The effect of memantine on behavioural sensitisation to methamphetamine in mice

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ABSTRACT: After repeated administration the psychostimulant methamphetamine (Met) produces a substantial increase in behavioural responses, which is termed behavioural sensitisation. Many studies have reported that *N*-methyl-D-aspartate (NMDA) receptors play an important role in the development and expression of behavioural sensitisation. Memantine (Mem) is used particularly for the treatment of Alzheimer's disease and acts as a non-competitive NMDA glutamate receptor antagonist, possessing a variety of psychotropic effects. For example, there are studies indicating that memantine prevents the expression of withdrawal symptoms in mice and causes reversal of opioid dependence. Although not all pharmacological mechanisms of memantine have been clarified yet, it is known that memantine inhibits NMDA receptor inward currents. Thus, the present study was designed to assess whether memantine would influence behavioural sensitisation to the stimulatory effects of methamphetamine on mouse locomotion. Mice were randomly allocated into four groups. They were given vehicle on Day 1of the experiment and after five days without application they were administered seven drug daily doses (*i.p.*) from Day 7 to Day 13 of the study, as follows: (a) $n_{1, 2}$: 2.5 mg/kg/day of Met; (b) n_3: combination Met + Mem at the doses of 2.5 mg/kg/day and 5 mg/kg/day, respectively; (c) n_4: Mem at the dose of 5 mg/kg/day. On Day 14 mice were given the first "challenge treatment" (a) n_1: Met, (b) n_2: Met + Mem, (c) n_3: Met, (d) n_4: Mem. The second "challenge treatment" was given after a six day wash-out period on Day 21: (a) n_1: Met, (b) n_2: Met + Mem, (c) n_3: Met, (d) n_4: Mem. Changes in locomotion were measured for a period of 3 min in the Open field on Days 1, 7, 14 and 21 to assess the sensitising phenomenon. Met pre-treatment significantly sensitised to the effects of the challenge doses (n_1). Mem given alone did not change the measured behavioural parameters after the acute dose but it significantly decreased locomotion after its repeated administration (n_4). Repeated pre-treatment with the Met + Mem combination (n_3) did not produce sensitisation after Met challenge doses and similarly, repeated pre-treatment with Met did not induce sensitisation after the challenge dose of Met + Mem (n_2). Thus, our results suggest that the role of the NMDA receptor antagonist memantine in the development and expression of behavioural sensitisation to Met seems to be an inhibitory one.

Keywords: behavioural sensitisation; methamphetamine; memantine; NMDA receptor antagonist; mice

List of abbreviations

GABA = gamma-aminobutyric acid, **i.p.** = intraperitoneally, **Mem** = memantine, **Met** = methamphetamine, **NAc** = nucleus accumbens, **NMDA** = *N*-methyl-D-aspartate, **V** = vehicle, **VTA** = ventral tegmental area

Robinson and Berridge (1993) first consistently describe a phenomenon that was termed behavioural sensitisation. This phenomenon occurs after repeated administration of a whole range of abused drugs and its typical features involve progressively increasing behavioural responses to the effects of the particular substances. It has been described in both laboratory animals and man (Tzschentke and Schmidt 1997; Steketee and Kalivas 2011). Behavioural sensitisation was, for example, re-

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ported for cocaine (Schroeder et al. 2012; Ramos et al. 2012), methylphenidate (Freese et al. 2012), morphine (Hofford et al. 2012), ethanol (Pastor et al. 2012) and methamphetamine (Horio et al. 2012; Landa et al. 2011, 2012).

It has been shown that behavioural sensitisation is a consequence of drug-induced neuroadaptive changes in a circuit involving particularly dopaminergic, glutamatergic and GABAergic interconnections between the ventral tegmental area (VTA), nucleus accumbens (NAc), prefrontal cortex and amygdala (Vanderschuren and Kalivas 2000; Nestler 2001). It has also been demonstrated that the phenomenon of sensitisation can be subdivided into two temporally defined domains, that are termed development (or initiation) and expression (Kalivas et al. 1993). The development of behavioural sensitisation is connected with progressive molecular and cellular alterations that culminate in a change in the processing of environmental and pharmacological stimuli by the CNS. Expression has been described as the enduring neural changes, which arise from the process of the development that directly mediate the sensitised behavioural response (Pierce and Kalivas 1997). There are data indicating that these processes differ not only temporally but also anatomically. Development of behavioural sensitisation to psychostimulant drugs is associated with the VTA and substantia nigra, whereas expression is particularly related to the neurotransmission in the NAc (Kalivas and Duffy 1993).

Various articles have described that interference with glutamatergic neurotransmission at *N*-methyl-D-aspartate (NMDA) receptors can disrupt both the development and the expression of sensitisation (Wolf 1998; Tzschentke and Schmidt 2003). It has been accepted that in particular NMDA-receptor antagonists block or interfere with behavioural plasticity. Nevertheless, there are also reports that co-administration of NMDA-receptor antagonists enhanced the effect of the sensitising drug (Tzschentke and Schmidt 1998).

In our previous study we tested the effect of the activating antiepileptic drug felbamate (that acts as an NMDA receptor antagonist) on behavioural sensitisation to methamphetamine (Landa et al. 2012). Another substance that also blocks NMDA glutamate receptors is memantine. Memantine is widely used in human medicine as a medication for Alzheimer's disease (Cummings et al. 2006). However, the full potential of memantine use has likely not been revealed so far. For example, it has been shown on the experimental level that memantine was able to attenuate chronic morphine-induced place-preference in rats (Chen et al. 2012). And moreover, there is also a recent report on the use of memantine in veterinary medicine for the treatment of canine compulsive disorders (Schneider et al. 2009).

Thus, since the role of glutamatergic transmission in the processes of behavioural sensitisation remains quite controversial and with regard to our previous results concerning the involvement of felbamate in sensitisation, we designed the present study to investigate a possible influence of memantine on sensitisation to methamphetamine in mice. In comparison with our previous study involving felbamate, in the present experimental design we focused on possible changes not only during the phase of development but also during the phase of expression.

MATERIAL AND METHODS

Animals

Mice (males, strain ICR, TOP-VELAZ s.r.o., Prague, Czech Republic) with an initial weight of 18–21 g were used. They were randomly allocated into four treatment groups. Animals were housed with free access to water and food in a room with controlled humidity and temperature, that was maintained under a 12-h phase lighting cycle. In order to minimise possible variability due to circadian rhythms behavioural measurements were always performed in the same time period between 1:00 p.m. and 3:00 p.m.

Apparatus

Locomotor activity was tested 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 the locomotor activity of the animal (such as Distance Travelled, fast movements, resting time, etc.) by registering the beam interruptions caused by movements of the body. Using this equipment we measured the Distance Travelled (trajectory in cm per 3 min).

Drugs

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

(+)Methamphetamine, (*d-N*,α-Dimethylphenylethylamine;*d*-Desoxyephedrine), (Sigma Chemical Co.) and memantine hydrochloride, (3,5-Dimethyl-1-adamantanamine hydrochloride), (H. Lundbeck A/S) were dissolved in saline.

Procedure

For the purposes of this study we devised an original dosage regimen. Mice were randomly divided into four groups (n_1 = 10, n_2 = 10, n_3 = 10, n_4 = 10). All animals were given vehicle on Day 1 of the experiment and after five days without application were administered drug doses on seven occasions – intraperitoneally, once daily from Day 7 to Day 13 of the study – as follows: (a) n_1, n_2: 2.5 mg/kg/day of Met; (b) n_3: combination Met + Mem at the doses of 2.5 mg/kg/day and 5.0 mg/kg/day, respectively; (c) n_4: Mem at the dose of 5.0 mg/kg/day. On Day 14 mice were given the first "challenge doses" (a) n_1: Met at the dose of 2.5 mg/kg, (b) n_2: Met + Mem at the doses of 2.5 mg/kg and 5.0 mg/kg, respectively, (c) n_3: Met at the dose of 2.5 mg/kg, (d) n_4: Mem at the dose of 5.0 mg/kg). The second "challenge doses" were given after a six day wash-out period on Day 21 (a) n_1: Met at the dose of 2.5 mg/kg, (b) n_2: Met + Mem at the doses of 2.5 mg/kg and 5.0 mg/kg/day, respectively, (c) n_3: Met at the dose of 2.5 mg/kg, (d) n_4: Mem at the dose of 5.0 mg/kg. Changes in locomotion were measured for a period of 3 minutes in the open field on Days 1, 7, 14 and 21 to assess the development and expression of behavioural sensitisation.

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

Data analysis

As the data were 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

Locomotion significantly increased ($P < 0.01$) after the 1st application of methamphetamine (Met) in the n_1 group compared to the application of vehicle (V) (see Figure 1; V versus Met). The 1st challenge dose of methamphetamine (Met1) produced a significant increase in Distance Travelled ($P < 0.01$) in animals pre-treated repeatedly with Met (see Figure 1; Met versus Met1). The 2nd challenge dose of methamphetamine (Met2) did not elicit any further significant increase ($P > 0.05$), (see Figure 1; Met1 versus Met2), however a highly significant increase ($P < 0.01$) occurred when comparing animals after the 2nd Met challenge dose to the mice after the 1st Met dose (see Figure 1; Met versus Met2).

In the group n_2 the 1st application of Met caused a significant increase ($P < 0.01$) in Distance Travelled

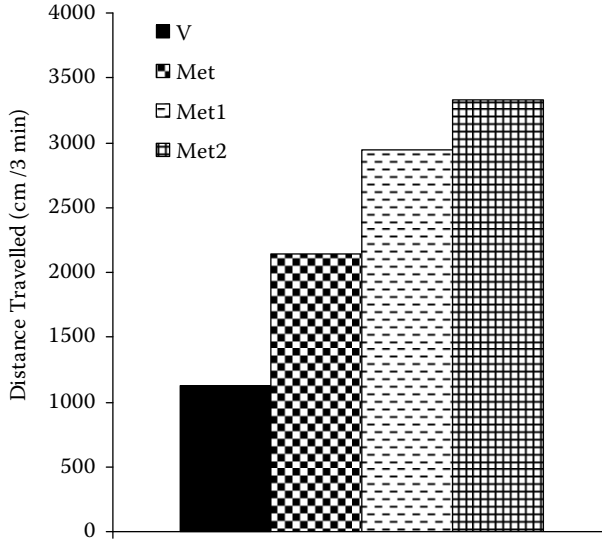

Figure 1. Effects of drug treatments in the group n_1 on Distance Travelled (cm/3 min) in the mouse open field test shown as medians (interquartile ranges Q1 to Q3)

V = mice after the 1st dose of vehicle, (interquartile range Q1 to Q3 = 1097.5–1258.3); Met = mice after the 1st dose of methamphetamine (2.5 mg/kg), (interquartile range Q1 to Q3 = 1632.0–2363.0); Met1 = mice repeatedly pre-treated with methamphetamine (2.5 mg/kg/day) after the 1st challenge dose of methamphetamine (2.5 mg/kg), (interquartile range Q1 to Q3 = 2416.0–3540.0); Met2 = mice repeatedly pre-treated with methamphetamine after the 2nd challenge dose of methamphetamine (2.5 mg/kg) following wash-out period, (interquartile range Q1 to Q3 = 2378.0–4049.0)
Statistical significances are as follows: V : Met ($P < 0.01$), Met : Met1 ($P < 0.01$), Met1 : Met2 (non-significant), Met : Met2 ($P < 0.01$); the non-parametric Wilcoxon matched-pairs signed-ranks test, two tailed

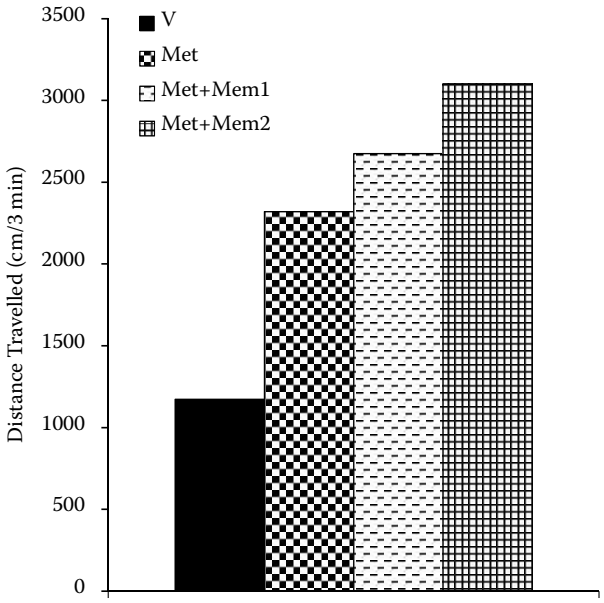

Figure 2. Effects of drug treatments in the group n_2 on Distance Travelled (cm/3 min) in the mouse open field test shown as medians (interquartile ranges Q1 to Q3)

V = mice after the 1st dose of vehicle, (interquartile range Q1 to Q3 = 1059.5–1380.8); Met = mice after the 1st dose of methamphetamine (2.5 mg/kg), (interquartile range Q1 to Q3 = 1914.0–3131.0); Met + Mem1 = mice repeatedly pre-treated with methamphetamine (2.5 mg/kg/day) after the 1st challenge dose of methamphetamine+memantine (2.5 mg/kg + 5.0 mg/kg), (interquartile range Q1 to Q3 = 2390.0–3248.0); Met + Mem2 = mice repeatedly pre-treated with methamphetamine after the 2nd challenge dose of methamphetamine + memantine (2.5 mg/kg + 5.0 mg/kg) following wash-out period, (interquartile range Q1 to Q3 = 2852.0–3326.0)
Statistical significances are as follows: V : Met ($P < 0.01$), Met : Met + Mem1 (non-significant), Met + Mem1 : Met + Mem2 (non-significant), Met : Met + Mem2 (non-significant); the non-parametric Wilcoxon matched-pairs signed-ranks test, two tailed

compared to the application of V (see Figure 2; V versus Met). The 1st challenge dose of the methamphetamine + memantine combination (Met + Mem1) did not significantly increase locomotion in animals pre-treated repeatedly with Met ($P > 0.05$) (see Figure 2; Met versus Met + Mem1) and there were also no significant change after the 2nd challenge dose of methamphetamine + memantine (Met + Mem2) (see Figure 2; Met + Mem1 versus Met + Mem2). Similarly, no statistically significant change was found between animals after the 1st Met administration and animals that received the 2nd challenge dose of Met + Mem2 (see Figure 2; Met versus Met + Met2).

In group n_3 the 1st application of the methamphetamine+memantine (Met + Mem) combination increased locomotor activity compared to the application of V in a highly significant manner ($P < 0.01$) (see Figure 3; V versus Met + Mem). The 1st challenge dose of methamphetamine (Met1) did not result in any significant change in locomotion when compared to animals after the 1st dose of Met + Mem ($P > 0.05$), (see Figure 3; Met + Mem versus Met1). There were no significant changes in locomotion after the 2nd methamphetamine challenge dose (Met2) compared to animals after the 1st Met challenge dose (see Figure 3; Met1 versus Met2). No statistically significant changes were

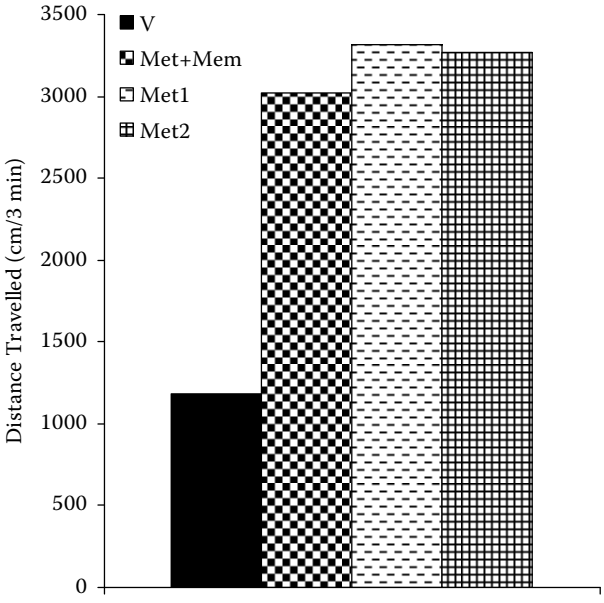

Figure 3. Effects of drug treatments in the group n_3 on Distance Travelled (cm/3 min) in the mouse open field test shown as medians (interquartile ranges Q1 to Q3)

V = mice after the 1st dose of vehicle, (interquartile range Q1 to Q3 = 1015.5–1333.7); Met + Mem = mice after the 1st dose of methamphetamine + memantine (2.5 mg/kg + 5.0 mg/kg), (interquartile range Q1 to Q3 = 1721.0–3519.0); Met1 = mice repeatedly pre-treated with combination Met + Mem (2.5 mg/kg/day + 5.0 mg/kg/day) after the 1st challenge dose of Met (2.5 mg/kg), (interquartile range Q1 to Q3 = 2031.0–4477.0); Met2 = mice repeatedly pre-treated with combination Met + Mem after the 2nd challenge dose of Met (2.5 mg/kg) following wash-out period, (interquartile range Q1 to Q3 = 2902.0–4409.0)
Statistical significances are as follows: V : Met + Mem ($P < 0.01$), Met + Mem : Met1 (non-significant), Met1 : Met2 (non-significant), Met + Mem:Met2 (non-significant); the non-parametric Wilcoxon matched-pairs signed-ranks test, two tailed

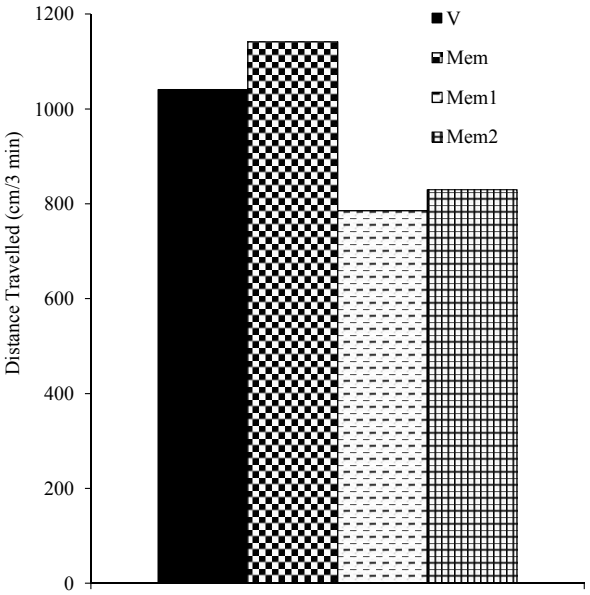

Figure 4. Effects of drug treatments in the group n_4 on Distance Travelled (cm/3 min) in the mouse open field test shown as medians (interquartile ranges Q1 to Q3)

V = mice after the 1st dose of vehicle, (interquartile range Q1 to Q3 = 939.9–1169.0); Mem = mice after the 1st dose memantine (5.0 mg/kg), (interquartile range Q1 to Q3 = 967.5–1373.5); Mem1 = mice repeatedly pre-treated with memantine (5.0 mg/kg/day) after the 1st challenge dose of Mem (5.0 mg/kg), (interquartile range Q1 to Q3 = 731.2–903.8); Mem2 = mice repeatedly pre-treated with Mem after the 2nd challenge dose of Mem (5.0 mg/kg) following wash-out period, (interquartile range Q1 to Q3 = 711.0–973.0) Statistical significances are as follows: V : Mem (non-significant), Mem : Mem1 ($P < 0.01$), Mem1 : Mem2 (non-significant), Mem : Mem2 ($P < 0.05$); the non-parametric Wilcoxon matched-pairs signed-ranks test, two tailed

found between animals after the 1st Met + Mem administration and animals that received the 2nd Met challenge dose (see Figure 3; Met+Mem versus Mem2).

Finally, in the group n_4 the first application of Mem did not affect Distance Travelled significantly ($p>0.05$) (see Figure 4; V versus Mem). The 1st memantine challenge dose (Mem1) provoked a highly significant decrease ($P < 0.01$) in locomotion in animals pre-treated repeatedly with Mem (see Figure 4; Mem versus Mem1). Mice that received the 2nd memantine challenge dose (Mem2) showed no statistically significant changes when compared with animals after the 1st Mem challenge dose (see Figure 4; Mem1 versus Mem2). There was, however, a significant decrease ($P < 0.05$) in locomotion between animals after the 1st dose of Mem and animals after administration of the 2nd Mem challenge dose (see Figure 4; Mem versus Mem2).

DISCUSSION

The results from the group n_1 were identical to the results from numerous of our previous studies and confirm the development of sensitisation to the stimulatory effects of methamphetamine (e.g. Landa et al. 2006a,b, 2011, 2012). In our experimental design we focused also on the expression of behavioural sensitisation and although there was a clear trend towards an increase in locomotion in mice after the second methamphetamine challenge dose when compared to sensitised animals, it did not reach statistical significance. Nevertheless behavioural sensitisation to the stimulatory effects of methamphetamine unambiguously persisted in this group even after the wash-out period.

Neither development, nor expression of behavioural sensitisation occurred in mice sensitised with methamphetamine (group n_2) in which mice were administered methamphetamine challenge doses in combination with memantine. This result is in accordance with the majority of similar experiments reporting the inhibitory effects of NMDA receptors antagonists on the development of sensitisation to amphetamines (Wolf 1998). The findings obtained in this experiment are also to a certain extent in compliance with our previous study where we tested the possible influence of another NMDA receptor antagonist, felbamate, on behavioural sensitisation to methamphetamine (Landa et al. 2012). This substance also inhibited, even in a more pronounced manner, sensitisation in mice repeatedly pre-treated with methamphetamine that were given a methamphetamine challenge dose together with felbamate. A felbamate challenge dose administered along with methamphetamine after repeated methamphetamine pre-treatment significantly decreased locomotion in the previous experiment, which was, however, not the case in the group of animals in the present study. These animals were repeatedly administered methamphetamine and the challenge dose consisted of a methamphetamine + memantine combination. There was a trend towards an increase in locomotion although this was non-significant. This difference between the effects of felbamate and memantine could support the hypothesis suggesting that NMDA antagonists

affect behavioural sensitisation in a substance-dependent manner. It is, for example, in accordance with the report of Bespalov et al. (2000) indicating that cocaine-conditioned behaviours can be selectively modulated by some, but not all, NMDA receptor antagonists.

Although the involvement of glutamatergic neurotransmission in the processes of behavioural sensitisation is widely reported (Stewart and Druhan 1993; Ohmori et al. 1994; Subramaniam et al. 1995; Li et al. 1997; Wolf 1998; Tzschentke and Schmidt 2003; Lee et al. 2011), there are also reports suggesting that NMDA receptor antagonists affect the action of addictive substances by different means. For example, Glick et al. (2001) reported that the non-competitive NMDA receptor antagonist dextromethorphan significantly decreased methamphetamine self-administration in rats; the authors nevertheless suggested that these findings could have been mediated via non-NMDA mechanisms. Similarly, Chen et al. (2012) reported that the NMDA receptor antagonist memantine significantly attenuated chronic morphine-induced place-preference in rats. These authors hypothesised that the development of opioid addiction could be associated with neuronal inflammation and degeneration and thus the attenuation of morphine-induced addiction behaviour by memantine may be due to its anti-inflammatory and neurotrophic effects rather than through NMDA receptor blockade. Despite these findings, results supporting the role of NMDA receptor in processes associated with drug addiction are reported much more frequently (Wolf et al. 1995; Shim et al. 2002; Hong et al. 2006; Yang et al. 2008).

Popik et al. (2003) in their study tried to compare the effects of memantine in mice on expression of place preferences that were conditioned with morphine administration (10 mg/kg) and furthermore with sexual encounters with females and consumption of regular laboratory food. Memantine in this experiment inhibited the expression of place preference conditioned with morphine and sexual encounter; however, it did not affect food-conditioned animals. Thus, these results suggested that antagonizing the NMDA receptor may not only affect drug-reinforced behaviour (Popik et al. 2003).

Similarly, Aguilar et al. (2009) tested the influence of memantine on sensitisation to the motor and rewarding effects of morphine. They revealed in mice that administration of morphine at the dose of 2 mg/kg was ineffective in animals pre-exposed to saline but induced a clear conditioned place preference in those pre-exposed to morphine. In contrast, mice pre-exposed to morphine + memantine did not acquire conditioned place preference. Only mice pre-exposed to morphine showed an increased motor response to morphine at a dose of 2 mg/kg. These results indicate that NMDA glutamatergic receptors were involved in the development of sensitisation to conditioned rewarding effects and that memantine blocked sensitisation to the rewarding effects of morphine (Aguilar et al. 2009). This is in accordance with our findings where repeated pre-treatment with the methamphetamine+memantine combination blocked the development of behavioural sensitisation to methamphetamine. On the other hand, the results obtained by Aguilar et al. (2009) are in contradiction with our previous results obtained in the study with another NMDA receptor antagonist felbamate (Landa et al. 2012), where pre-treatment with felbamate+methamphetamine resulted, after the methamphetamine challenge dose, in the development of sensitisation to the stimulatory effects of methamphetamine.

The concept of behavioural sensitisation formulated by Robinson and Berridge (1993, 2003) clearly indicates that sensitisation plays a very important role in the processes of craving and the reinstatement of compulsive drug-seeking behaviour. The majority of studies, including this article, suggest that glutamatergic modulators, in particular NMDA receptor antagonists, affect the sensitising phenomenon and that the influence of these substances is largely inhibitory. Our results support this suggestion also. Moreover, this notion has been successfully tested in humans dependent on opioids where memantine attenuated the expression of opioid physical dependence (Bisaga et al. 2001).

Despite somewhat controversial results reported in the literature, the use of NMDA receptor antagonists could in many cases serve as a useful method for blocking behavioural sensitisation, decrease the risk of relapses in ex-addicts and thus represents a promising pharmacological tool for possible treatment of substance dependence (David et al. 2006).

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