Prenatal methamphetamine exposure alters the effect of methamphetamine and cocaine challenge dose on behavior and nociception in adult male rats

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Introduction

✓ There are studies demonstrating that repeated administration of psychostimulants such as methamphetamine (MA) enhance locomotor activities tested in the Open field (OF) in response to treatment of the same or related drugs in rodents. This phenomenon is defined as behavioral sensitization or reverse tolerance (Suzuki et al. 2004). Once behavioral sensitization is established, it persists for several months (Cornish and Kalivas 2001).

✓ There are, however, no studies investigating possible sensitizing effect of prenatal MA exposure. Only few recent studies (Crozatier et al. 2003; Stanwood and Levitt 2003) examining the sensitizing effect of prenatal exposure to cocaine are available. They demonstrated that prenatally cocaine-exposed rats are more sensitive to acute cocaine injection than prenatally saline-exposed rats.

✓ There are studies showing that abuse of one drug may increase sensitivity of abusing another drug. This effect is called cross-sensitization (Arnold 2005; Bartoletti et al. 1985; Fattore et al. 2005; He and Grasing 2004; Leri et al. 2003; Liu et al. 2007; Valvassori et al. 2007). Cross-sensitization between amphetamine and cocaine was first demonstrated with locomotor activity (Bonate et al. 1997; Shuster et al. 1977).

✓ Recently we have shown that MA-induced analgesia develops faster in prenatally MA-exposed rats than in control animals (Yamamotová in press), although analgesic effect of the drug was in both groups similar (Franklin 1998). We also showed that analgesia was increasing in rostro-caudal direction.

✓ Therefore, the aim of the present study was to examine the effect of prenatal MA exposure on behavior and nociception after challenge dose of the same drug (MA) and drug with similar mechanism of action (CO) in adulthood.

Methods

✓ ***Prenatal exposure:*** Pregnant female rats were injected subcutaneously (s.c.) with MA (5 mg/kg) or saline (the same volume as MA) through the entire gestation.

✓ ***Challenge dose of drugs in adulthood:*** Adult male rats (postnatal day 90) from each group were divided into groups:

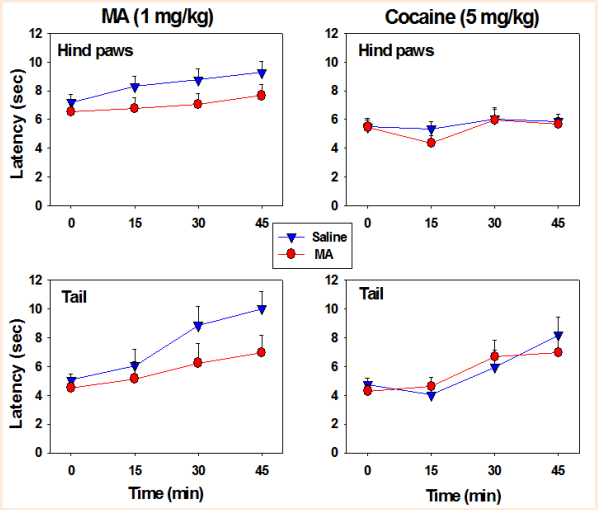
- administration of **methamphetamine** - animals received saline or MA in the dose of 1 mg/kg
- administration of **cocaine** – animals received saline or CO in the dose of 5 mg/kg

✓ ***Behavioral test – Open field:*** Laboras apparatus (Metris B.V., Netherlands) was used to test behavior in adult male rats. Immediately after single s.c. injection (saline or drug), the rat was placed to the testing Laboras cage. The behavior was monitored for 1 hour in the Laboras open field apparatus. Following parameters were analyzed in each animal in 10-minute intervals of testing: the duration spent by locomotion, immobility, rearing (exploratory behavior), grooming (comfortable behavior), the distance traveled, average and maximal speed of locomotion. Number of boli was recorded at the end of each test.

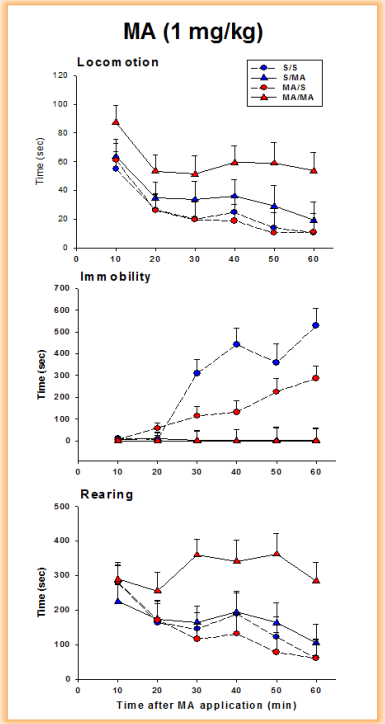
✓ ***Nociception - Plantar test:*** Latencies of withdrawal reflexes of hind paws and the tail on thermal nociceptive stimuli (Plantar Test, Ugo Basile, Comero, Italy) were repeatedly measured in 15-min intervals after the application of single s.c. injection (MA or CO). Last measurement was performed 45 min after the injection.

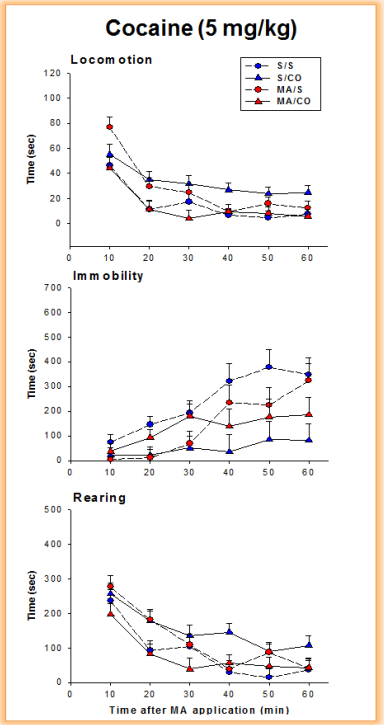
✓ ***Statistical analyses:*** Two-way ANOVA (prenatal drug x challenge injection) with repeated measure (minutes) with the Bonferroni *post hoc* t-test when appropriate was used. Significance level was set at $p<0.05$.

Results - Plantar



Results - Laboras





Summary

Methamphetamine

✓ Prenatal MA exposure increased the sensitivity to MA challenge dose in adulthood.
- MA/MA animals spent more time by locomotion and rearing.
- MA/MA animals had decreased pain threshold.

✓ Challenge dose of MA decreased immobility in both, prenatally MA- and saline-exposed rats.

Cocaine

✓ In the LABORAS test, prenatal MA exposure seems to induce rather desensitizing than sensitizing effect.
- Challenge dose of cocaine decreased the immobility in the second half of the LABORAS test. The difference was more apparent in prenatally saline-exposed animals.
- There was slight increase of locomotion and rearing after cocaine challenge dose, especially in animals prenatally exposed to saline.

✓ Challenge dose of cocaine show analgetic effect only at the tail, but not at the hind paws.

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Conclusion

✓ Our results suggest that prenatal MA exposure induces long-lasting changes in the sensitivity to drugs in adulthood. The sensitizing effect seems to be more apparent if the same drug is administered in adulthood.

Plans for future

✓ Our future studies will examine the possible sensitizing effect by using challenge dose of drugs with other mechanisms of action (morphine, THC). .

✓ In addition, drug-seeking behavior will be tested in adult animals prenatally exposed to MA, to show, whether prenatally MA-exposed animals are more predisposed to drug addiction in adulthood than control rats.

Laboras