The effect of felbamate on behavioural sensitisation to methamphetamine in mice

L. Landa[1], K. Slais[2], A. Sulcova[2]

[1]Faculty of Veterinary Medicine, University of Veterinary and Pharmaceutical Sciences, Brno, Czech Republic
[2]Central European Institute of Technology, Masaryk University, Brno, Czech Republic

ABSTRACT: It has been shown that methamphetamine (Met) similary to other psychostimulants induces a progressive augmentation of behavioural responses after repeated administration, so called behavioural sensitisation. Numerous studies refer to an important role for *N*-methyl-D-aspartate (NMDA) receptors in the development of behavioural sensitisation. Activating antiepileptic drugs of the newer second generation, such as felbamate (Fel), also invoke psychotropic effects. They may possess attention-enhancing and antidepressant activity, causing anxiety, insomnia, and agitation. Although not all pharmacological effects of felbamate are fully elucidated yet, many of its clinical effects may be related to the inhibition of NMDA currents. Thus, the present study was focused on investigating the influence of felbamate on sensitisation to the effects of methamphetamine on mouse locomotor behaviour in the Open field test. Mice of the albino out-bred strain ICR were randomly allocated into four groups and were administered drugs seven times (from the 7th to 13th day of the experiment) as follows: (a) $n_{1, 2}$: 2.5 mg/kg/day of Met; (b) n_3: 240 mg/kg/day of Fel; (c) n_4: Met + Fel. Locomotion in the Open field test was measured (a) after administration of vehicle on the 1st experimental day, (b) after the first dose of drugs given on the 7th day, and (c) on the 14th day after the "challenge doses" given that way (as follows): n_1: Met; n_2: Met + Fel, n_3: Fel; n_4: Met. The following significant behavioural changes were observed: (1) stimulatory influence of Met and sensitisation after repeated treatment (n_1); (2) inhibition of Met sensitisation in the case of a challenge dose combined with Fel (n_2); (3) augmentation of the sensitising effect of Met when sensitisation was induced by pre-treatment with Met + Fel (n_4); (4) no behavioural effect of the first dose of Fel, but inhibition of locomotion after repeated administration of the drug (n_3). The prevention of the development of Met sensitization in the group n_2 in which mice received the Met challenge dose with Fel mirrors the results of a majority of similar studies. Most findings are consistent with inhibitory effects of antagonists of the NMDA receptors on the development of sensitisation to amphetamines; nevertheless, also new findings are reported. In the presented paper, combined pre-treatment with Met + Fel in the group n_4 facilitated the development of sensitisation to Met stimulatory effects.

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

List of abbreviations

AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, **Fel** = febamate, **GABA** = gamma-aminobutyric acid **MDMA** = 3,4-methylenedioxymethamphetamine, **Met** = methamphetamine, **MK-801** = (5R,10S)-(+)-5-Methyl-10,11-dihydro-5H-dibenzo[a,d] cyclohepten-5,10-imine, **NBQX** = 2,3-dihydroxy-6-nitro-7-sulfamoyl-benzo[f] quinoxaline-2,3-dione, **NMDA** = N-methyl-D-aspartate, **THC** = Δ9-tetrahydrocannabinol, **V** = vehicle

Many drugs induce a progressive augmentation of behavioural responses, so called behavioural sensitisation following their repeated administration. This phenomenon was consistently described by Robinson and Berridge (1993) and it occurs in both animals and man (Tzschentke and Schmidt 1997). Behavioural sensitisation was described, for example, to ethanol (Bahi and Dreyer 2012), morphine

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(Farahmandfar et al. 2011), nicotine (Bhatti et al. 2009), THC (Δ9-tetrahydrocannabinol) (Cadoni et al. 2008), or MDMA (3,4-methylenedioxymethamphetamine) (Ball et al. 2011). In our laboratory, we developed an original dosage regimen that produced a reliable and robust behavioural sensitisation to stimulatory effects of methamphetamine (Met) in mice (Landa et al. 2006a,b, 2011).

The phenomenon of behavioural sensitisation is believed to be a consequence of drug-induced neuroadaptive changes in a circuit involving dopaminergic, glutamatergic and GABAergic interconnections between the ventral tegmental area, nucleus accumbens, prefrontal cortex and amygdala (Vanderschuren and Kalivas 2000; Nestler 2001). Numerous studies refer to the important involvement of glutamate *N*-methyl-D-aspartate (NMDA) receptors and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors in the process of behavioural sensitisation (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).

However, not all studies have reported results that are completely consistent. For example, Mead and Stephens (1998) found that administration of the AMPA receptor antagonist NBQX attenuated amphetamine-induced sensitisation in mice. Boudreau and Wolf (2005) suggested that drug-seeking responses were more effectively triggered in cocaine-sensitised rats due to increased cell surface expression of AMPA receptors in the nucleus accumbens. In contrast, Nelson et al. (2009) concluded that behavioural sensitisation to amphetamine was not accompanied by changes in glutamate receptor surface expression in the rat nucleus accumbens. Xia et al. (2011) showed that the effect of glutamate receptors was not associated solely with sensitisation to psychostimulants, because morphine treatment elicited changes in synaptic AMPA receptor expression in the mice hippocampus, a structure with an important role in learning and memory. Suto et al. (2004) described that in rats with amphetamine-induced sensitisation, a lower AMPA concentration could provoke re-instatement of cocaine seeking.

Felbamate (Fel) is an activating antiepileptic drug of the newer second generation (Vohora et al. 2010), and is therapeutically used in both humans and animals (Ruehlmann et al. 2001). Fel is characterised as an NMDA receptor antagonist (Germano et al. 2007), that blocks NMDA receptor-mediated currents (Kuo et al. 2004). Generally, antiepileptic drugs from this generation invoke psychotropic effects. They may exert attention-enhancing and antidepressant effects, and cause anxiety, insomnia, and agitation (Nadkarni and Devinsky 2005; Sharma et al. 2008). Felbamate was also reported to significantly inhibit the nociception induced by glutamate (Beirith et al. 2002). It has been shown that felbamate reduced the locomotor hypoactivity induced by repeated stress in mice (Pistovcakova et al. 2005).

Most findings are consistent with the hypothesis that antagonists of the NMDA receptors have inhibitory effects on behavioural sensitisation to amphetamines (Wolf 1998); however, there are also reports that co-administration of NMDA-receptor antagonists, e.g., dizocilpine enhances the effect of the sensitising drug (Tzschentke and Schmidt 1998). Thus, this issue remains quite controversial. According to our knowledge, none of the experiments which support the notion of inhibitory effects and summarised in the review of Wolf (1998) tested felbamate and methamphetamine together. Thus, the present study was designed to investigate the influence of felbamate on sensitisation to the effects of methamphetamine on mouse locomotor behaviour in the open field test; we particularly focused on possible changes in the development of methamphetamine sensitisation.

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. of controlled light/dark cycles (light on 6:00 a.m.–6:00 p.m.).

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.) dissolved in saline.

Felbamate (Taloxa® 600 mg, Schering-Plough) dissolved in distilled water.

Procedure

For the purposes of this study we used our in-house dosage regimen. Mice were randomly divided into four groups ($n_1 = 10$, $n_2 = 10$, $n_3 = 10$, $n_4 = 10$) 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 daily treated as follows: (a) $n_{1, 2}$ 2.5 mg/kg/day of Met, (b) n_3 240.0 mg/kg/day of Fel; (c) n_4 combination of Met + Fel at doses of 2.5 mg/kg/day and 240 mg/kg/day, respectively. 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 + Fel at the doses of 2.5 mg/kg and 240 mg/kg, respectively, n_3: Fel at the dose of 240 mg/kg, n_4: Met at the dose of 2.5 mg/kg. All doses of Met were administered intraperitoneally and all doses of Fel were administered orally. 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 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

The treatments in the group n_1 caused a significant increase ($P < 0.05$) 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 significant increase in Distance Travelled ($P < 0.05$) in animals pre-treated repeatedly with Met when compared to the animals after the 1st Met dose (see Figure 1; Met versus Met/Met).

Similarly, in the group n_2 the first administration of Met caused a significant increase ($P < 0.05$) in Distance Travelled compared to the application of V (see Figure 2; V versus Met). In contrast, the challenge dose of Met + Fel evoked a significant decrease ($P < 0.05$) in locomotion in animals pre-treated repeatedly with Met when compared to the animals after the 1st application of Met (see Figure 2; Met versus Met/Met + Fel).

In the group n_3 the 1st application of Fel did not affect locomotor activity in mice significantly ($P > 0.05$) (see Figure 3; V versus Fel), whereas the challenge dose of Fel induced a significant decrease ($P < 0.05$) in locomotion in animals pre-treated repeatedly with Fel when compared to the animals after the 1st dose of Fel (see Figure 3; Fel versus Fel/Fel).

Finally, in the group n_4 the first application of the Met + Fel combination did not affect Distance Travelled significantly ($P > 0.05$) (see Figure 4; V versus Met + Fel) and the challenge dose of Met evoked a significant increase ($P < 0.05$) in locomotion in animals pre-treated repeatedly with the combination Met + Fel when compared to the animals after the 1st dose of Met + Fel (see Figure 4; Met + Fel/Met versus Met + Fel).

DISCUSSION

The results obtained in the group n_1 are completely in accordance with the results from our previous studies that confirmed the development of sensitisation to methamphetamine stimulatory effects in an original dosage regimen applied in mice (Landa et al. 2006 a,b, 2011). A significant decrease in locomotion in mice sensitised with Met in the group n_2 in which mice received the Met challenge

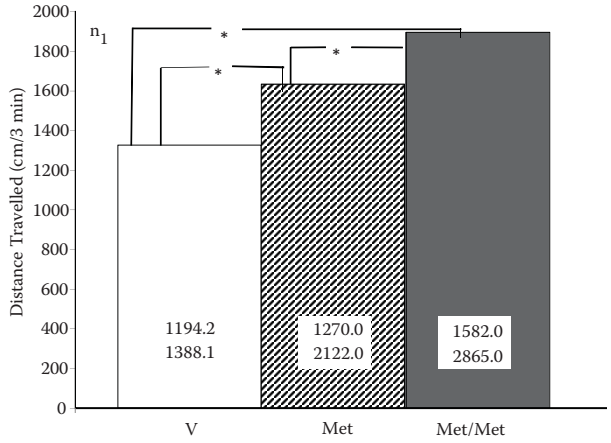

Figure 1. Effects of drug treatments in the group n_1 on Distance Travelled (cm/3 min) in the mouse open field test shown as median (interquartile range Q1 to Q3)

V = mice after the 1st dose of vehicle, Met = mice after the 1st dose of methamphetamine (2.5 mg/kg), Met/Met = mice sensitised with methamphetamine after the challenge dose of methamphetamine (2.5 mg/kg)

*$P < 0.05$, NS = non-significant; the non-parametric Wilcoxon matched-pairs signed-ranks test, two tailed

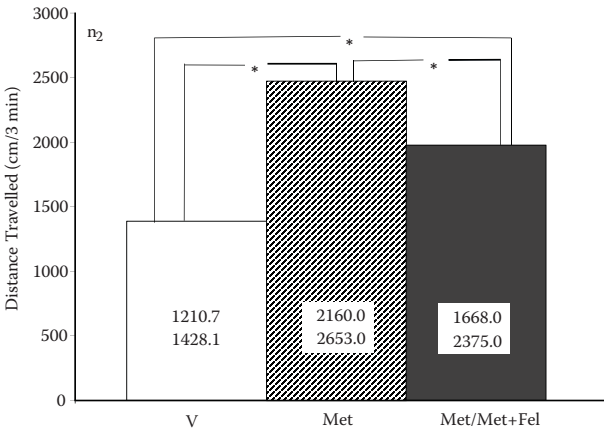

Figure 2. Effects of drug treatments in the group n_2 on Distance Travelled (cm/3 min) in the mouse open field test shown as median (interquartile range Q1 to Q3)

V = mice after the 1st dose of vehicle, Met = mice after the 1st dose of methamphetamine (2.5 mg/kg), Met/Met + Fel = mice sensitised with methamphetamine after the challenge dose of methamphetamine + felbamate (2.5 mg/kg + 240.0 mg/kg)

*$P < 0.05$, NS = non-significant; the non-parametric Wilcoxon matched-pairs signed-ranks test, two tailed

dose with Fel is in agreement with a majority of similar studies which described inhibitory effects of NMDA receptor antagonists on the development of sensitisation to amphetamines (Wolf 1998).

Despite the fact that felbamate is referred to as an activating antiepileptic drug its acute administration along with methamphetamine also inhibited the stimulatory effects of methamphetamine in the group n_4. Wolf et al. (1995) found that co-administration of N-methyl-D-aspartate antagonists MK-801 (dizocilpine maleate) with amphetamine prevented the development of behavioural sensitisation in rats. In their study animals were given either water + amphetamine or MK-801 + ampheta-

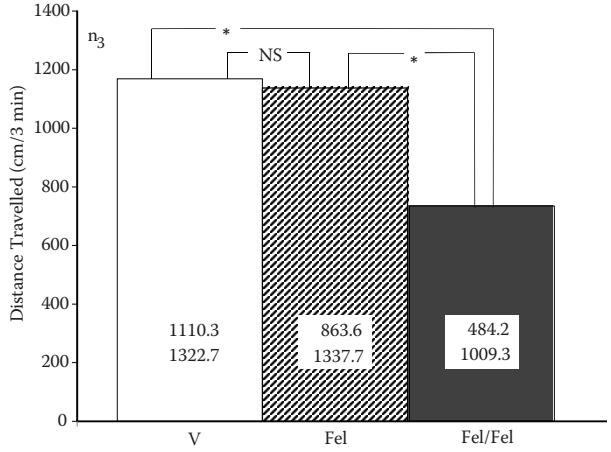

Figure 3. Effects of drug treatments in the group n_3 on Distance Travelled (cm/3 min) in the mouse open field test shown as median (interquartile range Q1 to Q3)

V = mice after the 1st dose of vehicle, Fel = mice after the 1st dose of felbamate (240.0 mg/kg), Fel/Fel = mice sensitised with felbamate after the challenge dose of felbamate (240.0 mg/kg)

*$P < 0.05$, NS = non-significant; the non-parametric Wilcoxon matched-pairs signed-ranks test, two tailed

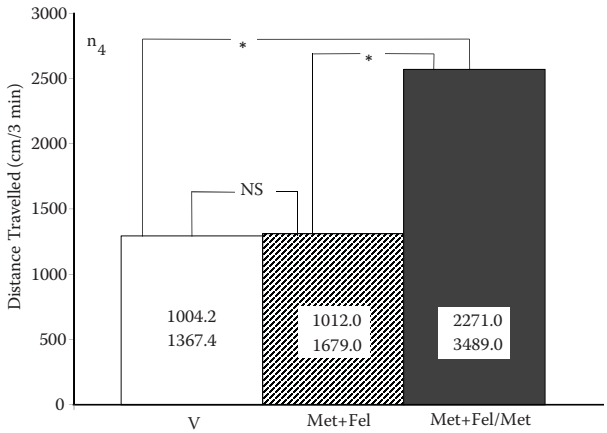

Figure 4. Effects of drug treatments in the group n_4 on Distance Travelled (cm/3 min) in the mouse open field test shown as median (interquartile range Q1 to Q3)

V = mice after the 1st dose of vehicle, Met + Fel = mice after the 1st dose of combination methamphetamine + felbamate (2.5 mg/kg + 240.0 mg/kg), Met + Fel/Met = mice sensitised with the combination methamphetamine + felbamate after the challenge dose of methamphetamine (2.5 mg/kg)

*$P < 0.05$, NS = non-significant; the non-parametric Wilcoxon matched-pairs signed-ranks test, two tailed

mine for six consecutive days. The challenge dose of amphetamine alone was administered on Day 8. Co-administration of MK-801 increased the locomotor response to acute amphetamine administration and repeated pre-treatment with the MK-801 + amphetamine combination prevented the development of sensitisation to a subsequent challenge dose of amphetamine. Similarly Wolf et al. (1995) found that co-administration of NMDA antagonist CGS 19755 augmented the locomotor response to acute amphetamine application and prevented the development of sensitisation after amphetamine challenge dose. Both these results are run counter to our findings because co-administration of felbamate and methamphetamine did not increase locomotory behaviour at all and repeated pre-treatment with the methamphetamine + felbamate combination elicited, after methamphetamine challenge, a significant increase in locomotion, i.e., development of behavioural sensitisation.

Similar findings to Wolf et al. (1995) and contradictory to our results were published by Shim et al. (2002). They also tested the effect of the NMDA receptor antagonist MK-801 on the development of sensitisation to nicotine in rats. The authors described that application of MK-801 plus nicotine evoked a marked increase in locomotor activity for the first four testing days; nevertheless, pre-treatment with MK-801 during the developmental phase inhibited nicotine-induced sensitisation in response to the nicotine challenge dose.

Abekawa et al. (2007) prenatally treated rats with MK-801; however, it was shown that prenatal exposure to MK-801 neither enhanced the acute effects of methamphetamine on postnatal day 35 nor the development of behavioural sensitisation to methamphetamine.

Carey et al. (1995) found that an NMDA receptor antagonist enhanced behavioural responses evoked by drug stimuli (cocaine) and in this way promoted behavioural sensitisation in rats, which is consistent with our results obtained in the group n_4 where repeated co-administration of methamphetamine + felbamate resulted, after the methamphetamine challenge dose, in the development of behavioural sensitisation to the stimulatory effects of methamphetamine.

Other reports suggest that the involvement of NMDA receptors in the processes of behavioural sensitisation could be substance-dependent. For example, Meyer and Phillips (2007) concluded that ethanol-induced behavioural sensitisation was not associated with increased behavioural sensitivity to NMDA receptor antagonists or altered sensitivity to NMDA receptor agonists. They concluded that their results were inconsistent with the hypothesis that ethanol-induced sensitization is associated with alterations in NMDA receptor-mediated processes.

On the other hand, Shim et al. (2002) found that the non-competitive NMDA receptor antagonist MK-801 prevented behavioural sensitisation to nicotine. Hong et al. (2006) focused on the effect of MK-801on nicotine sensitisation of nucleus accumbens dopamine release and found that MK-801 blocked this sensitisation, which speaks to a role for NMDA receptors in the development of behavioural sensitisation to nicotine.

Yang et al. (2008) studied the effects of ifenprodil, a selective antagonist of the NR2B subunit of NMDA receptors on morphine-induced reward and drug-seeking behaviour and behavioural sensitisation. They found that morphine-induced reward and drug-seeking behaviour were abolished when the NR2B subunits of NMDA receptors at the nucleus accumbens were blocked by ifenprodil. On the other hand, morphine-induced reward and drug-seeking behaviour and behavioural sensitisation were not affected when ifenprodil was injected at the ventral tegmental area. Only when ifenprodil was co-administered with morphine did it partially inhibit morphine-induced behavioural sensitisation. These results suggest that the role of the NMDA receptor in the development of sensitization could be dependent not only on the particular substance but also on the particular brain region that is affected.

Some authors have examined possible changes in the brain at the level of receptors. Nelson et al. (2009) tested whether behavioural sensitisation to amphetamine was associated with redistribution of glutamate receptors in the rat nucleus accumbens or dorsolateral striatum but revealed no significant changes in AMPA or NMDA receptor surface expression in both brain structures after withdrawal from the sensitising regimens of amphetamine. They compared these results with previous experiments suggesting increased surface and synaptic levels of AMPA receptors in the nucleus accumbens in rats with cocaine-induced sensitisation (Boudreau and Wolf 2005; Boudreau et al. 2007).

Taken together, behavioural sensitisation is a very complex phenomenon that evokes diverse neurophysiological and behavioural effects via various brain areas and neurochemical pathways. The involvement of glutamatergic receptors in the processes of behavioural sensitisation represents "only" one component. It can be concluded that the

role of NMDA receptors in the processes of sensitisation is of large importance, despite the rather conflicting results obtained from different studies that have dealt with various substances. Since the processes of behavioural sensitisation are believed to reflect neuroadaptive changes involved in psychotic disorders, particularly in addiction and since glutamatergic modulators show promise as a treatment for addiction in pre-clinical models (Bowers et al. 2010), it would be therefore worthwhile to perform further research aimed at elucidating the role of glutametergic component in behavioural sensitisation.

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Corresponding Author:

Prof. MUDr. Alexandra Sulcova, CSc., Masaryk University, CEITEC-Central European Institute of Technology, Kamenice 5/A19, 625 00 Brno, Czech Republic

Tel. +420 549 497 610, E-mail: sulcova@med.muni.cz