孕期類鴉片藥物暴露對子代甲基安非他命致敏化之影響

Development of Sensitization to Methamphetamine in Morphine, Methadone, and Buprenorphine Prenatally Exposed Offspring

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Objectives : Heroin use among young women of reproductive age has drawn much attention around the world. However, there is lack of information on long-term effects of prenatal exposure to opioids on their offspring. In our previous study, results obtained demonstrated that a marked change of the cross-tolerance to morphine occurred in prenatally buprenorphine-exposed offspring than others tested. In this study, this animal model was used to study effects of methamphetamine (METH)-induced behavioral sensitization in the offspring at their adulthood.

Methods : Rats were prenatally exposed to vehicle, morphine (2-4 mg/kg, 1 mg increment per week, twice a day), methadone (5 mg/kg on E3, than 7 mg/kg twice a day), and buprenorphine (3 mg/kg, once a day) from embryonic day 3 to day 20. Effects of prenatal exposure to opioids on METH-induced behavioral sensitization and conditioned place preference (CPP), levels of receptors' mRNA and cAMP in the nuclease accumbens (NAc) were studied at their adulthood.

Results : The distances and rate of development (slope) of locomotor activity induced by METH (2 mg/kg) were significantly increased in the prenatally buprenorphine-exposed group than those of other groups.

Prenatally buprenorphine-exposed offspring was more sensitive to lower dose of METH (0.5 mg/kg) in the conditioned place preference (CPP) test. There was lower mRNA expression of dopamine D1 receptor (D1R) in the NAc of the prenatally buprenorphine-exposed offspring, but no significant changes in μ-opioid, NOP, D2R and D3R were noted. Furthermore, significant alterations were observed in the basal level of cAMP and the D1R agonist SKF-38393 enhanced adenylyl cyclase activity in the prenatally buprenorphine-exposed group than that of the groups prenatally exposed to vehicle, morphine and methadone.

Conclusions：The study demonstrates that D1R and its down-regulated cAMP signals are involved in enhancing METH-induced behavioral sensitization in the prenatally buprenorphine-exposed offspring. The study reveals that prenatal exposure to buprenorphine caused long-term effects on the offspring and affected the dopaminergic system-related reward system.
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