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Influence of Environmental Enrichment on Morphine-Exposed Neonate Rats: Effect on Neurodevelopment and Long-term Memory

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Introduction: Stressful stimuli and the use of drugs in early life may affect neurodevelopment, altering behaviors, memory and nociceptive response. Environmental enrichment may be a non-pharmacological alternative to avoid the deleterious effects caused by repeated administration of morphine in a period of high neuroplasticity **Objective:** the aim of this study was to evaluate the short term effects of early EE in neurodevelopment, long-term memory and nociceptive response after neonatal morphine exposure in male rats. **Methods:** 28 pups were divided into four experimental groups: saline + standard housing (SS); saline + enriched housing (SE); morphine + standard housing (MS) or morphine + enriched housing (ME).The newborns received daily (P8-P14) subcutaneous injections of saline (5 µl) or morphine (5 µg/5 µl) and were submitted to manipulation or EE (P8-P21). The righting reflex (P9-P10) and negative geotaxis (P10, P12, P14, P16, P18, P20), the object recognition (P20) and the hot plate (P20) tests were used to evaluate neuromotor reflexes, long-term memory and thermal hyperalgesia, respectively. The results of the neurobehavioral tests and object recognition were analyzed using a generalized estimation equation (GEE). The nociceptive behavioral test was evaluated using non-parametric Kruskall Walis test. Data were expressed as mean ± standard error of the mean (SEM). All results were considered statistically significant if $p < 0.05$. The SPSS 20.0 software was used for statistics. CEUA 2018.0187. **Results:** Animals that received morphine showed slower response in the neuromotor reflexes compared to the saline group, an effect that was age-dependent. Animals that received morphine showed less ability to recognize a new object in the environment, an effect that was partially reversed by EE. Nociceptive response was not altered for morphine or EE groups. **Conclusion:** In summary, our study demonstrates that premature exposure to morphine negatively affects behavioral development and long-term memory in neonate rats, and that EE may be a non-pharmacological alternative to avoid the deleterious effects caused by repeated administration of opioids in a period of high neuroplasticity. In this way, the preclinical models involving this type of intervention are of high relevance.

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