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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 that has a significant impact on areas such as health, the economy, and public safety. Heroin use among young women of reproductive age has drawn much attention around the world. However, there is a lack of information on effects of prenatal exposure to opioids on their offspring. In this study, an animal model was established to study effects of prenatal exposure to opioids on offspring.

In this study, female pregnant Sprague-Dawley rats were sub-grouped to receive (1) vehicle, (2) 2-4 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. The experiments were conducted on animals 8-12 weeks old and with body weight between 250 and 350 g.

Results showed that prenatal exposure to buprenorphine caused higher mortality than other tested substance groups. Although we observed a significantly lower increase in body weight in all of the opioid-administered dams, the birth weight of the offspring was not altered in all treated groups. Moreover, no obvious behavioral abnormality or body-weight difference was noted during the growing period (8-12 weeks) in all offspring. When the male offspring received morphine injection twice a day for 4 days, the prenatally opioid-exposed rats more quickly developed tolerance to morphine (as shown by the tail-flick tests), most notably the prenatally buprenorphine-exposed offspring. However, the tolerance development to methadone or buprenorphine was not different in offspring exposed prenatally to methadone or buprenorphine, respectively, when compared with that of the vehicle controlled group. Similar results were also obtained in the female animals.

In conclusion, animals prenatally exposed to morphine, methadone, or buprenorphine developed tolerance to morphine faster than their controlled mates. In our animal model, prenatal exposure to buprenorphine also resulted in higher mortality and much less sensitivity to morphine-induced antinociception than prenatal exposure to morphine or methadone. This indicates that buprenorphine in higher doses may not be an ideal maintenance drug for treating pregnant women. This study provides a reference in selecting doses for clinical usage in treating pregnant heroin addicts.

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