The effect of sertindole on behavioural sensitisation to methamphetamine in mice

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ABSTRACT: Similarly to various other addictive substances, methamphetamine (Met) produces, following repeated application, a strong increase in behavioural responses (particularly locomotor behaviour), a phenomenon termed behavioural sensitisation. In our previous studies we tested the effects of various psychotropic drugs on behavioural sensitisation to Met, particularly the effects of cannabinoid receptor ligands with different intrinsic activities and felbamate and memantine, antagonists of *N*-methyl-D-aspartate (NMDA) receptors. In the present study we investigated the influence of the antipsychotic drug sertindole (Srt) on sensitisation to the effects of Met on mouse locomotor behaviour in the Open field test. Male mice were randomly divided into 4 groups and were administered drugs seven times (from the 7th to 13th day of the experiment) as follows: (a) $n_{1, 2}$: Met at the doses of 2.5 mg/kg/day; (b) n_3: Met + Srt at the doses of 2.5 mg/kg/day + 10.0 mg/kg/day; (c) n_4: Srt at the dose of 10.0 mg/kg/day. Locomotion in the Open field test was measured (a) after administration of vehicle on the 1st day, (b) after the 1st dose of drugs given on the 7th day, and (c) on the 14th day after the "challenge doses" administered in the following way: n_1: Met; n_2: Met+Srt, n_3: Met; n_4: Srt. We found the following significant behavioural changes: (1) a stimulatory influence of Met and development of sensitisation after repeated treatment (n_1); (2) an inhibition of Met sensitisation in the case of a combined challenge dose of Met + Srt (n_2); (3) a stimulatory effect of Met when animals were repeatedly pre-treated with Met + Srt (n_3); (4) a significant inhibition of locomotion after the 1st dose of Srt, that persisted even after the last Srt dose (n_4). Data concerning the involvement of sertindole in reward processes associated with drug addiction are not completely consistent and our results reflect this ambiguity to a certain extent. A combined challenge dose of Met + Srt administered after repeated pre-treatment with Met inhibited the development of behavioural sensitisation; on the other hand a Met challenge dose alone administered after repeated pre-treatment with Met + Srt produced a significant increase in locomotion.

Keywords: behavioural sensitisation; methamphetamine; sertindole; mice

List of abbreviations

AM 251 = *N*-(piperidin-1-yl)-5-(4-iodophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxamide, **JWH 015** = 1 propyl-2-methyl-3-(1-naphthoyl)indole, **Met** = methamphetamine, **NMDA** = *N*-methyl-D-aspartate, **Srt** = sertindole, **V** = vehicle

It is well established that repeated administration of the psychostimulant drug methamphetamine results in an increased behavioural response to this substance. This phenomenon is termed behavioural sensitisation and was described for the first time by Robinson and Berridge (1993). Behavioural sensitisation occurs not only for psychostimulants – amphetamine (Enman and Unterwald 2012; Fukushiro et al. 2012) or cocaine (Aracil-Fernandez et al. 2012; Ramos et al. 2012) but also for other psychotropic substances – e.g., morphine (Hofford et al. 2012; Niu et al. 2012), delta(9)-tetrahydrocannabinol (Cadoni et al. 2008), ethanol (Bahi and Dreyer 2012) and nicotine (Lee et al. 2012).

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It has been suggested that behavioural sensitisation is a consequence of drug-induced neuroadaptive changes in a circuit which involves particularly dopaminergic, glutamatergic and GABAergic interconnections between the ventral tegmental area, nucleus accumbens, prefrontal cortex and amygdala (Vanderschuren and Kalivas 2000; Nestler 2001). In our previous studies we investigated the possible effects of various psychotropic drugs on behavioural sensitisation to methamphetamine (particularly cannabinoids and NMDA receptor antagonists). We tested the effects of the CB_1 receptor agonist methanandamide, CB_1 receptor antagonist AM 251 and CB_2 receptor agonist JWH 015 (Landa et al. 2006a,b), and furthermore the effects of the glutametergic NMDA receptor antagonists felbamate (Landa et al. 2012a) and memantine (Landa et al. 2012b).

In the present set of experiments we investigated a possible interference of the antipsychotic drug sertindole with the sensitising phenomenon. Sertindol is a second-generation antipsychotic (neuroleptic) agent used in human medicine that was recently reintroduced into the market for the treatment of schizophrenia (Spina and Zoccali 2008). It acts as an antagonist of dopamine D_2, serotonin 5-HT_{2A}, 5-HT_{2C}, and α_1-adrenergic receptors (Muscatello et al. 2010). According to our knowledge, there are no reports on the use of sertindole in veterinary medicine; however, other drugs from the same group of antipsychotics (e.g., chlorpromazine) have been used for the treatment of aggressive behaviour in dogs (Blackshaw 1991).

It has been shown in experimental pharmacology that chronic administration of sertindole to rats inactivated dopamine neurons in the ventral tegmental area (Skarsfeldt 1992), which is a crucial structure for the development of behavioural sensitisation (Kalivas and Duffy 1993). Dopaminergic transmission also plays a substantial role in the process of sensitisation. Suzuki and Misawa (1995) reported that the dopamine D_2 receptor antagonist sertindole antagonised place preference in rats induced by morphine, cocaine and methamphetamine. Since these experiments with sertindole showed an unambiguous interference with dopaminergic neurotransmission and with methamphetamine brain mechanisms in the model of place preference, we therefore focused on possible effects of this substance on the development of behavioural sensitisation to the stimulatory effects of methamphetamine in mice, which is believed to play an important role in the processes of drug addiction.

MATERIAL AND METHODS

Animals

Male mice (strain ICR, TOP-VELAZ s.r.o., Prague, Czech Republic) with an initial weight of 18–21 g were used. Animals were randomly allocated into four treatment groups. In order to minimise possible variability due to circadian rhythms the behavioural observations were always performed in the same period between 1:00 p.m. and 3:00 p.m. and the animals were maintained under a 12-h light/dark cycle.

Apparatus

Locomotor activity was measured using an open-field equipped with Actitrack (Panlab, S.L., Spain). This device consists of two square-shaped frames that deliver beams of infrared rays into the space inside the square. A plastic box is placed in this square to act as an open-field arena (base 30 × 30 cm, height 20 cm), in which the animal can move freely. The apparatus software records locomotor activity of the animal by registering the beam interruptions caused by movements of the body. Using this equipment we have determined the Distance Travelled (trajectory in cm per 3 min).

Drugs

Vehicle and all drugs were always given in a volume adequate for drug solutions (10 ml/kg).

(+)Methamphetamine, (*d-N*,α-dimethylphenylethylamine;*d*-desoxyephedrine) (Sigma Chemical Co.) was dissolved in saline.

Sertindole, (1-(2-{4-[5-chloro-1-(4-fluorophenyl)-1H-indol-3-yl]-1-piperidinyl}ethyl)-2-imidazolidinone), (H. Lundbeck A/S) was ultrasonically suspended in Tween 80 (one drop in 10 ml saline); vehicle treatment as a control in this case contained the corresponding amount of Tween 80.

Procedure

Mice were randomly allocated into four groups ($n_1 = 9$, $n_2 = 10$, $n_3 = 10$, $n_4 = 10$) and all were given vehicle on Day 1 (10 ml/kg). There were no applications from Days 2 to 6. For the next seven days

animals were treated daily as follows: (a) $n_{1,2}$ 2.5 mg/kg/day of Met; (b) n_3 combination of Met + Srt at the doses of 2.5 mg/kg/day and 10.0 mg/kg/day, respectively; (c) n_4 10.0 mg/kg/day of Srt. On Day 14 all animals were given challenge doses in the following way: n_1: Met at the dose of 2.5 mg/kg, n_2: Met + Srt at the doses of 2.5 mg/kg and 10.0 mg/kg, respectively, n_3: Met at the dose of 2.5 mg/kg, n_4: Srt at the dose of 10.0 mg/kg. All doses of both Met and Srt were administered intraperitoneally. Changes in locomotion were measured for a period of 3 min in the open field on Days 1, 7 and 14 to assess the sensitising phenomenon.

The experimental protocol complies with the European Community guidelines for the use of experimental animals and was approved by the Animal Care Committee of the Masaryk University Brno, Czech Republic.

Data analysis

As the data was not normally distributed (according to the Kolmogorov-Smirnov test of normality), non-parametric statistics were used: Wilcoxon matched-pairs signed-ranks test, two tailed (statistical analysis package Statistica – StatSoft, Inc., Tulsa, USA).

RESULTS

The treatment administered to group n_1 caused a highly significant increase ($P < 0.01$) in locomotion after the 1st application of methamphetamine (Met) compared to the application of vehicle (V) (see Figure 1; V versus Met). The challenge dose of Met produced a further significant increase in

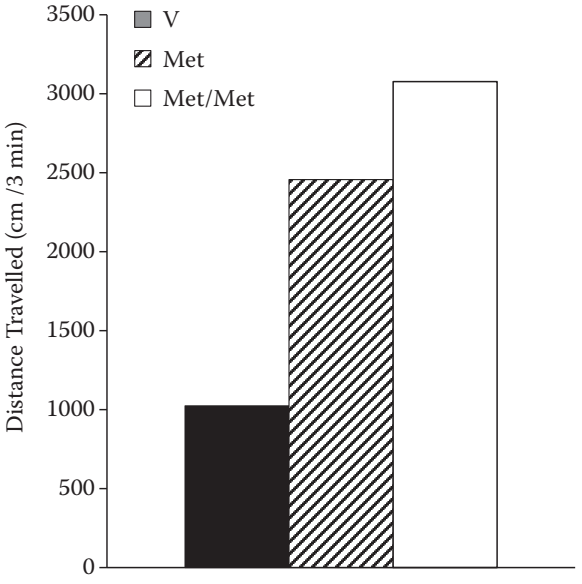

Figure 1. Effects of drug treatments in the group n_1 on Distance Travelled (cm/3 min) in the mouse open field test shown as medians (interquartile ranges Q1 to Q3)

V = mice after the 1st dose of vehicle, (interquartile range Q1 to Q3 = 798.6–1143.7); Met = mice after the 1st dose of methamphetamine (2.5 mg/kg), (interquartile range Q1 to Q3 = 1962.0–1603.0); Met/Met = mice repeatedly pretreated with methamphetamine after the challenge dose of methamphetamine (2.5 mg/kg), (interquartile range Q1 to Q3 = 2392.0–3182.0)

Statistical significances are as follows: V : Met ($P < 0.01$), Met : Met/Met ($P < 0.05$), V : Met/Met ($P < 0.01$); the non-parametric Wilcoxon matched-pairs signed-ranks test, two tailed

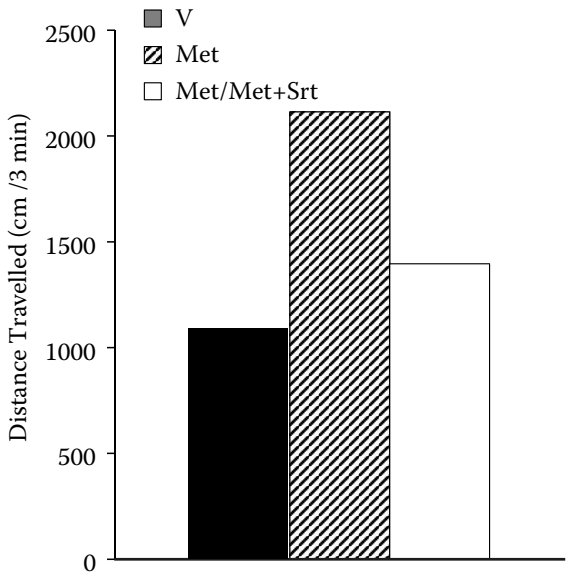

Figure 2. Effects of drug treatments in the group n_2 on Distance Travelled (cm/3 min) in the mouse open field test shown as medians (interquartile ranges Q1 to Q3)

V = mice after the 1st dose of vehicle, (interquartile range Q1 to Q3 = 880.2–1375.5); Met = mice after the 1st dose of methamphetamine (2.5 mg/kg), (interquartile range Q1 to Q3 = 1540.0–2493.0); Met/Met + Srt = mice repeatedly pretreated with methamphetamine after the challenge dose of methamphetamine + sertindole (2.5 mg/kg + 10.0 mg/kg), (interquartile range Q1 to Q3 = 743.0–2092.0)

Statistical significances are as follows: V : Met ($P < 0.01$), Met : Met/Met + Srt ($P < 0.05$), V : Met/Met + Srt (non-significant); the non-parametric Wilcoxon matched-pairs signed-ranks test, two tailed

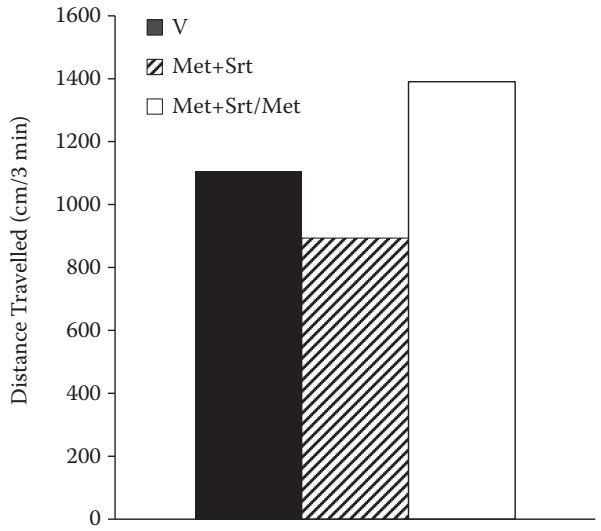

Figure 3. Effects of drug treatments in the group n_3 on Distance Travelled (cm/3 min) in the mouse open field test shown as medians (interquartile ranges Q1 to Q3)

V = mice after the 1st dose of vehicle, (interquartile range Q1 to Q3 = 795.7–1188.0); Met + Srt = mice after the 1st dose of combination methamphetamine + sertindole (2.5 mg/kg + 10.0 mg/kg), (interquartile range Q1 to Q3 = 735.2–1122.3); Met + Srt/Met = mice repeatedly pre-treated with the combination methamphetamine + sertindole after the challenge dose of methamphetamine (2.5 mg/kg), (interquartile range Q1 to Q3 = 1121.0–1869.0)

Statistical significances are as follows: V : Met + Srt (non-significant), Met + Srt : Met + Srt/Met ($P < 0.05$), V : Met + Srt/Met ($P < 0.05$); the non-parametric Wilcoxon matched-pairs signed-ranks test, two tailed

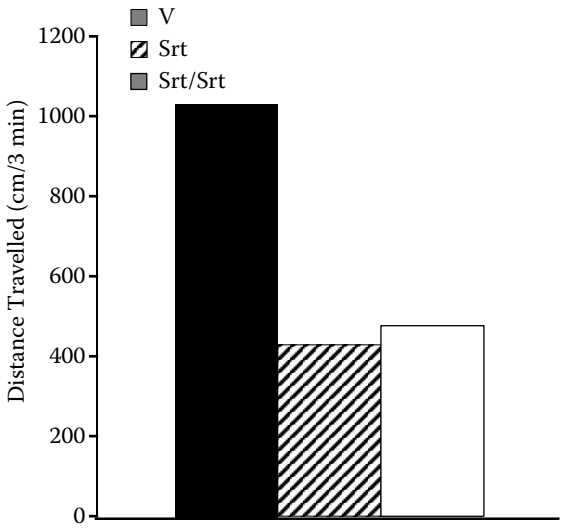

Figure 4. Effects of drug treatments in the group n_4 on Distance Travelled (cm/3 min) in the mouse open field test shown as medians (interquartile ranges Q1 to Q3)

V = mice after the 1st dose of vehicle, (interquartile range Q1 to Q3 = 922.2–1202.2); Srt = mice after the 1st dose of sertindole (10.0 mg/kg), (interquartile range Q1 to Q3 = 309.5–700.0); Srt/Srt = mice repeatedly pre-treated with sertindole after the challenge dose of sertindole (10.0 mg/kg), (interquartile range Q1 to Q3 = 410.3–639.8)

Statistical significances are as follows: V : Srt ($P < 0.01$), Srt : Srt/Srt (non-significant), V : Srt/Srt ($P < 0.01$); the non-parametric Wilcoxon matched-pairs signed-ranks test, two tailed

Distance Travelled ($P < 0.05$) in animals pre-treated repeatedly with Met (see Figure 1; Met versus Met/Met). A highly significant difference in locomotion was also found between mice after the administration of V and animals that received the Met challenge dose (see Figure 1; V versus Met/Met).

In group n_2 the 1st administration of Met caused a highly significant increase ($P < 0.01$) in Distance Travelled compared to the application of V (see Figure 2; V versus Met). In contrast, the challenge dose of Met + Srt provoked a significant decrease ($P < 0.05$) in locomotion in animals pre-treated repeatedly with Met (see Figure 2; Met versus Met/Met + Srt). No statistically significant increases ($P > 0.05$) were found between animals after the application of V compared to animals that were given the Met + Srt combination after repeated Met treatment (see Figure 2; V versus Met/Met + Srt).

In group n_3 the 1st application of the Met + Srt combination did not affect locomotor activity in mice significantly ($P > 0.05$) (see Figure 3; V versus Met + Srt), whereas the challenge dose of Met provoked a significant increase ($P < 0.05$) in locomotion in animals pre-treated repeatedly with Met + Srt (see Figure 3; Met + Srt versus Met + Srt/Met). There was a significant increase ($P < 0.05$) in locomotion in animals pre-treated with the Met + Srt combination after the Met challenge dose when compared with the animals that were administered V (see Figure 3; V versus Met + Srt/Met).

Finally, in group n_4 the 1st application of Srt caused a highly significant decrease in locomotion when compared with animals that received vehicle ($P < 0.01$) (see Figure 4; V versus Srt). The challenge dose of Srt did not affect Distance Travelled significantly ($P > 0.05$) in animals pre-treated repeatedly with Srt when compared with animals after the 1st Srt dose (see Figure 4; Srt versus Srt/Srt). A highly significant decrease ($P < 0.01$) in locomotion was found in mice after the administration of

V compared to animals that were repeatedly pre-treated with Srt and were administered the Srt challenge dose (see Figure 4; V versus Srt/Srt).

DISCUSSION

The results from the group of mice treated repeatedly with methamphetamine are entirely consistent with results from our previous studies (Landa et al. 2006a,b; 2011; 2012a,b) and again confirm the development of sensitisation to the stimulatory effects of methamphetamine on locomotor behaviour in this original dosage regimen used in mice. The 1st dose in the mice under the repeated treatment with sertindole elicited a significant decrease in locomotion that persisted also after the last of the eight daily doses. This finding is in agreement with the results of Suzuki and Misawa (1995) who reported that sertindole given alone produced neither preference nor aversion for the drug-associated place. Therefore, they suggested that sertindole had no potential for abuse. A challenge dose of a methamphetamine + sertindole combination given to animals repeatedly pre-treated with methamphetamine inhibited locomotion compared to the 1st methamphetamine dose, which is similar to observations made in human subjects dependent on methamphetamine, who were given another D_2 receptor antagonist risperidone, which went on to produce a decrease in methamphetamine use (Meredith et al. 2007). On the other hand, the use of a further antipsychotic drug, olanzapine, in humans dependent on cocaine did not support the usefulness of this substance for the treatment of cocaine dependence (Kampman et al. 2003).

Akdag et al. (2011) tested the effects of risperidone (a substance that similarly to sertindole also belongs to the group of atypical antipsychotics with similar multiple mechanisms of action and with a high selectivity for mesolimbic pathways) on nicotine-induced locomotor sensitisation in rats. Risperidone affects serotonin 5-HT_{2A-C} receptors, dopamine D_2 receptors, α_1- and α_2-adrenergic receptors and also histamine H_1 receptors (Akdag et al. 2011). These authors focused on both development and expression of sensitisation and found that repeated administration of nicotine provoked in their experimental design a robust sensitisation. Furthermore, they described that pre-treatment with risperidone inhibited the expression but not the development of nicotine-induced locomotor sensitisation in rats (Akdag et al. 2011). Thus, they concluded that risperidone blocked the continuation of nicotine-type addictive behaviour, whereas it was ineffective against the early adaptations in the development of nicotine addiction. Despite this, the antipsychotic drug risperidone may be of limited beneficial use in nicotine dependence treatment (Akdag et al. 2011). On the other hand, Meng et al. (1998) reported that a typical and an atypical antipsychotic drug, haloperidol and clozapine, respectively, blocked the development of behavioural sensitisation to amphetamine in rats. Our results showed an increase in animals that were repeatedly pre-treated with the methamphetamine + sertindole combination and challenged with a dose of methamphetamine, however this increase cannot be considered as development of sensitisation.

Prinssen et al. (2004) examined whether the ability of the dopamine D_2 receptor antagonists eticlopride and raclopride (substances primarily used in basic pharmacological research) to decrease cocaine-induced locomotion varied between non-sensitised and sensitised mice if they were challenged with cocaine. In this experiment the dopamine D_2 receptor antagonists eticlopride and raclopride were less efficient in inhibiting the locomotor effects of cocaine in sensitised mice compared to the non-sensitised animals. However, when the authors used the lowest doses to maximally increase locomotion in each of the repeated treatment conditions (10 and 40 mg/kg) both dopamine D_2 receptor antagonists inhibited the influence of cocaine on locomotor activity in non-sensitised and sensitised mice to a similar extent (Prinssen et al. 2004). Thus, these results indicate that the possible effects of dopamine receptor agonists are dose-dependent.

Data concerning the involvement of sertindole in reward processes associated with drug addiction are not completely consistent. Suzuki and Misawa (1995) reported that the dopamine D_2 receptor antagonist sertindole antagonised place preference in rats induced by morphine, cocaine and methamphetamine. On the other hand, Arnt (1992) tested the effect of various antipsychotic drugs (sertindole, clozapine, flupentixol, haloperidol) on the discriminative stimulus properties of amphetamine (i.e., dopamine stimulant) and LSD (i.e. 5-HT_2 receptor agonist) and found in rats that sertindole antagonised the effects of LSD, whereas those of *d*-amphetamine were unchanged. In contrast, Jackson et al. (1994) found that sertindole blocked amphetamine and phencyclidine-induced

motor stimulation in rats and similarly, Artn (1995) described that sertindole inhibited hypermotility induced by two dose levels of amphetamine. These data indicate that there is not only variability in doses but also probable differences among substances from the groups of antipsychotics in their ability to interfere with the action of various drugs of abuse. In addition, there are also further factors contributing to diversity in the action of D_2 receptor antagonists. For example, it has been shown that there was a difference between the effects of acute and chronic antipsychotic drug treatment on dopamine neurons. Whereas acute application increased dopamine neuron population activity, chronic administration (21 days) led to inactivation of dopamine neurons in the substantia nigra of rats (Grace et al. 1997).

Despite these controversies, it can be concluded that findings such as those reported by Suzuki and Misawa (1995) and also results from our study suggest that the use of sertindole holds therapeutic promise for the treatment of drug addiction, though further research is certainly required.

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