Deleterious effects of prenatal exposure to morphine on the spatial learning and hippocampal BDNF and long-term potentiation in juvenile rats: Beneficial influences of postnatal treadmill exercise and enriched environment

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\section*{A B S T R A C T}

Prenatal morphine exposure causes a variety of neurobehavioral alterations observed in later life. The present study investigated the effects of postnatal exercise and enriched environment (EE) on alterations in water maze learning and hippocampal long-term potentiation (LTP) and brain derived neurotrophic factor (BDNF) levels induced by exposure to morphine during prenatal period in rats. On gestation days 11–18, pregnant rats were injected twice daily with saline or morphine. Offspring were subjected to postnatal exercise and EE for 30 days and afterward, spatial learning and hippocampal LTP and BDNF levels were investigated. Prenatal morphine-exposure impaired the spatial learning and hippocampal LTP in both male and female offspring. Interestingly, postnatal exercise and EE increased performance in the water maze and improved LTP in both prenatally saline and morphine-exposed male and female rats. Prenatal morphine exposure also caused a reduction in the hippocampal BDNF levels in the female, but not male rats, and postnatal exercise and EE alleviated this deficit. Our results demonstrate that postnatal exercise and EE can improve deficits in water maze learning and hippocampal LTP and BDNF levels caused by prenatal morphine exposure.

\section*{1. Introduction}

Exposure to the drug of abuse can influence individuals throughout life, initiating in prenatal life. Exposure to opioids during pregnancy can predispose individuals to the expansion of physiological and affective deficits that continue through adulthood. In opioid addiction, children born to morphine – or heroin – addicted mothers have been shown to have greater mortality and deficit in the central nerve system (CNS) (Ostrea, Ostrea, & Simpson, 1997; Yanai et al., 2003).

Opioids are used routinely and effectively for the treatment of pains and their effects are caused by binding to classical opioid receptors and/or Toll-like receptors existing at CNS (Chaves, Remião, Cisternino, & Declèves, 2017). Exposure to opioids during prenatal life can change opioid receptor distribution and density, this, in turn, could affect the development of neural connections by accelerating or delaying neural outgrowth during fetal and/or postnatal periods (Vathy, 1995).

Prenatal contact to inflammatory or infectious insults can increase the risk of developing neuropsychiatric disorder in later life, including schizophrenia, bipolar disorder, and autism and prenatal immune activation induces adult onset of presynaptic hippocampal deficits (Giovannoli, Weber-Staiblauer, Schedlowi, Meyer, & Engler, 2016).

One of the most broadly abused substances is morphine, and its influences on prenatal development and infant consequences of addicted mothers have been well investigated. The effects of morphine on spatial learning and memory are controversial. Different studies indicate negative or positive effects of morphine on learning and memory processes in rodents (Classen & Mondadori, 1984; McNamara &

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