Enhancement of tolerance development to morphine in rats prenatally exposed to morphine, methadone and buprenorphine

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Abstract

Abuse of addictive substances is a serious problem which has significant impact on health, economy, public and society safety. Heroin use in young women at reproductive ages has drawn much attention around the world. However, there is a lack of information on effects of prenatal exposure of opioids on the offspring. In this study, an animal model was established to study effects of prenatal exposure of opioids. Female pregnant Sprague-Dawley rats were sub-grouped to receive (1) vehicle, (2) 2 to 4 mg/kg morphine (1 mg/kg increment per week), (3) 7 mg/kg methadone, and (4) 3 mg/kg buprenorphine, subcutaneously, once or twice a day from E3 to E20. These animals then waited for parturition. Results showed that prenatal exposure of buprenorphine caused higher mortality than that of the morphine or methadone administered group. Although we observed a signaticantly lower increase in body weight in all of the opioid-administered dams, prenatal exposure of opioids did not alter the birth weight of the offspring in all treated groups. There were no obvious behavioral abnormality and body weight changes being noted during the growing period (8-12 weeks) in all offsprings that have been prenatally exposed to opioids. When the male offsprings received morphine injection twice a day for a duration of 4 days, the prenatally opioid-exposed rats developed faster tolerance to morphine as shown by the tail-flick tests, most notably the prenatally buprenorphine-exposed offspring. At the 4^{th} day of morphine injection (the 7^{th}), a significant decrease in the area under the curve (AUC) was shown in the prenatally opioid-exposed animals in comparison to the prenatally saline-exposed group in the tail-flick test. However, the tolerance development to methadone or buprenorphine was not different in methadone or buprenorphine prenatally exposed offsprings, respectively, when compared with that of the vehicle controlled group. The similar results were also obtained in the female animals. The data indicate that animals prenatally exposed to morphine, methadone, or buprenorphine developed tolerance to morphine faster than their controlled mates.

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