SHORT REPORT

The change of behavioural methamphetamine effect after repeated MDMA administration in mice

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Introduction

Repeated administration of various drugs of abuse may result in an increased behavioural response to them. This phenomenon is described as behavioural sensitization (Robinson & Berridge 1993; Ohmori *et al* 2000). It is also known that an increased response to a drug may be elicited by previous repeated administration of another drug, a phenomenon known as cross-sensitization (Cadoni *et al* 2001). We focused our previous experiments on behavioural sensitization to methamphetamine (Met) and cannabinoids, which in the Czech Republic belong to the most frequently abused drugs. Data obtained from these experiments indicated that cannnabinoid use could increase the vulnerability to methamphetamine consumption, because pre-treatment with cannabinoid CB_1 receptor agonist methanandamide elicited behavioural cross-sensitization to Met stimulatory effects (Landa *et al* 2006). Another very popular drug of abuse is ecstasy (MDMA). Kalivas *et al.* (1998) reported a development of behavioural sensitization to its effects increasing motor activity in rats and Itzhak *et al.* (2004) in mice. Therefore, in the present study, we decided by analogy to test a possible cross-sensitization to Met with MDMA, and vice versa with Met repeated pre-treatment to MDMA effects.

Methods

For the purposes of the presented study we used our original dosage regimen. Male mice were randomly divided into 5 groups ($n_1 = 7$, $n_2 = 12$, $n_3 = 10$, $n_4 = 7$, $n_5 = 12$) and all were given vehicle on the Day 1 of the study. There were no applications from the Days 2 to 6. For the next 7 days animals were treated repeatedly as follows: a) $n_1 = 10.0$ ml/kg/day of vehicle, b) $n_{2,\,4}$ = 15 mg/kg/day of MDMA (dissolved in distilled water), c) $n_{3,\,5} = 2.5$ mg/kg/day of Met (dissolved in saline). On the Day 14 animals in 5 groups received substances according to this schema: $n_1 = 10.0$ ml/kg of vehicle, $n_{2,\,5} = 15$ mg/kg of MDMA, $n_{3,\,4} = 2.5$ mg/kg of Met. There were no applications in Days 15 to 20. On the Day 21 a challenge dose of Met (2.5 mg/kg) was given to the groups $n_{3,\,4}$ and a challenge dose of MDMA (15 mg/kg) to the groups $n_{2,\,5}$. The group n_1 was a control and animals were given vehicle (10 ml/kg). Locomotor activity (Distance Travelled) in the open field test was measured by Actitrack apparatus (Panlab, S.L., Spain) on the Days 1, 7, 14 and 21 (fifteen minutes after administration of Met and thirty minutes after administration of MDMA). Data were analysed using Kolmogorov-Smirnov test of normality and unpaired *t-test*.

Results and conclusions

The present results confirmed that the pre-treatment with methamphetamine led in mice to the development and expression of behavioural sensitization to its stimulatory effects in the open field test (n_3). Interestingly, we observed neither development nor expression of sensitization to MDMA repeated treatment (n_2), however development and expression of cross-sensitization occurred following methamphetamine challenge dose after MDMA pre-treatment (n_4), whereas no cross-sensitization was registered following MDMA challenge dose after methamphetamine pre-treatment (n_5) – for more details see ***Figure 1***.

No signs of behavioural sensitization after repeated MDMA treatment (group n_2) in this study are in conflict with our previous studies (Landa *et al* 2005) and also with findings of other authors (Itzhak *et al* 2004). As the strain of the animals and the dosage regimens were the same as in our previous experiments, the reason for this could be a seasonal variability. The

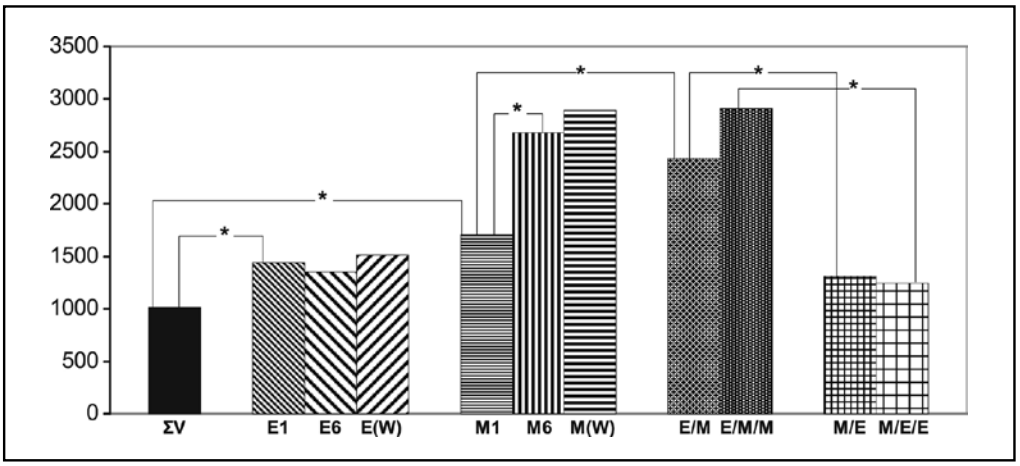

Figure 1: Effects of drug treatments on Distance Travelled (cm/3 min) in the mouse open field test shown as means:
ΣV = mean value of the total vehicle treated mice ($n_1+n_2+n_3+n_4+n_5$), E1 = 1st dose of MDMA; E6 = 6th dose of MDMA, E(W) = "challenge dose" of MDMA following wash-out period (n_2); M1 = 1st dose of methamphetamine, M6 = 6th dose of methamphetamine, M(W) = "challenge dose" of methamphetamine following wash-out period (n_3); E/M = 1st dose of methamphetamine after repeated MDMA pre-treatment, E/M/M = "challenge dose" of methamphetamine following wash-out period after repeated MDMA pre-treatment and the 1st methamphetamine dose(n_4); M/E = 1st dose of MDMA after repeated methamphetamine pre-treatment, M/E/E = "challenge dose" of MDMA following wash-out period after repeated methamphetamine pre-treatment and the 1st MDMA dose (n_5).
* = $p < 0.05$ - the unpaired t test

occurrence of cross-sensitization in group n_4 (pre-treatment with MDMA, methamphetamine challenge doses) was the most important finding of this study. It suggests a sensitizing influence of MDMA that could contribute in individuals experienced with MDMA to a possible increase in their inclination to methamphetamine intake. Nevertheless, the results did not show this phenomenon also reversely after MDMA challenge following methamphetamine pre-treatment.

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