jan;60(1):175–9.

84. Johnson F, Wardle J. Variety, Palatability, and Obesity. Adv Nutr An Int Rev J. 2014 Nov 1;5(6):851–9.

85. Hetherington MM. Cues to overeat: psychological factors influencing overconsumption. Proc Nutr Soc. 2007;66(1):113–23.

86. Moller P, Koster EP. Variety and overeating: comments on long-term habituation to food. Am J Clin Nutr. 2012 Apr 1;95(4):981–981.

87. Louis-Sylvestre J, Le Magnen J. [Cephalic phase of insulin secretion and the variety of the food in rat feed]. Reprod Nutr Dev. 1983;23(2 B):351–6.

88. Bellisle F, Louis-Sylvestre J, Demozay F, Blazy D, Le Magnen J. Cephalic phase of insulin secretion and food stimulation in humans: a new perspective. Am J Physiol. 1985 Dec;249(6 Pt 1):E639-45.

89. Louis-Sylvestre J, Le Magnen J. Palatability and preabsorptive insulin release. Neurosci Biobehav Rev. 1980;4 Suppl 1:43–6.

90. Mucellini AB, Molle RD, Rodrigues DM, Machado TD, Reis RS, Toazza R, et al. Insulin sensitivity, hippocampal size and the vicious cycle of obesity in individuals born small for gestational age. Manuscr Submitt Publ. 2017;

91. Harrison LM, Duggins A, Friston KJ. Encoding uncertainty in the hippocampus. Neural Networks. 2006 Jun;19(5):535–46.

92. Schiffer A-M, Ahlheim C, Wurm MF, Schubotz RI. Surprised at All the Entropy: Hippocampal, Caudate and Midbrain Contributions to Learning from Prediction Errors. Kiebel SJ, editor. PLoS One. Public Library of Science; 2012 May 3;7(5):e36445.

93. Bermudez-Rattoni F, Núñez-Jaramillo L, Balderas I. Neurobiology of Taste-recognition Memory Formation. Chem Senses. Oxford University Press; 2005 Jan 1;30(Supplement 1):i156–7.

94. French SJ, Totterdell S. Individual nucleus accumbens-projection neurons receive both basolateral amygdala and ventral subicular afferents in rats. Neuroscience. 2003;119(1):19–31.

95. Vucetic Z, Totoki K, Schoch H, Whitaker KW, Hill-Smith T, Lucki I, et al. Early life protein restriction alters dopamine circuitry. Neuroscience. 2010 Jun 30;168(2):359–70.

96. Silveira PP, Pokhvisneva I, Gaudreau H, Atkinson L, Fleming AS, Sokolowski MB, et al. Fetal growth interacts with multilocus genetic score reflecting dopamine signaling capacity to predict spontaneous sugar intake in children. Appetite. 2017 Oct;

97. Delahaye F, Breton C, Risold P-Y, Enache M, Dutriez-Casteloot I, Laborie C, et al. Maternal Perinatal Undernutrition Drastically Reduces Postnatal Leptin Surge and Affects the Development of Arcuate Nucleus Proopiomelanocortin Neurons in Neonatal Male Rat Pups. Endocrinology. 2008 Feb;149(2):470–5.

98. Yousheng Jia Y, Nguyen T, Desai M, Ross MG. Programmed Alterations in Hypothalamic Neuronal Orexigenic Responses to Ghrelin Following Gestational Nutrient Restriction. Reprod Sci. SAGE PublicationsSage CA: Los Angeles, CA; 2008 Sep 18;15(7):702–9.

99. Orozco-Solís R, Matos RJB, Lopes de Souza S, Grit I, Kaeffer B, Manhães de Castro R, et al. Perinatal nutrient restriction induces long-lasting alterations in the circadian expression pattern of genes regulating food intake and energy metabolism. Int J Obes. Nature Publishing Group; 2011 Jul 9;35(7):990–1000.

100. Remmers F, Verhagen LAW, Adan RAH, Delemarre-van de Waal HA. Hypothalamic Neuropeptide Expression of Juvenile and Middle-Aged Rats after Early Postnatal Food Restriction. Endocrinology. 2008 Jul;149(7):3617–25.

101. Vieau D, Sebaai N, Léonhardt M, Dutriez-Casteloot I, Molendi-Coste O, Laborie C, et al. HPA axis programming by maternal undernutrition in the male rat offspring. Psychoneuroendocrinology. 2007 Aug;32:S16–20.

102. Wixey JA, Chand KK, Colditz PB, Bjorkman ST. Review: Neuroinflammation in intrauterine growth restriction. Placenta. 2017 Jun;54:117–24.

5. CONSIDERAÇÕES FINAIS

Esta tese de Doutorado teve como objetivo geral testar a hipótese do ciclo vicioso da obesidade em indivíduos nascidos com baixo peso, investigando, através de um delineamento translacional, se a resistência à insulina estaria associada ao processamento cognitivo diferencial frente aos alimentos nestes sujeitos. Os pressupostos desta hipótese foram inicialmente discutidos e revisados na carta ao editor *Tackling obesity: challenges ahead* e no artigo de revisão *Hippocampal insulin resistance and altered food decision-making as players on obesity risk*.

No artigo clínico *The vicious cycle of obesity: insulin sensitivity and cognitive processes involved in eating behavior of individuals born small for gestational age*, o primeiro objetivo foi investigar se a sensibilidade à insulina estaria correlacionada à ativação cerebral diferencial frente a imagens de alimentos hiperpalatáveis, assim como se estaria associada a variações na memória implícita alimentar, em adolescentes saudáveis representando todo o espectro de peso ao nascer. Os resultados mostraram que o índice de resistência à insulina se correlacionou positivamente com a ativação do cúneo, região reconhecida na atenção visual, e negativamente com o lobo frontal médio esquerdo, giro frontal superior e precúneo, áreas com papel no controle cognitivo inibitório, quando imagens de alimentos hiperpalatáveis eram visualizadas, em comparação à visualização de objetos neutros. Além disso, o índice de resistência à insulina e a insulinemia apresentaram-se mais altos nos indivíduos que não escolheram o seu lanche consumido meses antes no teste de escolha do lanche, mostrando prejuízo na memória alimentar implícita. Com esses dados, sugeriu-se que a sensibilidade à insulina está correlacionada com o processamento cognitivo alimentar, podendo fazer parte da modulação do comportamento alimentar de risco para doenças relacionadas à obesidade.

O artigo clínico também teve como objetivo averiguar se o baixo peso ao nascer estaria associado a um comportamento alimentar obesogênico e à alteração do tamanho hipocampal e da sensibilidade à insulina em adolescentes. Foi encontrado que os indivíduos nascidos com baixo peso consumiram alimentos com maior densidade calórica e

apresentaram prejuízo na memória alimentar implícita e menor volume do subículo hipocampal. Ainda, a interação entre o índice de resistência à insulina e a razão de peso ao nascer prediz a ingestão alimentar externa. A partir dessas evidências, concluiu-se que alterações no hipocampo e na sensibilidade à insulina estão associadas às diferenças no comportamento alimentar de indivíduos pequenos para a idade gestacional, o que indica que os processos cognitivos e a regulação hormonal parecem ser elementos da ingestão alimentar de risco para complicações metabólicas destes sujeitos.

O artigo experimental *Hippocampal insulin sensitivity and behavioral reactivity to food cues in adult rats exposed to poor fetal growth* investigou se a restrição fetal induzida por desnutrição gestacional em ratos teria implicações na função hipocampal dependente de insulina, na memória e previsibilidade alimentares, no consumo de dieta hiperpalatável e no estado metabólico e peso corporal. Além disso, verificou se a exposição crônica à dieta hiperpalatável influenciaria nesses desfechos. Encontrou-se o baixo peso ao nascer associado ao um estado de pré-resistência à insulina hipocampal, ao aumento na fosforilação do receptor glutamatérgico dessa região induzida por insulina e a reduzidas ingestão e entropia quando a previsibilidade da recompensa alimentar hiperpalatável foi alterada. Quando os animais restritos ingeriram cronicamente a dieta hiperpalatável, foram capazes de reconhecer a novidade alimentar e apresentaram maior peso corporal ao longo do experimento. Esses resultados indicaram que o baixo peso ao nascer altera a função insulínica hipocampal e, quando, associado à ingestão crônica de dieta hiperpalatável, parece alterar o comportamento alimentar em favor do ganho de peso corporal.

Com base nas evidências encontradas e sintetizadas na Tabela 1, sugere-se que a resistência à insulina parece (a) modificar a habilidade de estabelecer um padrão alimentar e (b) estar associada às modificações funcionais do hipocampo no baixo peso ao nascer, (c) o que pode explicar as mudanças de comportamento alimentar nesta população. Portanto, as evidências sustentam a hipótese de que os indivíduos nascidos com baixo peso seriam mais propensos ao ciclo vicioso da obesidade, indicando que a resistência à insulina pode estar modulando as funções hipocampais que participam dos processos cognitivos frente aos alimentos (Figura 1): desde a infância, são mais sensíveis à insulina e preferem alimentos

hiperpalatáveis; a maior ingestão desses alimentos induz progressivamente a resistência à insulina; a alteração na sinalização de insulina hipocampal prejudica a formação da memória alimentar e o controle inibitório frente a pistas alimentares; o maior consumo crônico de alimentos hiperpalatáveis rompe o equilíbrio e surgem as doenças metabólicas relacionadas à obesidade na vida adulta.

Tabela 1. Principais evidências e conclusões da pesquisa empírica.

Artigo clínico – parte I	Artigo clínico – parte II	Artigo experimental
Evidências: - A maior resistência à insulina está associada ao comprometimento da memória alimentar implícita; - Quanto maior a resistência à insulina, maior ativação de áreas cerebrais associadas à atenção e menor ativação das associadas ao controle inibitório em frente a imagens de alimentos hiperpalatáveis. **Conclusões:** A resistência à insulina sugere modificar a habilidade de estabelecer um padrão alimentar.	**Evidências:** - O baixo peso ao nascer está associado ao comprometimento da memória alimentar implícita; - A resistência à insulina interage com o peso ao nascer ao modular a ingestão alimentar externa; - O baixo peso ao nascer está associado à redução do volume do subículo hipocampal; - O baixo peso ao nascer está associado a uma ingestão mais densamente calórica. **Conclusões:** A resistência à insulina e as modificações estruturais do hipocampo podem ter um papel no comportamento alimentar alterado dos indivíduos com baixo peso ao nascer.	**Evidências:** - O baixo peso ao nascer junto à ingestão crônica de dieta hiperpalatável está associado ao reconhecimento da novidade alimentar; - O baixo peso ao nascer está associado a menor ingestão e reduzida entropia quando há mudança na previsibilidade alimentar; - O baixo peso ao nascer está associado à resistência à insulina hipocampal e essa associação é incrementada quando junto à ingestão crônica de dieta hiperpalatável; - O baixo peso ao nascer está associado ao aumento da fosforilação do receptor glutamatérgico hipocampal induzido por insulina; - O baixo peso ao nascer junto à ingestão crônica de dieta hiperpalatável está associado ao maior ganho de peso corporal. **Conclusões:** A restrição de crescimento fetal está associada à alteração na função insulínica do hipocampo, sendo mais evidente com a ingestão de dieta hiperpalatável, o que pode explicar as mudanças de comportamento alimentar e maior ganho de peso corporal.

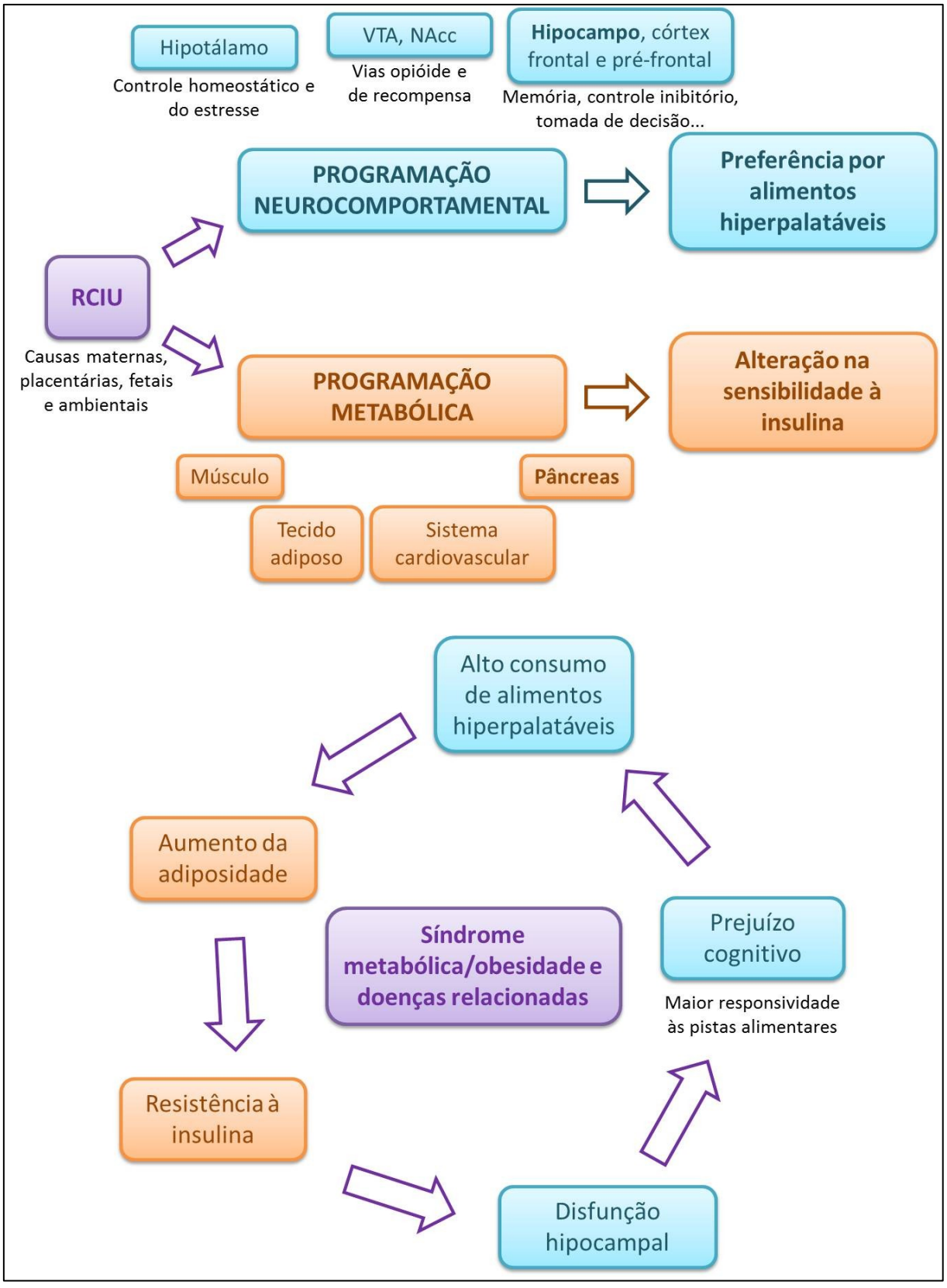

Figura 1. O ciclo vicioso da obesidade na restrição de crescimento intrauterino.

Convém considerar que o comportamento alimentar é influenciado não apenas por fatores genéticos e epigenéticos, mas também por questões culturais, e que as ciências biomédicas trabalham principalmente com probabilidades. Por tanto, os indivíduos nascidos com restrição de crescimento intrauterino não estão predeterminados às doenças metabólicas, mas possuem maior chance de desenvolvê-las do que a população em geral. As implicações dos achados desta tese estão, principalmente, em destacar a importância da vida alimentar precoce, já que é o período em que ocorre o aprendizado e o estabelecimento de hábitos alimentares saudáveis, através dos processos cognitivos relacionados à alimentação, dentre eles as memórias alimentares implícitas. A qualidade do padrão alimentar, que é influenciado pelo ambiente nutricional *intrautero* e modelado durante a vida pós-natal (78,79,180–183), pode prevenir ou aumentar a predisposição a disfunções e doenças crônicas não transmissíveis na idade adulta nas populações de risco. Além disso, os dados encontrados contribuem para o desenvolvimento de estratégias para a prevenção e reversão das morbidades metabólicas, através de (re)educação alimentar e utilização de fármacos que auxiliem na melhoria da sensibilidade à insulina, assim como a promoção de intervenções em processos cognitivos relacionados à alimentação, como o treinamento de habilidades executivas que diminuam o consumo excessivo de alimentos hiperpalatáveis (146,147).

É importante ponderar, no entanto, que são necessários estudos adicionais para compreender de forma completa a modulação dos processos cognitivos relacionados à alimentação na RCIU. Por exemplo, é preciso investigar como a atenção e a memória interagem no comportamento alimentar, dado que a atenção às pistas alimentares é maior em obesos e em comedores restritos, possivelmente interferindo na formação de memórias alimentares e gerando o consumo excessivo eventual (152). Considerando isto, o fortalecimento das memórias alimentares, através da evocação das informações da refeição precedente (como tamanho, composição, horário) e da redução de distrações durante as refeições, além do planejamento antecipado do que se servir na refeição subsequente, podem auxiliar os indivíduos nascidos com baixo peso a evitar o consumo alimentar aumentado/hiperpalatável induzido pelas pistas alimentares. Além disso, é necessário integrar o conhecimento dos mecanismos neurobiológicos envolvidos no apetite, na

saciedade, na recompensa, na impulsividade e na interpretação das pistas alimentares para elucidar de forma clara o comportamento alimentar desses indivíduos (31). Do mesmo modo, as alterações de outros mecanismos envolvidos no desenvolvimento da adiposidade e da síndrome metabólica, como a mudança na expressão e sinalização da leptina, da grelina, da colecistoquinina, da adiponectina, do *fat mass and obesity associated gene* ou gene associado à massa gorda e obesidade (112,184–186), devem ser agregadas ao papel da insulina na modulação do comportamento alimentar na RCIU. É importante também incrementar a investigação da sinalização da insulina no hipocampo e em outras regiões corticolímbicas, a fim de esclarecer como este hormônio interfere no controle cognitivo da alimentação nos indivíduos pequenos para a idade gestacional.

Por fim, esta tese apontou evidências do efeito da resistência à insulina nos processos cognitivos relacionados à alimentação, contribuindo para a compreensão do ciclo vicioso para a obesidade em humanos e roedores nascidos com baixo peso. Considerando que as intervenções dietéticas podem ser melhoradas através do conhecimento da neurobiologia do comportamento alimentar (187), os achados deste trabalho contribuem para a elaboração de estratégias específicas de prevenção e reversão das morbidades metabólicas crônicas para essa população vulnerável.

6. REFERÊNCIAS DA TESE

. Richardson DK, Gray JE, Gortmaker SL, Goldmann DA, Pursley DM, McCormick MC. Declining severity adjusted mortality: evidence of improving neonatal intensive care. Pediatrics. 1998 Oct;102(4 Pt 1):893–9.

2. Saleem T, Sajjad N, Fatima S, Habib N, Ali SR, Qadir M. Intrauterine growth retardation--small events, big consequences. Ital J Pediatr. BioMed Central; 2011 Sep 7;37:41.

3. Fanaroff AA, Hack M, Walsh MC. The NICHD neonatal research network: changes in practice and outcomes during the first 15 years. Semin Perinatol. 2003 Aug;27(4):281–7.

4. Murki S, Sharma D. Intrauterine Growth Retardation - A Review Article. J Neonatal Biol. OMICS International; 2014 Mar 26;3(3).

5. Slancheva B, Mumdzhiev H. [Small for gestational age newborns--definition, etiology and neonatal treatment]. Akush Ginekol (Sofiia). 2013;52(2):25–32.

6. Chatelain P. Children born with intra-uterine growth retardation (IUGR) or small for gestational age (SGA): long term growth and metabolic consequences. Endocr Regul. 2000 Mar;34(1):33–6.

7. Lee PA, Chernausek SD, Hokken-Koelega ACS, Czernichow P, International Small for Gestational Age Advisory Board. International Small for Gestational Age Advisory Board consensus development conference statement: management of short children born small for gestational age, April 24-October 1, 2001. Pediatrics. 2003 Jun;111(6 Pt 1):1253–61.

8. Campbell MK, Cartier S, Xie B, Kouniakis G, Huang W, Han V. Determinants of Small for Gestational Age Birth at Term. Paediatr Perinat Epidemiol. 2012 Nov;26(6):525–33.

9. Zhang J, Merialdi M, Platt LD, Kramer MS. Defining normal and abnormal fetal growth: promises and challenges. Am J Obstet Gynecol. 2010 Jun;202(6):522–8.

10. Bischoff AR, Pokhvisneva I, Léger É, Gaudreau H, Steiner M, Kennedy JL, et al. Dynamic interaction between fetal adversity and a genetic score reflecting dopamine function on developmental outcomes at 36 months. Burd I, editor. PLoS One. Public Library of Science; 2017 May 15;12(5):e0177344.

11. Sharma D, Shastri S, Farahbakhsh N, Sharma P. Intrauterine growth restriction – part 1. J Matern Neonatal Med. 2016 Dec 16;29(24):3977–87.
12. Kingdom J, Huppertz B, Seaward G, Kaufmann P. Development of the placental villous tree and its consequences for fetal growth. Eur J Obstet Gynecol Reprod Biol. 2000 Sep;92(1):35–43.
13. Black RE, Victora CG, Walker SP, Bhutta ZA, Christian P, de Onis M, et al. Maternal and child undernutrition and overweight in low-income and middle-income countries. Lancet. 2013 Aug 3;382(9890):427–51.
14. Salam RA, Das JK, Bhutta ZA. Impact of intrauterine growth restriction on long-term health. Curr Opin Clin Nutr Metab Care. 2014 May;17(3):249–54.
15. Rosenberg A. The IUGR Newborn. Semin Perinatol. 2008 Jun;32(3):219–24.
16. Longo S, Bollani L, Decembrino L, Di Comite A, Angelini M, Stronati M. Short-term and long-term sequelae in intrauterine growth retardation (IUGR). J Matern Neonatal Med. 2013 Feb 3;26(3):222–5.
17. Barker DJ, Winter PD, Osmond C, Margetts B, Simmonds SJ. Weight in infancy and death from ischaemic heart disease. Lancet (London, England). 1989 Sep 9;2(8663):577–80.
18. Barker DJ, Hales CN, Fall CH, Osmond C, Phipps K, Clark PM. Type 2 (non-insulin-dependent) diabetes mellitus, hypertension and hyperlipidaemia (syndrome X): relation to reduced fetal growth. Diabetologia. 1993 Jan;36(1):62–7.
19. Hales CN, Barker DJ. Type 2 (non-insulin-dependent) diabetes mellitus: the thrifty phenotype hypothesis. Diabetologia. 1992 Jul;35(7):595–601.
20. Kim JB. Dynamic cross talk between metabolic organs in obesity and metabolic diseases. Exp Mol Med. Korean Society for Biochemistry and Molecular Biology; 2016 Mar 11;48(3):e214.
21. Barker DJP. The developmental origins of chronic adult disease. Acta Paediatr Suppl. Norway; 2004 Dec;93(446):26–33.
22. Eriksson JG. Developmental Origins of Health and Disease – from a small body size at birth to epigenetics. Ann Med. 2016 Aug 17;48(6):456–67.
23. Thorn SR, Rozance PJ, Brown LD, Hay WW, Jr. The intrauterine growth restriction

phenotype: fetal adaptations and potential implications for later life insulin resistance and diabetes. Semin Reprod Med. NIH Public Access; 2011 May;29(3):225–36.

24. Barker DJ, Bull AR, Osmond C, Simmonds SJ. Fetal and placental size and risk of hypertension in adult life. BMJ. BMJ Publishing Group; 1990 Aug 4;301(6746):259–62.
25. Barker DJ, Osmond C. Infant mortality, childhood nutrition, and ischaemic heart disease in England and Wales. Lancet (London, England). 1986 May 10;1(8489):1077–81.
26. Barker DJ, Osmond C, Golding J, Kuh D, Wadsworth ME. Growth in utero, blood pressure in childhood and adult life, and mortality from cardiovascular disease. BMJ. BMJ Publishing Group; 1989 Mar 4;298(6673):564–7.
27. Bo S, Cavallo-Perin P, Scaglione L, Ciccone G, Pagano G. Low birthweight and metabolic abnormalities in twins with increased susceptibility to Type 2 diabetes mellitus. Diabet Med. 2000 May;17(5):365–70.
28. Barnett AH, Eff C, Leslie RD, Pyke DA. Diabetes in identical twins. A study of 200 pairs. Diabetologia. 1981 Feb;20(2):87–93.
29. Baird J, Osmond C, MacGregor A, Snieder H, Hales CN, Phillips DIW. Testing the fetal origins hypothesis in twins: the Birmingham twin study. Diabetologia. 2001 Jan 10;44(1):33–9.
30. Morris MJ, Beilharz JE, Maniam J, Reichelt AC, Westbrook RF. Why is obesity such a problem in the 21st century? The intersection of palatable food, cues and reward pathways, stress, and cognition. Neurosci Biobehav Rev. 2015 Nov;58:36–45.
31. Portella AK, Silveira PP. Neurobehavioral determinants of nutritional security in fetal growth-restricted individuals. Ann N Y Acad Sci. United States; 2014 Dec;1331:15–33.
32. Mucellini AB, Manfro GG, Silveira PP. Tackling obesity: Challenges ahead. Lancet. 2015;386(9995):740.
33. Ravelli AC, van Der Meulen JH, Osmond C, Barker DJ, Bleker OP. Obesity at the age of 50 y in men and women exposed to famine prenatally. Am J Clin Nutr. United States; 1999 Nov;70(5):811–6.
34. Rich-Edwards JW, Colditz GA, Stampfer MJ, Willett WC, Gillman MW, Hennekens CH, et al. Birthweight and the risk for type 2 diabetes mellitus in adult women. Ann Intern

Med. 1999 Feb 16;130(4 Pt 1):278–84.

35. Dahri S, Snoeck A, Reusens-Billen B, Remacle C, Hoet JJ. Islet function in offspring of mothers on low-protein diet during gestation. Diabetes. 1991 Dec;40 Suppl 2:115–20.
36. Snoeck A, Remacle C, Reusens B, Hoet JJ. Effect of a low protein diet during pregnancy on the fetal rat endocrine pancreas. Biol Neonate. 1990;57(2):107–18.
37. Duran Fernandez-Feijoo C, Carrasco Carrasco C, Villalmazo Francisco N, Cebria Romero J, Fernandez Lorenzo JR, Jimenez-Chillaron JC, et al. Influence of catch up growth on spatial learning and memory in a mouse model of intrauterine growth restriction. PLoS One. United States; 2017;12(5):e0177468.
38. Dulloo AG, Jacquet J, Solinas G, Montani JP, Schutz Y. Body composition phenotypes in pathways to obesity and the metabolic syndrome. Obes Rev. 2010;13(S2):1–5.
39. Lillioja S, Mott DM, Howard B V., Bennett PH, Yki-Järvinen H, Freymond D, et al. Impaired Glucose Tolerance as a Disorder of Insulin Action. N Engl J Med. Massachusetts Medical Society ; 1988 May 12;318(19):1217–25.
40. Weyer C, Bogardus C, Mott DM, Pratley RE. The natural history of insulin secretory dysfunction and insulin resistance in the pathogenesis of type 2 diabetes mellitus. J Clin Invest. American Society for Clinical Investigation; 1999 Sep 15;104(6):787–94.
41. Clark A, Wells CA, Buley ID, Cruickshank JK, Vanhegan RI, Matthews DR, et al. Islet amyloid, increased A-cells, reduced B-cells and exocrine fibrosis: quantitative changes in the pancreas in type 2 diabetes. Diabetes Res. 1988 Dec;9(4):151–9.
42. Stefan Y, Orci L, Malaisse-Lagae F, Perrelet A, Patel Y, Unger RH. Quantitation of Endocrine Cell Content in the Pancreas of Nondiabetic and Diabetic Humans. Diabetes. American Diabetes Association; 1982 Aug 1;31(8):694–700.
43. Simmons RA, Templeton LJ, Gertz SJ. Intrauterine growth retardation leads to the development of type 2 diabetes in the rat. Diabetes. 2001 Oct;50(10):2279–86.
44. Petrik J, Reusens B, Arany E, Remacle C, Coelho C, Hoet JJ, et al. A Low Protein Diet Alters the Balance of Islet Cell Replication and Apoptosis in the Fetal and Neonatal Rat and Is Associated with a Reduced Pancreatic Expression of Insulin-Like Growth Factor-II [1]. Endocrinology. 1999 Oct;140(10):4861–73.
45. Garofano A, Czernichow P, Bréant B. Beta-cell mass and proliferation following late

fetal and early postnatal malnutrition in the rat. Diabetologia. Springer-Verlag; 1998 Aug 19;41(9):1114–20.

46. Vaiserman AM. Early-Life Nutritional Programming of Type 2 Diabetes: Experimental and Quasi-Experimental Evidence. Nutrients. Multidisciplinary Digital Publishing Institute (MDPI); 2017 Mar 5;9(3).
47. Kwak SH, Park KS. Recent progress in genetic and epigenetic research on type 2 diabetes. Exp Mol Med. 2016 Mar 11;48(3):e220.
48. Ong TP, Ozanne SE. Developmental programming of type 2 diabetes. Curr Opin Clin Nutr Metab Care. 2015 Jul;18(4):354–60.
49. Limesand SW, Rozance PJ, Smith D, Hay WW. Increased insulin sensitivity and maintenance of glucose utilization rates in fetal sheep with placental insufficiency and intrauterine growth restriction. AJP Endocrinol Metab. 2007 Oct 23;293(6):E1716–25.
50. Limesand SW, Jensen J, Hutton JC, Hay WW. Diminished β-cell replication contributes to reduced β-cell mass in fetal sheep with intrauterine growth restriction. Am J Physiol Integr Comp Physiol. American Physiological Society; 2005 May;288(5):R1297–305.
51. Cohen E, Baerts W, van Bel F. Brain-Sparing in Intrauterine Growth Restriction: Considerations for the Neonatologist. Neonatology. Karger Publishers; 2015;108(4):269–76.
52. Geva R, Eshel R, Leitner Y, Valevski AF, Harel S. Neuropsychological Outcome of Children With Intrauterine Growth Restriction: A 9-Year Prospective Study. Pediatrics. 2006 Jul 1;118(1):91–100.
53. Flood K, Unterscheider J, Daly S, Geary MP, Kennelly MM, McAuliffe FM, et al. The role of brain sparing in the prediction of adverse outcomes in intrauterine growth restriction: results of the multicenter PORTO Study. Am J Obstet Gynecol. 2014 Sep;211(3):288.e1-288.e5.
54. Hernandez-Andrade E, Benavides Serralde JA, Cruz-Martinez R. Can anomalies of fetal brain circulation be useful in the management of growth restricted fetuses? Prenat Diagn. 2012 Feb;32(2):103–12.
55. Yanney M, Marlow N. Paediatric consequences of fetal growth restriction. Semin Fetal Neonatal Med. 2004 Oct;9(5):411–8.

56. van den Broek AJM, Kok JH, Houtzager BA, Scherjon SA. Behavioural problems at the age of eleven years in preterm-born children with or without fetal brain sparing: A prospective cohort study. Early Hum Dev. 2010 Jun;86(6):379–84.
57. Figueras F, Cruz-Martinez R, Sanz-Cortes M, Arranz A, Illa M, Botet F, et al. Neurobehavioral outcomes in preterm, growth-restricted infants with and without prenatal advanced signs of brain-sparing. Ultrasound Obstet Gynecol. 2011 Sep;38(3):288–94.
58. Starčević M, Predojević M, Butorac D, Tumbri J, Konjevoda P, Kadić AS. Early functional and morphological brain disturbances in late-onset intrauterine growth restriction. Early Hum Dev. 2016 Feb;93:33–8.
59. El Ayoubi M, Patkai J, Bordarier C, Desfrere L, Moriette G, Jarreau P-H, et al. Impact of fetal growth restriction on neurodevelopmental outcome at 2 years for extremely preterm infants: a single institution study. Dev Med Child Neurol. 2016 Dec;58(12):1249–56.
60. Allen MC. Developmental outcome and followup of the small for gestational age infant. Semin Perinatol. 1984 Apr;8(2):123–56.
61. Guellec I, Lapillonne A, Renolleau S, Charlaluk M-L, Roze J-C, Marret S, et al. Neurologic Outcomes at School Age in Very Preterm Infants Born With Severe or Mild Growth Restriction. Pediatrics. 2011 Apr 1;127(4):e883–91.
62. Morsing E, Asard M, Ley D, Stjernqvist K, Marsal K. Cognitive Function After Intrauterine Growth Restriction and Very Preterm Birth. Pediatrics. 2011 Apr 1;127(4):e874–82.
63. Kutschera J, Urlesberger B, Maurer U, Müller W. [Small for gestational age - Somatic, neurological and cognitive development until adulthood]. Z Geburtshilfe Neonatol. 2002 Apr;206(2):65–71.
64. Grantham-McGregor SM. Small for gestational age, term babies, in the first six years of life. Eur J Clin Nutr. 1998 Jan;52 Suppl 1:S59-64.
65. Martorell R, Ramakrishnan U, Schroeder DG, Melgar P, Neufeld L. Intrauterine growth retardation, body size, body composition and physical performance in adolescence. Eur J Clin Nutr. 1998 Jan;52 Suppl 1:S43-52-3.

66. Bickle Graz M, Tolsa J-F, Fischer Fumeaux CJ. Being Small for Gestational Age: Does it Matter for the Neurodevelopment of Premature Infants? A Cohort Study. PLoS One. Public Library of Science; 2015;10(5):e0125769.
67. Chaudhari S, Otiv M, Khairnar B, Pandit A, Hoge M, Sayyad M. Pune low birth weight study - birth to adulthood - cognitive development. Indian Pediatr. 2013 Sep;50(9):853–7.
68. Eixarch E, Figueras F, Hernández-Andrade E, Crispi F, Nadal A, Torre I, et al. An Experimental Model of Fetal Growth Restriction Based on Selective Ligature of Uteroplacental Vessels in the Pregnant Rabbit. Fetal Diagn Ther. 2009;26(4):203–11.
69. Tolcos M, Petratos S, Hirst JJ, Wong F, Spencer SJ, Azhan A, et al. Blocked, delayed, or obstructed: What causes poor white matter development in intrauterine growth restricted infants? Prog Neurobiol. 2017 Jul;154:62–77.
70. Hsiao EY, Patterson PH. Placental regulation of maternal-fetal interactions and brain development. Dev Neurobiol. 2012 Oct;72(10):1317–26.
71. Dieni S, Rees S. Dendritic morphology is altered in hippocampal neurons following prenatal compromise. J Neurobiol. 2003 Apr;55(1):41–52.
72. Fung C, Ke X, Brown AS, Yu X, McKnight RA, Lane RH. Uteroplacental insufficiency alters rat hippocampal cellular phenotype in conjunction with ErbB receptor expression. Pediatr Res. 2012 Jul 24;72(1):2–9.
73. Mallard C, Loeliger M, Copolov D, Rees S. Reduced number of neurons in the hippocampus and the cerebellum in the postnatal guinea-pig following intrauterine growth-restriction. Neuroscience. 2000;100(2):327–33.
74. Chen W-F, Chang H, Wong C-S, Huang L-T, Yang C-H, Yang S-N. Impaired expression of postsynaptic density proteins in the hippocampal CA1 region of rats following perinatal hypoxia. Exp Neurol. 2007 Mar;204(1):400–10.
75. Dieni S, Rees S. BDNF and TrkB protein expression is altered in the fetal hippocampus but not cerebellum after chronic prenatal compromise. Exp Neurol. 2005 Apr;192(2):265–73.
76. Schober ME, McKnight RA, Yu X, Callaway CW, Ke X, Lane RH. Intrauterine growth restriction due to uteroplacental insufficiency decreased white matter and altered

NMDAR subunit composition in juvenile rat hippocampi. Am J Physiol Regul Integr Comp Physiol. American Physiological Society; 2009 Mar 1;296(3):R681-92.

77. Sommer JU, Schmitt A, Heck M, Schaeffer EL, Fendt M, Zink M, et al. Differential expression of presynaptic genes in a rat model of postnatal hypoxia: relevance to schizophrenia. Eur Arch Psychiatry Clin Neurosci. 2010 Nov 14;260(S2):81–9.
78. Mennella JA. Development of food preferences: Lessons learned from longitudinal and experimental studies. Food Qual Prefer. 2006;17(7–8):635–7.
79. Mennella JA, Jagnow CP, Beauchamp GK. Prenatal and postnatal flavor learning by human infants. Pediatrics. NIH Public Access; 2001 Jun;107(6):E88.
80. Dalle Molle R, Bischoff AR, Portella AK, Silveira PP. The fetal programming of food preferences: current clinical and experimental evidence. J Dev Orig Health Dis. 2016 Jun 28;7(3):222–30.
81. Portella AK, Silveira PP. Neurobehavioral determinants of nutritional security in fetal growth-restricted individuals. Ann N Y Acad Sci. 2014 Dec;1331(1):15–33.
82. Portella AK, Kajantie E, Hovi P, Desai M, Ross MG, Goldani MZ, et al. Effects of in utero conditions on adult feeding preferences. J Dev Orig Health Dis. 2012 Jun 6;3(3):140–52.
83. Dalle Molle R, Silveira PP. Small for gestational age children have specific food preferences. J Pediatr. 2015 Jun;166(6):1547.
84. El-Haddad MA, Desai M, Gayle D, Ross MG. In Utero Development of Fetal Thirst and Appetite: Potential for Programming. J Soc Gynecol Investig. 2004 Apr 28;11(3):123–30.
85. Ross MG, Desai M. Developmental Programming of Offspring Obesity, Adipogenesis, and Appetite. Clin Obstet Gynecol. 2013 Sep;56(3):529–36.
86. Vickers MH, Breier BH, McCarthy D, Gluckman PD. Sedentary behavior during postnatal life is determined by the prenatal environment and exacerbated by postnatal hypercaloric nutrition. Am J Physiol - Regul Integr Comp Physiol. 2003 Jul;285(1):R271–3.
87. Kaseva N, Wehkalampi K, Strang-Karlsson S, Salonen M, Pesonen A-K, Räikkönen K, et al. Lower Conditioning Leisure-Time Physical Activity in Young Adults Born Preterm at

Very Low Birth Weight. Myer L, editor. PLoS One. 2012 Feb 27;7(2):e32430.

88. Kajantie E, Strang-Karlsson S, Hovi P, Räikkönen K, Pesonen A-K, Heinonen K, et al. Adults Born at Very Low Birth Weight Exercise Less than Their Peers Born at Term. J Pediatr. 2010 Oct;157(4):610–616.e1.

89. Ayres C, Agranonik M, Portella AK, Filion F, Johnston CC, Silveira PP. Intrauterine growth restriction and the fetal programming of the hedonic response to sweet taste in newborn infants. Int J Pediatr. Egypt; 2012;2012:657379.

90. Rotstein M, Stolar O, Uliel S, Mandel D, Mani A, Dollberg S, et al. Facial Expression in Response to Smell and Taste Stimuli in Small and Appropriate for Gestational Age Newborns. J Child Neurol. 2015 Oct 18;30(11):1466–71.

91. Laureano DP, Molle RD, Portella AK, Silveira PP. Facial Expressions in Small for Gestational Age Newborns. J Child Neurol. 2016 Mar 30;31(3):398–9.

92. Silveira PP, Agranonik M, Faras H, Portella AK, Meaney MJ, Levitan RD. Preliminary evidence for an impulsivity-based thrifty eating phenotype. Pediatr Res. United States; 2012 Mar;71(3):293–8.

93. Migraine A, Nicklaus S, Parnet P, Lange C, Monnery-Patris S, Des Robert C, et al. Effect of preterm birth and birth weight on eating behavior at 2 y of age. Am J Clin Nutr. American Society for Nutrition; 2013 Jun 1;97(6):1270–7.

94. Oliveira A, de Lauzon-Guillain B, Jones L, Emmett P, Moreira P, Ramos E, et al. Birth Weight and Eating Behaviors of Young Children. J Pediatr. 2015 Jan;166(1):59–65.e3.

95. Escobar RS, O'Donnell KA, Colalillo S, Pawlby S, Steiner M, Meaney MJ, et al. Better quality of mother-child interaction at 4 years of age decreases emotional overeating in IUGR girls. Appetite. England; 2014 Oct;81:337–42.

96. Reis RS, Dalle Molle R, Machado TD, Mucellini AB, Rodrigues DM, Bortoluzzi A, et al. Impulsivity-based thrifty eating phenotype and the protective role of n-3 PUFAs intake in adolescents. Transl Psychiatry. United States; 2016 Mar;6:e755.

97. Barbieri MA, Portella AK, Silveira PP, Bettiol H, Agranonik M, Silva AA, et al. Severe intrauterine growth restriction is associated with higher spontaneous carbohydrate intake in young women. Pediatr Res. United States; 2009 Feb;65(2):215–20.

98. Kaseva N, Wehkalampi K, Hemio K, Hovi P, Jarvenpaa A-L, Andersson S, et al. Diet and

nutrient intake in young adults born preterm at very low birth weight. J Pediatr. United States; 2013 Jul;163(1):43–8.

99. Crume TL, Scherzinger A, Stamm E, McDuffie R, Bischoff KJ, Hamman RF, et al. The long-term impact of intrauterine growth restriction in a diverse U.S. cohort of children: the EPOCH study. Obesity (Silver Spring). NIH Public Access; 2014 Feb;22(2):608–15.
100. Lussana F, Painter RC, Ocke MC, Buller HR, Bossuyt PM, Roseboom TJ. Prenatal exposure to the Dutch famine is associated with a preference for fatty foods and a more atherogenic lipid profile. Am J Clin Nutr. United States; 2008 Dec;88(6):1648–52.
101. Stein AD, Rundle A, Wada N, Goldbohm RA, Lumey LH. Associations of gestational exposure to famine with energy balance and macronutrient density of the diet at age 58 years differ according to the reference population used. J Nutr. United States; 2009 Aug;139(8):1555–61.
102. Perala M-M, Mannisto S, Kaartinen NE, Kajantie E, Osmond C, Barker DJP, et al. Body size at birth is associated with food and nutrient intake in adulthood. PLoS One. United States; 2012;7(9):e46139.
103. Alves MB, Dalle Molle R, Desai M, Ross MG, Silveira PP. Increased palatable food intake and response to food cues in intrauterine growth-restricted rats are related to tyrosine hydroxylase content in the orbitofrontal cortex and nucleus accumbens. Behav Brain Res. Netherlands; 2015;287:73–81.
104. Dalle Molle R, Laureano DP, Alves MB, Reis TM, Desai M, Ross MG, et al. Intrauterine growth restriction increases the preference for palatable foods and affects sensitivity to food rewards in male and female adult rats. Brain Res. Netherlands; 2015 Aug;1618:41–9.
105. da Silva AAM, Borba TKF, de Almeida Lira L, Cavalcante TCF, de Freitas MFL, Leandro CG, et al. Perinatal undernutrition stimulates seeking food reward. Int J Dev Neurosci. 2013 Aug;31(5):334–41.
106. Martimiano PH de M, da Silva GR, Coimbra VF da SA, Matos RJB, de Souza BFP, da Silva AAM, et al. Perinatal malnutrition stimulates motivation through reward and enhances drd1a receptor expression in the ventral striatum of adult mice. Pharmacol

Biochem Behav. Elsevier; 2015 Jul 1;134:106–14.

107. Lira LA, Almeida LCA, da Silva AAM, Cavalcante TCF, de Melo DDCB, de Souza JA, et al. Perinatal undernutrition increases meal size and neuronal activation of the nucleus of the solitary tract in response to feeding stimulation in adult rats. Int J Dev Neurosci. 2014 Nov;38:23–9.
108. Desai M, Gayle D, Han G, Ross MG. Programmed Hyperphagia Due to Reduced Anorexigenic Mechanisms in Intrauterine Growth-Restricted Offspring. Reprod Sci. 2007 May 6;14(4):329–37.
109. Shin B-C, Dai Y, Thamotharan M, Gibson LC, Devaskar SU. Pre- and postnatal calorie restriction perturbs early hypothalamic neuropeptide and energy balance. J Neurosci Res. 2012 Jun;90(6):1169–82.
110. Puglianiello A, Germani D, Cianfarani S. Exposure to Uteroplacental Insufficiency Reduces the Expression of Signal Transducer and Activator of Transcription 3 and Proopiomelanocortin in the Hypothalamus of Newborn Rats. Pediatr Res. 2009 Aug;66(2):208–11.
111. Delahaye F, Breton C, Risold P-Y, Enache M, Dutriez-Casteloot I, Laborie C, et al. Maternal Perinatal Undernutrition Drastically Reduces Postnatal Leptin Surge and Affects the Development of Arcuate Nucleus Proopiomelanocortin Neurons in Neonatal Male Rat Pups. Endocrinology. 2008 Feb;149(2):470–5.
112. Yousheng Jia Y, Nguyen T, Desai M, Ross MG. Programmed Alterations in Hypothalamic Neuronal Orexigenic Responses to Ghrelin Following Gestational Nutrient Restriction. Reprod Sci. SAGE PublicationsSage CA: Los Angeles, CA; 2008 Sep 18;15(7):702–9.
113. Orozco-Solís R, Matos RJB, Lopes de Souza S, Grit I, Kaeffer B, Manhães de Castro R, et al. Perinatal nutrient restriction induces long-lasting alterations in the circadian expression pattern of genes regulating food intake and energy metabolism. Int J Obes. Nature Publishing Group; 2011 Jul 9;35(7):990–1000.
114. Remmers F, Verhagen LAW, Adan RAH, Delemarre-van de Waal HA. Hypothalamic Neuropeptide Expression of Juvenile and Middle-Aged Rats after Early Postnatal Food Restriction. Endocrinology. 2008 Jul;149(7):3617–25.

115. García AP, Palou M, Priego T, Sánchez J, Palou A, Picó C. Moderate caloric restriction during gestation results in lower arcuate nucleus NPY- and αMSH-neurons and impairs hypothalamic response to fed/fasting conditions in weaned rats. Diabetes, Obes Metab. 2010 Mar 30;12(5):403–13.

116. Plagemann A, Harder T, Rake A, Melchior K, Rohde W, Dörner G. Hypothalamic nuclei are malformed in weanling offspring of low protein malnourished rat dams. J Nutr. 2000 Oct;130(10):2582–9.

117. Fukami T, Sun X, Li T, Desai M, Ross MG. Mechanism of Programmed Obesity in Intrauterine Fetal Growth Restricted Offspring: Paradoxically Enhanced Appetite Stimulation in Fed and Fasting States. Reprod Sci. 2012 Apr 16;19(4):423–30.

118. Desai M, Li T, Ross MG. Fetal Hypothalamic Neuroprogenitor Cell Culture: Preferential Differentiation Paths Induced by Leptin and Insulin. Endocrinology. 2011 Aug;152(8):3192–201.

119. Desai M, Li T, Ross MG. Hypothalamic neurosphere progenitor cells in low birth-weight rat newborns: Neurotrophic effects of leptin and insulin. Brain Res. 2011 Mar 10;1378:29–42.

120. Orozco-Solís R, Matos RJB, Guzmán-Quevedo O, Lopes de Souza S, Bihouée A, Houlgatte R, et al. Nutritional Programming in the Rat Is Linked to Long-Lasting Changes in Nutrient Sensing and Energy Homeostasis in the Hypothalamus. Tena-Sempere M, editor. PLoS One. 2010 Oct 21;5(10):e13537.

121. Cunha F da S, Dalle Molle R, Portella AK, Benetti C da S, Noschang C, Goldani MZ, et al. Both Food Restriction and High-Fat Diet during Gestation Induce Low Birth Weight and Altered Physical Activity in Adult Rat Offspring: The “Similarities in the Inequalities” Model. Andrews Z, editor. PLoS One. Public Library of Science; 2015 Mar 4;10(3):e0118586.

122. Desai M, Gayle D, Babu J, Ross MG. Programmed obesity in intrauterine growth-restricted newborns: modulation by newborn nutrition. Am J Physiol Regul Integr Comp Physiol. 2005 Jan 2;288(1):R91-6.

123. Tamashiro KLK, Moran TH. Perinatal environment and its influences on metabolic programming of offspring. Physiol Behav. 2010 Jul;100(5):560–6.

124. Manuel-Apolinar L, ROCHA L, DAMASIO L, TESORO-CRUZ E, ZARATE A. Role of prenatal undernutrition in the expression of serotonin, dopamine and leptin receptors in adult mice: Implications of food intake. Mol Med Rep. 2014 Feb;9(2):407–12.

125. Vucetic Z, Totoki K, Schoch H, Whitaker KW, Hill-Smith T, Lucki I, et al. Early life protein restriction alters dopamine circuitry. Neuroscience. 2010 Jun 30;168(2):359–70.

126. Peciña S, Smith KS, Berridge KC. Hedonic Hot Spots in the Brain. Neurosci. 2006 Dec 29;12(6):500–11.

127. Laureano DP, Dalle Molle R, Alves MB, Luft C, Desai M, Ross MG, et al. Intrauterine growth restriction modifies the hedonic response to sweet taste in newborn pups - Role of the accumbal mu-opioid receptors. Neuroscience. United States; 2016 May;322:500–8.

128. Dellschaft NS, Alexandre-Gouabau M-C, Gardner DS, Antignac J-P, Keisler DH, Budge H, et al. Effect of pre- and postnatal growth and post-weaning activity on glucose metabolism in the offspring. J Endocrinol. 2015 Jan 12;224(2):171–82.

129. Óvilo C, González-Bulnes A, Benítez R, Ayuso M, Barbero A, Pérez-Solana ML, et al. Prenatal programming in an obese swine model: sex-related effects of maternal energy restriction on morphology, metabolism and hypothalamic gene expression. Br J Nutr. 2014 Feb 5;111(4):735–46.

130. Vieau D, Sebaai N, Léonhardt M, Dutriez-Casteloot I, Molendi-Coste O, Laborie C, et al. HPA axis programming by maternal undernutrition in the male rat offspring. Psychoneuroendocrinology. 2007 Aug;32:S16–20.

131. Lesage J, Blondeau B, Grino M, Bréant B, Dupouy JP. Maternal Undernutrition during Late Gestation Induces Fetal Overexposure to Glucocorticoids and Intrauterine Growth Retardation, and Disturbs the Hypothalamo-Pituitary Adrenal Axis in the Newborn Rat [1]. Endocrinology. 2001 May;142(5):1692–702.

132. Dallman MF, Pecoraro N, Akana SF, Fleur SE la, Gomez F, Houshyar H, et al. Chronic stress and obesity: A new view of “comfort food.” PNAS. 2003;100(20).

133. Dallman MF, Pecoraro NC, Fleur SE la. Chronic stress and comfort foods: Self-medication and abdominal obesity. Brain Behav Immun. 2005;19:275–80.

134. Reis RS, Dalle Molle R, Machado TD, Mucellini AB, Rodrigues DM, Bortoluzzi A, et al. Impulsivity-based thrifty eating phenotype and the protective role of n-3 PUFAs intake in adolescents. Transl Psychiatry. 2016 Mar 15;6(3):e755.

135. Alves MB, Dalle Molle R, Desai M, Ross MG, Silveira PP. Increased palatable food intake and response to food cues in intrauterine growth-restricted rats are related to tyrosine hydroxylase content in the orbitofrontal cortex and nucleus accumbens. Behav Brain Res. 2015;

136. Cintra L, Díaz-Cintra S, Galván A, Kemper T, Morgane PJ. Effects of protein undernutrition on the dentate gyrus in rats of three age groups. Brain Res. 1990 Nov 5;532(1–2):271–7.

137. Debassio WA, Kemper TL, Galler JR, Tonkiss J. Prenatal malnutrition effect on pyramidal and granule cell generation in the hippocampal formation. Brain Res Bull. 1994;35(1):57–61.

138. Leitner Y, Heldman D, Harel S, Pick CG. Deficits in spatial orientation of children with intrauterine growth retardation. Brain Res Bull. 2005 Sep 30;67(1–2):13–8.

139. Geva R, Eshel R, Leitner Y, Fattal-Valevski A, Harel S. Memory functions of children born with asymmetric intrauterine growth restriction. Brain Res. 2006 Oct 30;1117(1):186–94.

140. Lodygensky GA, Seghier ML, Warfield SK, Tolsa CB, Sizonenko S, Lazeyras F, et al. Intrauterine Growth Restriction Affects the Preterm Infant's Hippocampus. Pediatr Res. 2008 Apr;63(4):438–43.

141. Davidson TL, Kanoski SE, Schier LA, Clegg DJ, Benoit SC. A Potential Role for the Hippocampus in Energy Intake and Body Weight Regulation. Curr Opin Pharmacol. 2007 Dec 26;7(6):613–6.

142. Kanoski SE, Grill HJ. Hippocampus Contributions to Food Intake Control: Mnemonic, Neuroanatomical, and Endocrine Mechanisms. Biol Psychiatry. 2015 Sep;

143. Higgs S. Cognitive processing of food rewards. Appetite. 2016 Sep;104:10–7.

144. Stevenson RJ, Francis HM. The hippocampus and the regulation of human food intake. Psychol Bull. 2017 Oct;143(10):1011–32.

145. Mucellini AB, Fonseca NK de O da, Manfro GG, Silveira PP. Hippocampal insulin

resistance and altered food decision-making as players on obesity risk. Neurosci Biobehav Rev. United States; 2017 Mar;77:165–76.

146. Jansen A, Havermans RC, Nederkoorn C. Cued Overeating. In: Handbook of Behavior, Food and Nutrition. New York, NY: Springer New York; 2011. p. 1431–43.
147. Jansen A. A learning model of binge eating: cue reactivity and cue exposure. Behav Res Ther. 1998 Mar;36(3):257–72.
148. Bouton ME. Learning and the persistence of appetite: Extinction and the motivation to eat and overeat. Physiol Behav. 2011 Apr 18;103(1):51–8.
149. Boggiano MM, Dorsey JR, Thomas JM, Murdaugh DL. The Pavlovian power of palatable food: lessons for weight-loss adherence from a new rodent model of cue-induced overeating. Int J Obes. 2009 Jun 7;33(6):693–701.
150. Berthoud H-R. Metabolic and hedonic drives in the neural control of appetite: Who's the boss? Current Opinion in Neurobiology. 2011. p. 888–96.
151. Boswell RG, Kober H. Food cue reactivity and craving predict eating and weight gain: a meta-analytic review. Obes Rev. 2016 Feb;17(2):159–77.
152. Castellanos EH, Charboneau E, Dietrich MS, Park S, Bradley BP, Mogg K, et al. Obese adults have visual attention bias for food cue images: evidence for altered reward system function. Int J Obes. 2009 Sep 21;33(9):1063–73.
153. Berridge KC, Ho C-Y, Richard JM, DiFeliceantonio AG. The tempted brain eats: Pleasure and desire circuits in obesity and eating disorders. Brain Res. Elsevier; 2010 Sep 2;1350:43–64.
154. Davis C, Zai C, Levitan RD, Kaplan AS, Carter JC, Reid-Westoby C, et al. Opiates, overeating and obesity: a psychogenetic analysis. Int J Obes (Lond). England; 2011 Oct;35(10):1347–54.
155. Demos KE, Kelley WM, Heatherton TF. Dietary restraint violations influence reward responses in nucleus accumbens and amygdala. J Cogn Neurosci. 2011;23.
156. Wimmer GE, Braun EK, Daw ND, Shohamy D. Episodic memory encoding interferes with reward learning and decreases striatal prediction errors. J Neurosci. United States; 2014 Nov;34(45):14901–12.
157. Kahn I, Shohamy D. Intrinsic connectivity between the hippocampus, nucleus

accumbens, and ventral tegmental area in humans. Hippocampus. United States; 2013 Mar;23(3):187–92.

158. Wimmer GE, Shohamy D. Preference by association: how memory mechanisms in the hippocampus bias decisions. Science. United States; 2012 Oct;338(6104):270–3.
159. Ward A, Mann T. Don't mind if I do: disinhibited eating under cognitive load. J Pers Soc Psychol. 2000 Apr;78(4):753–63.
160. Vohs KD, Heatherton TF. Self-Regulatory Failure: A Resource-Depletion Approach. Psychol Sci. 2000 May 6;11(3):249–54.
161. Mela DJ. Determinants of food choice: relationships with obesity and weight control. Obes Res. 2001 Nov;9 Suppl 4(November):249S–255S.
162. Carr KA, Daniel TO, Lin H, Epstein LH. Reinforcement pathology and obesity. Curr Drug Abuse Rev. 2011 Sep;4(3):190–6.
163. Epstein LH, Carr KA, Cavanaugh MD, Paluch RA, Bouton ME. Long-term habituation to food in obese and nonobese women. Am J Clin Nutr. 2011 Aug 1;94(2):371–6.
164. Price M, Higgs S, Lee M. Self-reported eating traits: Underlying components of food responsivity and dietary restriction are positively related to BMI. Appetite. 2015 Dec;95:203–10.
165. Higgs S, Robinson E, Lee M. Learning and Memory Processes and Their Role in Eating: Implications for Limiting Food Intake in Overeaters. Curr Obes Rep. Current Science Inc.; 2012 Jun 21;1(2):91–8.
166. Kahneman D, Krueger AB, Schkade DA, Schwarz N, Stone AA. A Survey Method for Characterizing Daily Life Experience: The Day Reconstruction Method. Science (80-). 2004 Dec 3;306(5702):1776–80.
167. Robinson MD, Clore GL. Belief and feeling: evidence for an accessibility model of emotional self-report. Psychol Bull. 2002 Nov;128(6):934–60.
168. Wang JX, Cohen NJ, Voss JL. Covert rapid action-memory simulation (CRAMS): A hypothesis of hippocampal–prefrontal interactions for adaptive behavior. Neurobiol Learn Mem. 2015;117:22–33.
169. Furlong TM, Jayaweera HK, Balleine BW, Corbit LH. Binge-Like Consumption of a Palatable Food Accelerates Habitual Control of Behavior and Is Dependent on

Activation of the Dorsolateral Striatum. J Neurosci. 2014 Apr 2;34(14):5012–22.

170. Docteur A, Urdapilleta I, Defrance C, Raison J. Implicit and Explicit Memory Bias for Words Related To Food, Shape and Body Parts in Obese and Normal Weight Females. Curr Psychol Lett. 2008;24(2):52–62.
171. Jurdak N, Lichtenstein AH, Kanarek RB. Diet-induced obesity and spatial cognition in young male rats. Nutr Neurosci. 2008 Apr;11(2):48–54.
172. Cserjési R, Molnár D, Luminet O, Lénárd L. Is there any relationship between obesity and mental flexibility in children? Appetite. 2007;49(3):675–8.
173. Davidson TL, Hargrave SL, Swithers SE, Sample CH, Fu X, Kinzig KP, et al. Inter-relationships among diet, obesity and hippocampal-dependent cognitive function. Neuroscience. 2013/09/04. Center for Behavioral Neuroscience, American University, Washington, DC, United States. Electronic address: terryd@american.edu.; 2013;253:110–22.
174. Davidson TL, Sample CH, Swithers SE. An application of Pavlovian principles to the problems of obesity and cognitive decline. Neurobiol Learn Mem. United States; 2014 Feb;108:172–84.
175. Hargrave SL, Jones S, Davidson TL. The Outward Spiral: A vicious cycle model of obesity and cognitive dysfunction. Curr Opin Behav Sci. 2016 Jun;9:40–6.
176. Tannenbaum J, Bennett BT. Russell and Burch's 3Rs then and now: the need for clarity in definition and purpose. J Am Assoc Lab Anim Sci. American Association for Laboratory Animal Science; 2015 Mar;54(2):120–32.
177. Russel WMS, Burch RL. The Principles of Humane Experimental Technique. Wheathampstead : Universities Federation for Animal Welfare.; 1959.
178. Swanson AM, David AL. Animal models of fetal growth restriction: Considerations for translational medicine. Placenta. 2015 Jun;36(6):623–30.
179. Suckow MA, Weisbroth SH, Franklin CL. The laboratory rat. Elsevier; 2006. 912 p.
180. Birch LL, McPhee L, Steinberg L, Sullivan S. Conditioned flavor preferences in young children. Physiol Behav. Elsevier; 1990 Mar 1;47(3):501–5.
181. Birch LL. Development of food preferences. Annu Rev Nutr. 1999 Jul;19(1):41–62.
182. Trabulsi JC, Mennella JA. Diet, sensitive periods in flavour learning, and growth. Int

Rev Psychiatry. 2012;24(3):219–30.

183. Sullivan EL, Grove KL. Metabolic imprinting in obesity. Forum Nutr. 2010;63:186–94.

184. Kyriakakou M, Malamitsi-Puchner A, Militsi H, Boutsikou T, Margeli A, Hassiakos D, et al. Leptin and adiponectin concentrations in intrauterine growth restricted and appropriate for gestational age fetuses, neonates, and their mothers. Eur J Endocrinol. 2008 Mar 1;158(3):343–8.

185. Nagata E, Nakagawa Y, Yamaguchi R, Fujisawa Y, Sano S, Satake E, et al. Altered Gene Expressions of Ghrelin, PYY, and CCK in the Gastrointestinal Tract of the Hyperphagic Intrauterine Growth Restriction Rat Offspring. Horm Metab Res. 2011 Mar 24;43(3):178–82.

186. Mayeur S, Cisse O, Gabory A, Barbaux S, Vaiman D, Vambergue A, et al. Placental expression of the obesity-associated gene FTO is reduced by fetal growth restriction but not by macrosomia in rats and humans. J Dev Orig Health Dis. 2013 Apr 20;4(2):134–8.

187. Stevenson RJ. Psychological correlates of habitual diet in healthy adults. Psychol Bull. 2017 Jan;143(1):53–90.

7. ANEXOS

7.1. CARTA DE APROVAÇÃO DA PESQUISA EXPERIMENTAL

HCPA - HOSPITAL DE CLÍNICAS DE PORTO ALEGRE
GRUPO DE PESQUISA E PÓS-GRADUAÇÃO

COMISSÃO DE ÉTICA NO USO DE ANIMAIS

A Comissão de Ética no Uso de Animais (CEUA/HCPA) analisou o projeto:

Projeto: 130544
Data da Versão do Projeto: 24/03/2014

Pesquisadores:
PATRICIA PELUFO SILVEIRA
AMANDA BRONDANI MUGELLINI

Título: PAPEL DA INSULINA SOBRE A MEMÓRIA E O COMPORTAMENTO ANSIOSO RELACIONADOS AOS ALIMENTOS EM UM MODELO DE RESTRIÇÃO DE CRESCIMENTO INTRAUTERINO EM RATOS

Este projeto foi APROVADO em seus aspectos éticos e metodológicos de acordo com as Diretrizes e Normas Nacionais e Internacionais, especialmente a Lei 11.794 de 08/10/2008, que estabelece procedimentos para o uso científico de animais.

- Os membros da CEUA/HCPA não participaram do processo de avaliação de projetos onde constam como pesquisadores.
- Toda e qualquer alteração do Projeto deverá ser comunicada à CEUA/HCPA.
- O pesquisador deverá apresentar relatórios semestrais de acompanhamento e relatório final ao CEUA/HCPA.

Porto Alegre, 28 de março de 2014.

Profª Irací Lucena da Silva Torres
Coordenadora CEUA/HCPA

7.2. CARTA DE APROVAÇÃO DA PESQUISA CLÍNICA

HCPA - HOSPITAL DE CLÍNICAS DE PORTO ALEGRE
GRUPO DE PESQUISA E PÓS-GRADUAÇÃO

COMISSÃO CIENTÍFICA

A Comissão Científica do Hospital de Clínicas de Porto Alegre analisou o projeto:

Projeto: 120254
Data da Versão do Projeto:

Pesquisadores:
GISELE GUS MANFRO
PATRICIA PELUFO SILVEIRA
GIOVANNI ABRAHAO SALUM JUNIOR
ROBERTA DALLE MOLLE
RAFAELA BEHS JARROS
VERA LUCIA BOSA
ANDRESSA BORTOLUZZI
DIOGO ARAÚJO DE SOUSA
NATAN PEREIRA GOSMANN

Título: Restrição do crescimento intra-uterino e trajetória desenvolvimental de adolescentes e adultos com e sem transtorno de ansiedade: desfechos em saúde mental, nutricional, epigenéticos, biomarcadores e de neuroimagem funcional

Este projeto foi **APROVADO** em seus aspectos éticos, metodológicos, logísticos e financeiros para ser realizado no Hospital de Clínicas de Porto Alegre.
Esta aprovação está baseada nos pareceres dos respectivos Comitês de Ética e do Serviço de Gestão em Pesquisa.

- Os pesquisadores vinculados ao projeto não participaram de qualquer etapa do processo de avaliação de seus projetos.

- O pesquisador deverá apresentar relatórios semestrais de acompanhamento e relatório final ao Grupo de Pesquisa e Pós-Graduação (GPPG)

Porto Alegre, 08 de novembro de 2012.

Profª Nadine Clausell
Coordenadora GPPG

7.3. TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO DA PESQUISA CLÍNICA

DADOS DE IDENTIFICAÇÃO DO PARTICIPANTE DA PESQUISA OU RESPONSÁVEL LEGAL

1. NOME: .....

2. RESPONSÁVEL LEGAL: .....
NATUREZA (grau de parentesco, tutor, curador etc.): .....

DADOS SOBRE A PESQUISA

1. TÍTULO DO PROTOCOLO DE PESQUISA

"Restrição do crescimento intrauterino e trajetória desenvolvimental de adolescentes e adultos com e sem transtorno de ansiedade: desfechos em saúde mental, nutricional, epigenéticos, biomarcadores e de neuroimagem funcional"

2. Pesquisadores responsáveis: Gisele Gus Manfro e Patrícia Pelufo Silveira
CARGO/FUNÇÃO: Professora da Faculdade de Medicina/ Professora da Faculdade de Medicina
UNIDADE: Departamento de Psiquiatria e Medicina Legal da Universidade Federal do Rio Grande do Sul, coordenadora do PROTAIA/ Departamento de Pediatria e Puericultura
Pesquisadores executantes: Andressa Bortoluzzi, Diogo Souza, Giovanni Abrahão Salum Júnior, Rafaela Behs Jarros, Roberta Dalle Molle Rudineia Toazza, Natan Pereira Gosmann
Pesquisadores Colaboradores PUC: Augusto Buchweitz, Alexandre Franco

3. Avaliação do risco da pesquisa: ( ) risco mínimo **(x) risco baixo** ( ) risco médio ( ) risco maior

4. **Duração da pesquisa:** A duração total deste projeto está prevista para 1,5 anos.

5. Justificativa e objetivos

Os transtornos de ansiedade iniciam na infância e podem se manter até a vida adulta. Eles também podem influenciar os diferentes hábitos alimentares. Como é comum a diminuição de crescimento do feto durante a gravidez e isto poderia aumentar a chance do desenvolvimento de doenças do metabolismo e psiquiátricas, estamos estudando como isto ocorre e suas consequências, a fim de propiciar a prevenção e um melhor tratamento dessas doenças. O objetivo desse trabalho é investigar se a restrição de crescimento do feto durante a gestação está associada a alterações no desenvolvimento de adolescentes e adultos com e sem ansiedade investigando: (1) como se iniciam e se mantém os transtornos de ansiedade; (2) como se iniciam e se mantém os diferentes comportamentos alimentares e os indicadores de composição corporal; (3) as modificações na forma como os genes se expressam e (4) o funcionamento cerebral.

6. Procedimentos

Procedimentos para seleção de sujeitos que vão entrar na pesquisa:

Se você **pai e/ou mãe ou responsável (em caso do participante ser menor de 18 anos)** autorizar a participação de seu filho (a) na pesquisa, você e seu filho (a) serão convidados a participar de:

Observação: Embora os pais participem dessa avaliação, no caso de crianças pequenas, acompanhando seu filho e ajudando a responder alguns questionários sobre os sentimentos e hábitos alimentares, achamos importante lembrar que todas as fases de avaliação serão para chegarmos ao diagnóstico dos sintomas que o **participante do estudo apresenta** e não referente ao diagnóstico dos pais.

(1) Avaliação diagnóstica psiquiátrica, com duração de 1h30min. Nesta avaliação, vocês irão preencher alguns questionários sobre os próprios sentimentos e comportamentos no dia-a-dia e a forma como sua família se relaciona. É possível que vocês se sintam cansados e constrangidos por ter que responder tantos questionários sobre suas emoções.

(2) Avaliação Neuropsicológica. Nesta avaliação, será feita algumas atividades como contar números e completar figuras, ou seja, atividades escolares comuns.

(3) Avaliação Nutricional. Nesta avaliação, será feita uma avaliação das medidas do corpo, ou seja, peso, altura, avaliação do comportamento alimentar e do nível de atividade física do seu filho, através de perguntas sobre os hábitos alimentares dele e suas atividades diárias.

(4) Será feita uma coleta de saliva para avaliar possíveis marcadores dos genes do seu filho (a) que possam ter alguma associação com os transtornos de ansiedade.

(5) Avaliação do funcionamento do cérebro através de uma máquina de ressonância magnética funcional onde seu filho (a) ficará por aproximadamente 40 minutos dentro dela e realizará algumas tarefas simples como responder a algumas perguntas ou ouvir algumas histórias. Esse exame será realizado na PUCRS (Pontifícia Universidade Católica do Rio Grande do Sul, Av. Ipiranga, 6681 - Partenon - Porto Alegre/RS) e informará como algumas áreas do seu cérebro funcionam.

7. Riscos e inconveniências

Haverá acompanhamento dos pesquisadores em todas as etapas do projeto e dos seus procedimentos, porém lembramos que as tarefas a serem realizadas para a conclusão deste projeto possuem alguns riscos e/ou inconveniências para o participante: você e seu filho (a) poderão ficar cansados com o preenchimento dos questionários, já que são vários. Também podem se sentir ansiosos ou constrangidos por responder perguntas sobre seus próprios sentimentos e comportamentos no dia-a-dia, pois os conteúdos envolvem emoções, hábitos alimentares e de atividade física que podem ser desagradáveis. Tentaremos minimizar estes possíveis efeitos utilizando avaliadores treinados e instrumentos curtos. O exame do funcionamento do cérebro é um exame pelo qual não são conhecidos riscos para os participantes, porém é um pouco barulhento, o que pode fazer com que seu filho (a) se incomode com os ruídos e se sinta desconfortável em ficar deitado durante todo o tempo do exame. Vocês terão que se deslocar de sua casa por duas ou três vezes para que as coletas e o exame possam ser feitos.

8. Potenciais benefícios

Embora os resultados desta pesquisa possam não ajudar seu filho (a) diretamente, vocês terão uma avaliação clínica sobre diagnóstico em psiquiatria e uma avaliação neuropsicológica ou seja, as táticas que o cérebro dele (a) usa para resolver algumas tarefas; maior conhecimento acerca dos transtornos de ansiedade na infância e adolescência o que poderá ajudar no entendimento sobre a doença; maior conhecimento acerca do consumo alimentar do seu filho (a), bem como a composição corporal; e um exame de imagem sobre como o cérebro dele funciona durante a realização de algumas tarefas.

Gostaríamos ainda de deixá-lo ciente dos seguintes direitos que seu filho (a) terá:

a) **Garantia do uso dos dados colhidos apenas para a finalidade especificada nesse estudo:** Os dados obtidos somente serão usados para o fim previsto neste projeto de pesquisa e qualquer outro uso terá que se solicitar a sua autorização.
b) **Sigilo e privacidade:** As informações produzidas nesta tarefa serão mantidas em lugar seguro, com códigos e a identificação só poderá ser realizada pelo pessoal envolvido diretamente com o projeto. Caso o material venha a ser utilizado para publicação científica ou atividades didáticas, não serão utilizados nomes que possam vir a identificá-lo.
c) **Direito à informação**: Em qualquer momento do estudo você poderá obter mais informações com a Prof. Dra. **Gisele Gus Manfro** e/ou Prof. Dra. **Patrícia Pelufo** pelo telefone (0xx51) 3358-8983 ou (0xx51) 3359-8019, que estarão aptas a solucionar suas dúvidas. Você poderá solicitar informações de qualquer conhecimento significativo descoberto durante este projeto.
d) **Direito de informação sobre aspectos éticos da pesquisa:** Se você tiver alguma consideração ou dúvida sobre a ética da pesquisa, entre em contato com o Comitê de Ética em Pesquisa (CEP) – localizado no Hospital de Clínicas, no 2º andar, sala 2227, com horário de atendimento das 8h às 17h, Fone/Fax: (0xx51) 3359-7640
e) **Despesas e compensações**: Não há despesas pessoais, ou seja, não será cobrado nada a você em qualquer fase do estudo, incluindo exames e consultas. Também não há compensação financeira ou qualquer tipo de pagamento relacionado à sua participação. Se existir qualquer despesa adicional, ela será custeada pelo orçamento da pesquisa. Em caso de dano pessoal, diretamente causado pelos procedimentos ou tratamentos propostos neste estudo (nexo causal comprovado), você tem direito a tratamento médico na Instituição, bem como às indenizações legalmente estabelecidas.
f) **Direito a não participar ou interromper sua participação no estudo**: Você tem liberdade para se recusar a participar ou retirar seu consentimento, em qualquer fase da pesquisa, sem penalização alguma e sem prejuízo ao seu cuidado ou do seu filho (a).
g) **Garantia de assistência e de continuidade do tratamento:** Seu filho (a) será devidamente acompanhado e assistido durante todo o período de sua participação no projeto, bem como será encaminhado para a rede de assistência a saúde na ocasião de necessidade de cuidados adicionais.

Acredito ter sido suficientemente informado a respeito das informações que li ou que foram lidas para mim, descrevendo o estudo: "Restrição do crescimento intrauterino e trajetória desenvolvimental de adolescentes e adultos com e sem transtorno de ansiedade: desfechos em saúde mental, nutricional, epigenéticos, biomarcadores e de neuroimagem funcional"

Eu discuti com o pesquisador (a) sobre a minha decisão em autorizar meu filho (a) participar desse estudo. Ficaram claros para mim quais são os propósitos do estudo, os procedimentos a serem realizados, seus desconfortos e riscos, as garantias de confidencialidade e de esclarecimentos permanentes. Ficou claro também que a participação do meu filho (a) é isenta de despesas e terá garantia do acesso a tratamento hospitalar quando necessário. Concordo voluntariamente na minha participação do meu filho (a) e poderei retirar o meu consentimento a qualquer momento, antes ou durante o mesmo, sem penalidades ou prejuízo ou perda de qualquer benefício que eu possa ter adquirido, ou no meu atendimento neste Serviço.

Nome do participante:_____

_____ Data ____/___/___
Assinatura do (a) participante (em caso de maiores de 18 anos ou se a criança mesma puder fazê-la)

Nome do (a) representante legal:_____
_____ Data ___/___/___
Assinatura do (a) representante legal

Para casos de pacientes menores de 18 anos, analfabetos, semianalfabetos ou portadores de deficiência auditiva ou visual.

Nome do pesquisador (a):_____

_____
Assinatura do pesquisador (a) Data ___/___/___

(Somente para o responsável do projeto)
Declaro que obtive de forma apropriada e voluntária o Consentimento Livre e Esclarecido deste paciente ou representante legal para a participação neste estudo.

Este Termo de Consentimento Livre e Esclarecido (TCLE) é elaborado em duas vias, uma via fica com o participante e a outra com o pesquisador (a).

7.4. PRODUÇÃO CIENTÍFICA

Artigos publicados

1. Rodrigues, D. M.; Reis, R. S.; Molle, R. D.; Machado, T. D.; Mucellini, A. B.; Bortoluzzi, A.; Toazza, R.; Perez, J. A.; Salum, G. A.; Agranonik, M.; Minuzzi, L.; Levitan, R. D.; Buchweitz, A.; Franco, A. R.; Manfro, G. G.; Silveira, P. P. *Decreased comfort food intake and allostatic load in adolescents carrying the A3669G variant of the glucocorticoid receptor gene.* **Appetite**, p. 21-28, 2017. Fator de impacto: 3.403

2. Mucellini, A. B.; Fonseca, N. K. O.; Manfro, G. G.; Silveira, P. P. *Hippocampal insulin resistance and altered food decision-making as players on obesity risk.* ***Neuroscience and Biobehavioral Reviews***, 2017. Fator de impacto: 8.299

3. Reis, R. S.; Molle, R. D.; Machado, T. D.; Mucellini, A. B.; Rodrigues, D. M.; Bortoluzzi, A.; Bigonha, S. M.; Toazza, R.; Salum, G. A.; Minuzzi, L.; Buchweitz, A.; Franco, A.; Peluzio, M. C. G.; Manfro, G. G.; Silveira, P.P. *Impulsivity-based thrifty eating phenotype and the protective role of n-3 PUFAs intake in adolescents*. **Translational Psychiatry**, 2016. Fator de impacto: 4.73

4. Machado, T. D.; Molle, R. D.; Reis, R. S.; Rodrigues, D. M.; Mucellini, A. B. ; Minuzzi, L.; Rosa, A. F.; Buchweitz, A.; Toazza, R.; Ergang, B. C.; Cunha, A. C. A.; Salum, G. A.; Manfro, G. G.; Silveira, P.P. *Interaction between perceived maternal care, anxiety symptoms and the neurobehavioral response to palatable foods in adolescents*. **Stress** (Luxembourg. Print), 2016. Fator de impacto: 2.59

5. Toazza, R.; Franco, A. R.; Buchweitz, A.; Molle, R. D.; Rodrigues, D. M. ; Reis, R. S.; Mucellini, A. B.; Esper, N. B.; Aguzzoli, C.; Silveira, P. P.; Salum, G. A.; Manfro, G. G. *Amygdala-based intrinsic functional connectivity and anxiety disorders in adolescents and young adults*. **Psychiatry Research-Neuroimaging**, 2016. Fator de impacto: 1.878

6. Mucellini, A. B.; Manfro, G. G.; Silveira, P. P. *Tackling obesity: challenges ahead.* **Lancet** (British edition), 2015. Fator de impacto: 47.831

Artigos submetidos

1. Mucellini, A. B.; Dalle Molle, R.; Rodrigues, D. M.; Machado, T. D.; Reis, R. S.; Fonseca, N. K. O.; Franco, A. R.; Buchweitz, A.; Bortoluzzi, A.; Toazza, R.; Salum, G. A.; Nassim, M.; Meaney, M. J.; Silveira, P. P.; Manfro, G. G. *Insulin sensitivity associated with brain activation to palatable food images and implicit learned food preferences.* **Journal of Clinical Endocrinology and Metabolism**, 2017

2. Fonseca, N. K. O.; Machado T.; Dalle Molle, R.; Reis R. S.; Mucellini, A. B.; Rodrigues, D. M.; Toazza R.; Bortoluzzi A.; Manfro G. G.; Silveira, P. P. *Interaction between stress responsiveness and insulin sensitivity on eating behavior in adolescents*. **Nutritional Neuroscience**, 2017

3. Dalle Molle, R.; Minuzzi, L.; Machado, T. D.; Reis R. S.; Rodrigues, D. M.; Mucellini, A. B.; Franco, A.; Buchweitz, A.; Bortoluzzi, A.; Manfro, G. G.; Silveira, P.P. *Intrauterine growth programming of adolescent feeding behavior and related brain mechanisms.* **Nature Neuroscience**, 2015

Apresentações em eventos científicos

1. Mucellini, A. B.; Molle, R. D.; Machado, T. D.; Reis, R. S.; Ergang, B. C.; Rodrigues, D. M.; Bortoluzzi, A.; Toazza, R.; Silveira, Patrícia Pelufo; Manfro, G. G. *Impairment of memory related to food is associated with high levels of insulin and HOMA-IR in adolescents*. **XXII Annual Meeting of the Society for the Study of Ingestive Behavior**, 2014, Seattle.

2. Mucellini, A. B.; Reis, R. S.; Molle, R. D.; Machado, T. D.; Rodrigues, D. M.; Ergang, B. C.; Bortoluzzi, A.; Toazza, R.; Silveira, P.P.; Manfro, G. G. *Insulinemia, HOMA-IR e circunferência abdominal estão associados positivamente a prejuízos na memória relacionada aos alimentos em adolescentes*. **XXXIV Semana Científica do Hospital de Clínicas de Porto Alegre**, 2014, Porto Alegre.

3. Mucellini, A. B.; Molle, R. D.; Rodrigues, D. M.; Reis, R. S.; Machado, T. D.; Bortoluzzi, A.; Toazza, R.; Salum, G. A.; Manfro, G. G.; Silveira, P.P. *Low birth weight is associated with impairment of memory related to food in adolescents*. **IV International**

Symposium on Metabolic Programming and Stress & I Meeting of Ibero-American DOHaD Chapter, 2014, Ponta Grossa.

4. Reis, R. S.; Dalle Molle, R.; Machado, T. D.; Bortoluzzi, A.; Bigonha, S. M.; Mucellini, A. B.; Rodrigues, D. M.; Bernardi, J. R.; Peluzio, M. C. G.; Manfro, G. G.; Silveira, P. P. *Interaction between birth weight and the serum DHA concentration on external eating domain in adolescents and young adults.* **XII Annual Meeting of the Society for the Study of Ingestive Behavior**, 2014, Seattle.

5. Rodrigues, D. M.; Bortoluzzi, A.; Blaya, C.; Leistner-Segal, S.; Bosa, V. L.; Goldani, M. Z.; Mucellini, A. B.; Reis, R. S.; Molle, R. D.; Machado, T. D.; Toazza, R.; Manfro, G. G.; Silveira, P. P. *Polimorfismo A3669G do gene do receptor do glicocorticoide reduz consumo de açúcares, níveis glicêmicos e resistência à insulina em uma amostra de adolescentes.* **Cérebro, Comportamento e Emoções**, 2014, Gramado.

6. Machado, T. D.; Dalle Molle, R. D.; Reis, R. S.; Rodrigues, D. M.; Mucellini, A. B.; Ergang, B. C.; Salum, G. A.; Manfro, G. G.; Silveira, P. P. *A qualidade do cuidado materno recebido na infância interage com os níveis de cortisol e ansiedade na vida adulta, afetando o consumo calórico num ambiente novo em humanos.* **Cérebro, Comportamento e Emoções**, 2014, Gramado.

7. Reis, R. S.; Molle, R. D.; Machado, T. D.; Bortoluzzi, A.; Bigonha, S. M.; Mucellini, A. B.; Rodrigues, D. M.; Peluzio, M. C. G.; Manfro, G. G.; Silveira, P.P. *Interação entre o peso ao nascer e a concentração sérica de DHA no domínio ingestão externa em adolescentes e adultos jovens*. **XXXIV Semana Científica do HCPA**, 2014, Porto Alegre.

8. Machado, T. D.; Molle, R. D.; Reis, R. S.; Rodrigues, D. M.; Mucellini, A. B.; Ergang, B. C.; Toazza, R.; Manfro, G. G.; Silveira, P. P. *A qualidade do cuidado materno recebido na infância interage com os níveis de cortisol e ansiedade na vida adulta, afetando o consumo calórico num ambiente novo em humanos.* **XXXIV Semana Científica do HCPA**, 2014, Porto Alegre.

9. Mucellini, A. B.; Molle, R. D.; Rodrigues, D. M.; Reis, R. S.; Machado, T. D.; Minuzzi, L.; Franco, A.; Buchweitz, A.; Bortoluzzi, A.; Toazza, R.; Salum, G. A.; Manfro, G. G.; Silveira, P.P. *Intrauterine growth restriction (IUGR) is associated with impairment of memory related*

to food and differential brain activation in response to palatable food images in adolescents. **IX World Congress on Developmental Origins of Health and Disease**, 2015, Cape Town.

10. Toazza, R.; Franco, A.; Salum, G. A.; Desouza, D.; Dalle Molle, R.; Rodrigues, D. M.; Reis, R. S.; Mucellini, A. B.; Flores, S. M.; Silveira, P.P.; Buchweitz, A.; Manfro, G. G. *Emotional Narratives Processing in Adolescents and Young Adults with Anxiety Disorders*. **XXI Annual Meeting of the Organization for Human Brain Mapping**, 2015, Honolulu.

11. Correa, C. N.; Mucellini, A. B.; Dalle Molle, R. D.; Machado, T. D.; Reis, T.; Henriques, T. P.; Pardo, G. V. E.; Manfro, G. G.; Silveira, P.P. *Ontogeny of anxiety-like behavior in juvenile male rats caused by neonatal stress model: behavioral and hippocampal 5HT1A receptor evaluations.* **IX IBRO World Congress on Neuroscience**, 2015, Rio de Janeiro.

12. Toazza, R.; Franco, A.; Salum, G. A.; Desouza, D. ; Dalle Molle, R. D.; Rodrigues, D. M.; Reis, R. S.; Mucellini, A. B.; Flores, S. M.; Silveira, P.P.; Buchweitz, A.; Manfro, G. G *Emotional narratives processing in adolescents and young adults with anxiety disorders.* **VIII World Congress on Brain, Behavior and Emotions**, 2015, Porto Alegre.

13. Mucellini, A. B.; Borges, M. B.; Salvador, A. P.; Cunha, A. C. A.; Manfro, G. G.; Silveira, P.P. *Efeito da restrição de crescimento intrauterino (RCIU) e da dieta hiperlipídica-sacarídica na memória alimentar de ratos.* **IX Oficina de Neurociências**, 2016, Bento Gonçalves.

14. Mucellini, A. B.; Salvador, A. P.; Borges, M. B.; Laureano, D. P.; Manfro, G. G.; Silveira, P.P. *Resistência à insulina periférica e hipotalâmica em ratos nascidos com restrição de crescimento intrauterino (RCIU) e alimentados com dieta hiperlipídica e hipersacarídica.* **IX Oficina de Neurociências**, 2016, Bento Gonçalves.

15. Laureano, D. P.; Alves, M. B.; Miguel, P. M.; Machado, T. D.; Reis, A. R.; Mucellini, A. B.; Silva, F. C.; Molle, R. D.; Desai, M.; Ross, M. G.; Silveira, P.P. *Nascer pequeno modifica a resposta ao alimento doce - estudo da via dopaminérgica*. **II Prêmio Ciência nos Primeiros 1000 dias**, 2016, São Paulo.

16. Borges, M. B.; Mucellini, A. B.; Silva, F. C.; Silveira, P.P.; Rasia Filho, A. A.. *Estudo sobre o efeito da restrição de crescimento intrauterino no perfil metabólico de ratos*

expostos a ambientes neutro, saudável e obesogênico. **XXXVI Semana Científica do HCPA**, 2016, Porto Alegre.

17. Fonseca, N. K. O.; Mucellini, A. B.; Dalle Molle, R.; Rodrigues, D. M.; Reis, R. S.; Machado, T. D.; Bortoluzzi, A.; Toazza, R.; Agranonik, M.; Salum, G. A.; Manfro, G. G.; Silveira, P.P. *Negative correlation between caloric consumption and cognitive competence in young people*. **IX World Congress on Brain, Behavior and Emotions 2016**, Buenos Aires.

18. Laureano, D. P.; Alves, M. B.; Miguel, P. M.; Machado, T. D.; Reis, A. R.; Mucellini, A. B.; Cunha, F. S.; Dalle Molle, R; Ross, M. G.; Desai, M.; Silveira, P.P. *Exposure to intrauterine growth restriction (IUGR) modifies the accumbal dopamine response to palatable food intake and its modulation by insulin in adulthood in rats.* **Neuroscience Meeting Planner**, 2016, San Diego.

19. Rodrigues, D. M.; Reis, R. S.; Dalle Molle, R. D.; Machado, T. D.; Mucellini, A. B.; Toazza, R.; Perez, J. A.; Salum, G. A.; Agranonik, M.; Minuzzi, L.; Levitan, R. D.; Buchweitz, A.; Franco, A. R.; Manfro, G. G.; Silveira, P. P. Decreased comfort food intake and allostatic load associated with frontoparietal brain activity in relationship to a functional polymorphism of the glucocorticoid receptor gene. **Society for Behavioral Neuroendocrinology Annual Meeting Program**, 2016, Montreal.

20. Mucellini, A. B.; Rodrigues, D. M.; Dalle Molle, R.; Machado, T. D.; Reis, R. S.; Minuzzi, L.; Franco, A. R.; Buchweitz, A.; Bortoluzzi, A.; Toazza, R.; Salum, G. A.; Silveira, P. P.; Manfro, G. G. *Low birth weight is associated with altered food choice and brain activation in adolescents*. **V International Symposium on Metabolic Programming and Stress & II Meeting of Ibero-American DOHaD Chapter**, 2016, São Luís.

21. Mucellini, A. B.; Machado, T. D.; Borges, M. B.; Salvador, A. P.; Cunha, A. C. A.; Laureano, D. P.; Manfro, G. G.; Silveira, P. P. *IUGR associated with palatable diet leads to differential food memory and insulin resistance in rats*. **V International Symposium on Metabolic Programming and Stress & II Meeting of Ibero-American DOHaD Chapter**, 2016, São Luís.

22. Laureano, D. P.; Alves, M. B.; Miguel, P. M.; Machado, T. D.; Reis, A. R.; Mucellini, A. B.; Silva, F. C.; Dalle Molle, R. *Intrauterine growth restriction persistently*

changes the degree of reward to the sweet food - study of dopaminergic pathway. **V International Symposium on Metabolic Programming and Stress & 2nd Meeting of Ibero-American DOHaD Chapter**, 2016, São Luis.

23. Dalle Molle, R.; Minuzzi, L.; Machado, T. D.; Reis, R. S.; Rodrigues, D. M.; Mucellini, A. B.; Franco, A.; Buchweitz, A.; Manfro, G. G.; Silveira, P. P. *Eating Behavior in Fetal Growth Restricted Adolescents: Programming Goes Beyond Food Preferences.* **V 5th International Symposium on Metabolic Programming and Stress & 2nd Meeting of Ibero-American DOHaD Chapter**, 2016, São Luis.

24. Cunha, F. S.; Dalle Molle, R.; Machado, T. D.; Laureano, D. P.; Mucellini, A. B.; Alves, M. B.; Silveira, P.P. *Intrauterine Growth Restriction (IUGR) alters the Place Conditioning in Rats?.* **V International Symposium on Metabolic Programming and Stress & 2nd Meeting of Ibero-American DOHaD Chapter**, 2016, São Luis.

25. Tofolo, L. P.; Mucellini, A. B.; Laureano, D. P.; Machado, T. D.; Alves, M. B.; Figueroa, C.; Palma-Rigo, K.; Mathias, P. C. F.; Silveira, P.P. *Feeding behavior changes in detrained young adult rats exposed to high-fatsugar diet intake*. **V International Symposium on Metabolic Programming and Stress & 2nd Meeting of Ibero-American DOHaD Chapter**, 2016, São Luis.

26. Mucellini, A. B.; Rodrigues, D. M.; Dalle Molle, R.; Machado, T. D.; Reis, R. S.; Minuzzi, L.; Agranonik, M; Franco, A. R.; Buchweitz, A.; Toazza, R.; Salum, G. A.; Bortoluzzi, A.; Silveira, P. P.; Manfro, G. G. *Low birth weight is associated with altered food choice and brain activation in adolescents*. **X World Congress on Brain, Behavior and Emotions**, 2017, Porto Alegre.

27. Mucellini, A. B.; Borges, M. B.; Salvador, A. P.; Laureano, D. P.; Alves, M. B.; Manfro, G. G.; Silveira, P. P. *IUGR associated with palatable diet leads to differential food memory and insulin resistance in rats.* **X World Congress on Brain, Behavior and Emotions**, 2017, Porto Alegre.

7.5. PRÊMIOS CIENTÍFICOS

Honor David Barker Award

Melhor apresentação oral – Mucellini, A. B.; Molle, R. D.; Rodrigues, D. M.; Reis, R. S.; Machado, T. D.; Bortoluzzi, A.; Toazza, R.; Salum, G. A.; Manfro, G. G.; Silveira, P.P. *Low birth weight is associated with impairment of memory related to food in adolescents*. **IV International Symposium on Metabolic Programming and Stress & I Meeting of Ibero-American DOHaD Chapter, 2014**, Ponta Grossa.

4th INTERNATIONAL SYMPOSIUM ON METABOLIC PROGRAMMING AND STRESS

&

1st MEETING OF IBERO-AMERICAN DOHaD CHAPTER
DEVELOPMENTAL ORIGINS OF HEALTH AND DISEASE

Certificate of Participation

We certify that **Amanda Brondani Mucellini**
won the *Honor David Barker Award* (Short Communication) in the 4th International Symposium on Metabolic Programming and Stress and 1st Meeting of Ibero-American DOHaD Chapter - Developmental Origins of Health and Disease, held from November 13th until November 16th, Ponta Grossa, Brazil.

Ponta Grossa, **November 16th**, 2014.

Paulo C.F. Mathias

Prêmio Ciência nos Primeiros 1000 dias

Segundo melhor trabalho de pesquisa avançada – Laureano, D. P.; Alves, M. B.; Miguel, P. M.; Machado, T. D.; Reis, A. R.; Mucellini, A. B.; Silva, F. C.; Molle, R. D.; Desai, M.; Ross, M. G.; Silveira, P.P. *Nascer pequeno modifica a resposta ao alimento doce - estudo da via dopaminérgica*. **II Prêmio Ciência nos Primeiros 1000 dias**, 2016, São Paulo.