SENSITIVITY TO METHAMPHETAMINE IN ADULTHOOD IS INCREASED IN RATS PRENATALLY EXPOSED TO THE SAME DRUG

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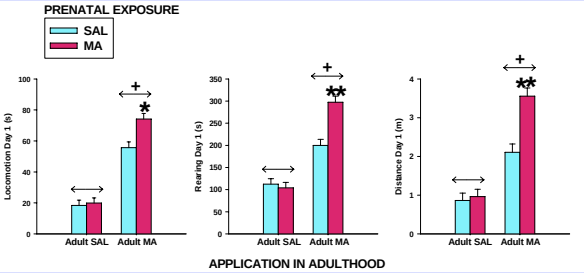
INTRODUCTION

- Intermittent administration of psychostimulants such as methamphetamine (MA) was shown to induce behavioral sensitization in adult individuals (Stewart et al., 1993).
- Once sensitized, the individuals may remain hypersensitive to the drug activating effects for months or years (Camp & Robinson, 1991).
- Experimental studies demonstrated that previous experience with amphetamines increased place preference and drug self-administration in rats (Pierre & Vezina, 1997, Shippenberg & Heidbreder, 1995). In humans, behavioral sensitization is assumed to be responsible for drug abuse relapse (Bartlett et al., 1997).
- Since half of MA users are women of reproductive age, there is an increased risk of negative consequences for their children (Williams et al., 2003).
- Prenatal exposure to MA increased sensitivity to the neurotoxic effects of MA in adult mice (Heller et al., 2001). Prenatal exposure to cocaine increased sensitivity to psychostimulant effects of amphetamine in adulthood (Glatt et al., 1999).
- In contrast, profound behavioral tolerance to amphetamine challenge was shown in rabbit offspring prenatally exposed to cocaine (Stanwood et al., 2003).
- **The aim** of the present study was to find out whether **prenatal exposure to MA is able to affect behavior and responsiveness to MA challenge in adulthood.**

RESULTS I

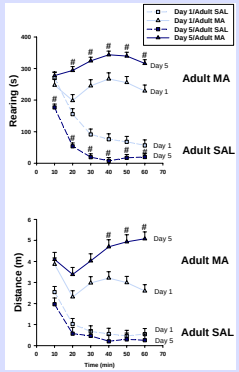
Acute MA in adulthood vs prenatal exposure



Values are means ± SEM (n=8). +p<0.0001 vs. Adult SAL, *p<0.01 vs. SAL/ Adult MA, **p<0.001 vs. SAL/Adult MA

RESULTS II

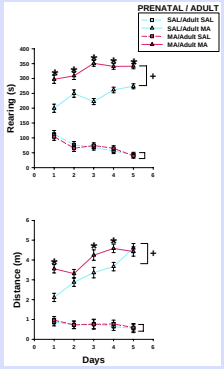
Behavioral sensitization



Values are means ± SEM (n=16). #p<0.01 vs. Day 1

RESULTS III

Chronic MA in adulthood vs prenatal exposure



Values are means ± SEM (n=8). +p<0.0001 vs. Adult SAL, *p<0.01 vs. SAL/ Adult MA

METHODS

Drug administration:

- Prenatal exposure – pregnant dams were injected daily with MA 5 mg/kg or saline (SAL) subcutaneously (s.c.) during the whole gestation. The offspring were marked according to the prenatal exposure by using the intradermal application of black India ink; MA group in the left foot pad, SAL group in the right foot pad.
- Application in adulthood – adult male offspring were injected with MA 1 mg/kg or SAL s.c. every day immediately prior to testing. Each animal was administered the same treatment during the whole testing period.

Experimental groups (Prenatal exposure / Application in adulthood):
1) SAL / Adult SAL; 2) SAL / Adult MA; 3) MA / Adult SAL; 4) MA / Adult MA.

Behavioral testing:

- Behavior of adult male offspring was tested in the LABORAS apparatus (Metris B.V., Netherlands), during the dark phase of the light/dark cycle – fully automated behavior tracking and evaluation (Fig. 1).
- One animal was tested for 5 consecutive days. The test started by placing a rat into the center of the LABORAS cage for 1h daily. The animals were not habituated to the apparatus, so they were exposed to a novel environment on the first day of the testing and we could observe the rate of their habituation to that environment during the following 4 days.
- Monitored behaviors: time (s) spent by locomotion, exploratory behavior (rearing), immobility, distance traveled (m) and average speed (cm/s) were evaluated in 10-minute intervals (window) of the 1h period.

Statistics: Three-way ANOVA (Prenatal exposure x Application in adulthood x Window) was used for each behavior separately. Fisher's LSD test was used for post-hoc analysis. Differences were considered significant if $p < 0.05$.

FIGURE I

Laboras (Metris B.V., Netherlands)

SUMMARY

- Acute MA 1 mg/kg in adulthood increased locomotion, rearing, average speed and distance traveled and decreased immobility in the LABORAS.
- Chronic MA administration in adulthood further increased the psychomotor activation during the 5 days' testing period and thus, elicited behavioral sensitization in both prenatally exposed groups.
- Although prenatal MA exposure did not affect the baseline behavior in adulthood, rats prenatally exposed to MA spent more time by rearing and had longer trajectory after both, acute and chronic MA application in adulthood than rats with SAL exposure in prenatal period.

CONCLUSION

Prenatal exposure to MA 5 mg/kg increases the sensitivity to application of the same drug in adulthood and thus, is able to elicit long-term changes, which are located probably in the mesolimbic dopamine system.

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