

Impact of cannabinoid receptor ligands on behavioural sensitization to antiaggressive methamphetamine effects in the model of mouse agonistic behaviour

Leos LANDA, Karel SLAIS & Alexandra SULCOVA

Masaryk University, Faculty of Medicine, Department of Pharmacology,
Tomesova 12, 662 43 Brno, Czech Republic

Correspondence to: Leos Landa
Masaryk University, Faculty of Medicine, Department of Pharmacology
Tomesova 12, 662 43 Brno, Czech Republic
EMAIL: landa@med.muni.cz
TEL: +420 5 4949 5097
FAX: +420 5 4949 2364

Submitted: November 27, 2006

Accepted: December 5, 2006

Key words: **cannabinoids; methamphetamine; behavioural sensitization; agonistic behaviour; mice; antiaggressive effect**

Neuroendocrinol Lett 2006; **27**(6):703–710 PMID: 17187025 NEL270606A08 ©Neuroendocrinology Letters www.nel.edu and node.nel.edu

Abstract

OBJECTIVES: Psychostimulants and cannabinoids can elicit so called behavioural sensitization after repeated administration, a gradually increased behavioural response to a drug. This phenomenon if conditioned by previous pre-treatment with different drug is termed cross-sensitization. The present study was focused on a possible sensitisation to antiaggressive effect of methamphetamine and cross-sensitization to this effect after repeated pre-treatment with cannabinoid CB₁ and CB₂ receptor ligands with different intrinsic activity (CB₁ agonist methanandamide, CB₂ agonist JWH 015, and CB₁ antagonist AM 251).

METHODS: Behavioural interactions of singly-housed mice with non-aggressive group-housed partners were video-taped and behavioural elements of agonistic behaviour of isolates were recorded in four categories: sociable, timid, aggressive and locomotor.

RESULTS: Repeated administration of methamphetamine elicited a significant sensitization to its antiaggressive effects. Methanandamide pre-treatment provoked cross-sensitization to this methamphetamine effect, whereas pre-treatment with JWH 015 did not. Combined pre-treatment with methamphetamine+AM 251 suppressed the sensitization to antiaggressive effects of methamphetamine.

CONCLUSIONS: Our findings have shown that it is possible to provoke sensitization not only to the stimulatory effects as stated widespread in the literature but also to inhibitory antiaggressive effects of methamphetamine. Furthermore, we confirmed our working hypothesis that it is possible to elicit either cross-sensitization to inhibitory effects of methamphetamine conditioned by repeated pre-treatment with cannabinoid CB₁ receptor agonist methanandamide, or suppression of methamphetamine sensitizing influence by co-administration of CB₁ receptor antagonist.

Abbreviations:

AM 251	– CB ₁ receptor antagonist,
Al	– alert posture,
At	– attack,
Cl	– climbing over the partner,
De	– defensive posture (upright),
Es	– escape,
Fo	– following the partner,
JWH 015	– CB ₂ receptor agonist,
Re	– rearing,
Ss	– social sniffing,
Tr	– tail rattling,
Ur	– aggressive unrest (threat),
Wa	– walking

Introduction

Repeated administration of various substances can elicit a long-lasting increase in behavioural response, which is well known phenomenon termed behavioural sensitization, described consistently for the first time by Robinson and Berridge [1]. Since that time, behavioural sensitization has been described for instance to cannabinoids [2], opioids [3] or psychostimulants [4, 5].

In addition it has been shown that this increased response to a certain drug can be also achieved by previous repeated administration of another drug, a phenomenon called cross-sensitization. It was documented among others after repeated exposure with THC to opioids [2, 6] or with caffeine and amphetamine to nicotine [7].

The most frequently observed features of behavioural sensitization are stimulatory effects of drugs. In laboratory rodents an increase in locomotor/exploratory activities is considered as the most common symptom of behavioural sensitization. Besides this augmented stimulation, sensitization can occur to some other types of behaviour – like defensive-escape activities [8] and there are also reports on sensitization to inhibitory drug actions such as catalepsy [9].

Results of previous study run in our laboratory suggested an interaction between endocannabinoid system and methamphetamine brain mechanisms in the I.V. drug self-administration model in rats [10]. This was further confirmed by other experiments realised using the mouse open field test where we unambiguously found that pre-treatment with CB₁ receptor agonist methanandamide elicited cross-sensitization to methamphetamine effect and on the contrary, combined pre-treatment with methamphetamine+AM 251 suppressed sensitization to methamphetamine [11]. All these findings speak in favour of the suggested interaction between endocannabinoid system activity and methamphetamine CNS mechanisms and moreover they support further views of other authors that ligands blocking CB₁ receptors offer a novel approach for treatment of addiction [12].

In our earlier experiments acute methamphetamine administration elicited an inhibition of aggressivity in the model of mouse agonistic interactions [13]. Thus, we decided to test in the present study if the repeated administration of methamphetamine would more pronounce this effect, i.e. elicit behavioural sensitization to its antiaggressive effects. Furthermore, the present study

was designed to investigate the effects of pre-treatments with cannabinoid CB₁ receptor agonist methanandamide and CB₁ receptor antagonist AM 251 on sensitization to methamphetamine antiaggressive effects. Finally, as the presence of CB₂ receptors was also confirmed in some areas of the brain [14, 15, 16] and we are experienced with behavioural effect of CB₂ receptor agonist JWH 015 in mice [17], we decided to test a possible effect of pre-treatment with CB₂ receptor agonist JWH 015 on sensitization to methamphetamine antiaggressive effects. All these experiments were performed using the model of mouse agonistic behaviour.

Material and methods

Animals

In all experiments mice males (strain ICR, TOP-VELAZ s. r. o., Prague, Czech Republic) with an initial weight of 18–21 g were used. 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. Experimental sessions were always performed in the same light period (8:00 – 11:00 a.m.) in order to minimise possible variability due to circadian rhythms.

The experimental protocols of all experiments comply with the European Community guidelines for the use of experimental animals and were approved by the Animal Care Committee of the Masaryk University Brno, Faculty of Medicine, Czech Republic.

Model of agonistic behaviour

The model of agonistic behaviour used in this study was based on intraspecies social conflict in adult male mice [18, 19] and it consists of observation of behaviour in individually-housed mice on dyadic interactions with group-housed partners in neutral environment of the observational plastic box (base 30 x 20 cm, height 20 cm). After 30 min adaptation of singly-housed mice in the neutral cages their four minute dyadic behavioural interactions of singly-housed mice with non-aggressive group-housed partners were video-taped. After each interaction the neutral cage sawdust bedding was replaced. The behavioural element recording was performed later by an experimenter who was unaware of treatment of the mouse groups using the keyboard of the computer-compatible system OBSERVER 3.1 (Noldus Information Technology b.v., Holland).

Whereas the group-housed partner does not display aggressiveness, individually-housed mice can be according to their behaviour in control interaction (vehicle treatment) divided into 3 categories: a) aggressive mice (showing at least one attack towards the opponents in the control interactions); b) timid mice (showing majority of defensive-escape behaviour even in absence of partner's attacks and no attack); c) sociable mice (animals without aggressive or defensive-escape behaviour, showing however high frequency of approaches to partner and its sniffing or climbing over the partner – acts considered

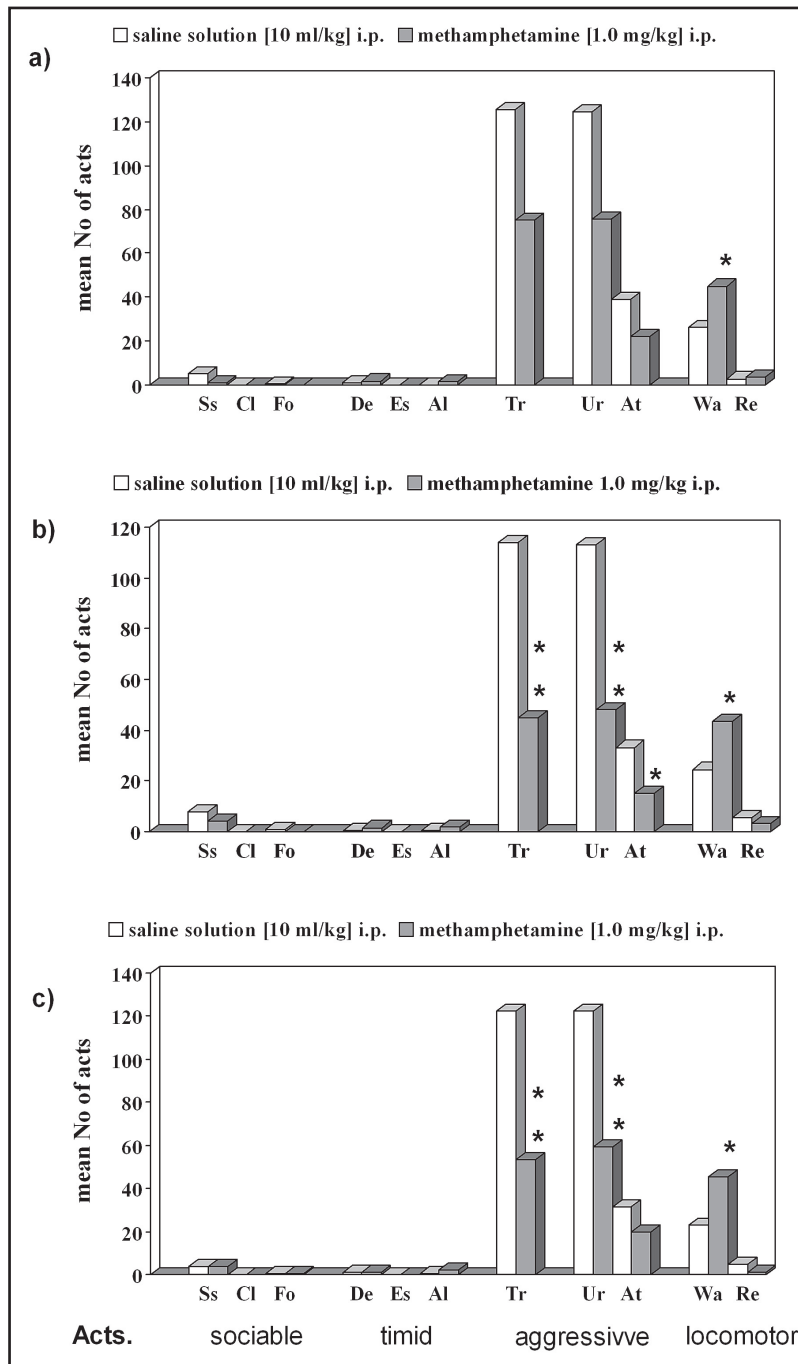


Figure 1: The effect of methamphetamine “challenge dose” in singly-housed aggressive mice on agonistic interactions with non-aggressive group-housed partners: **a)** repeatedly pre-treated with saline solution ($n_1=11$), **b)** repeatedly pre-treated with methamphetamine ($n_2=18$), **c)** repeatedly pre-treated with methanadamide ($n_3=19$). Behavioural acts: Sociable – Ss (social sniffing), Cl (climbing over the partner), Fo (following the partner); Timid: De (defensive posture), Es (escape), Al (alert posture); Aggressive: Tr (tail rattling), Ur (aggressive unrest), At (attack); Locomotor: Wa (walking), Re (rearing). i.p. – intraperitoneally, * = $p < 0.05$, ** = $p < 0.01$, the nonparametric Wilcoxon matched pairs test.

to be sociable. Behavioural elements of four subtypes were recorded: sociable – social sniffing [Ss], following the partner [Fo], climbing over the partner [Cl]; timid – defensive posture (upright) [De], escape [Es], alert posture [Al]; aggressive – attack [At], aggressive unrest (threat) [Ur], tail rattling [Tr]; locomotor – walking [Wa], rearing [Re]. Just aggressive singly-housed mice were chosen as subjects in the present study.

Substances

(+)-Methamphetamine, (d-N, α -Dimethylphenylethylamine;d-Desoxyephedrine), (Sigma Chemical Co.) dissolved in saline.

(R)-(+)-Methanandamide, (R)-N-(2-hydroxy-1-methylethyl)-5Z,8Z,11Z-eicosotetraenamide) supplied pre-dissolved in anhydrous ethanol 5 mg/ml (Tocris Cookson Ltd., UK) was diluted in saline to the concentration giving the chosen dose to be administered to ani-

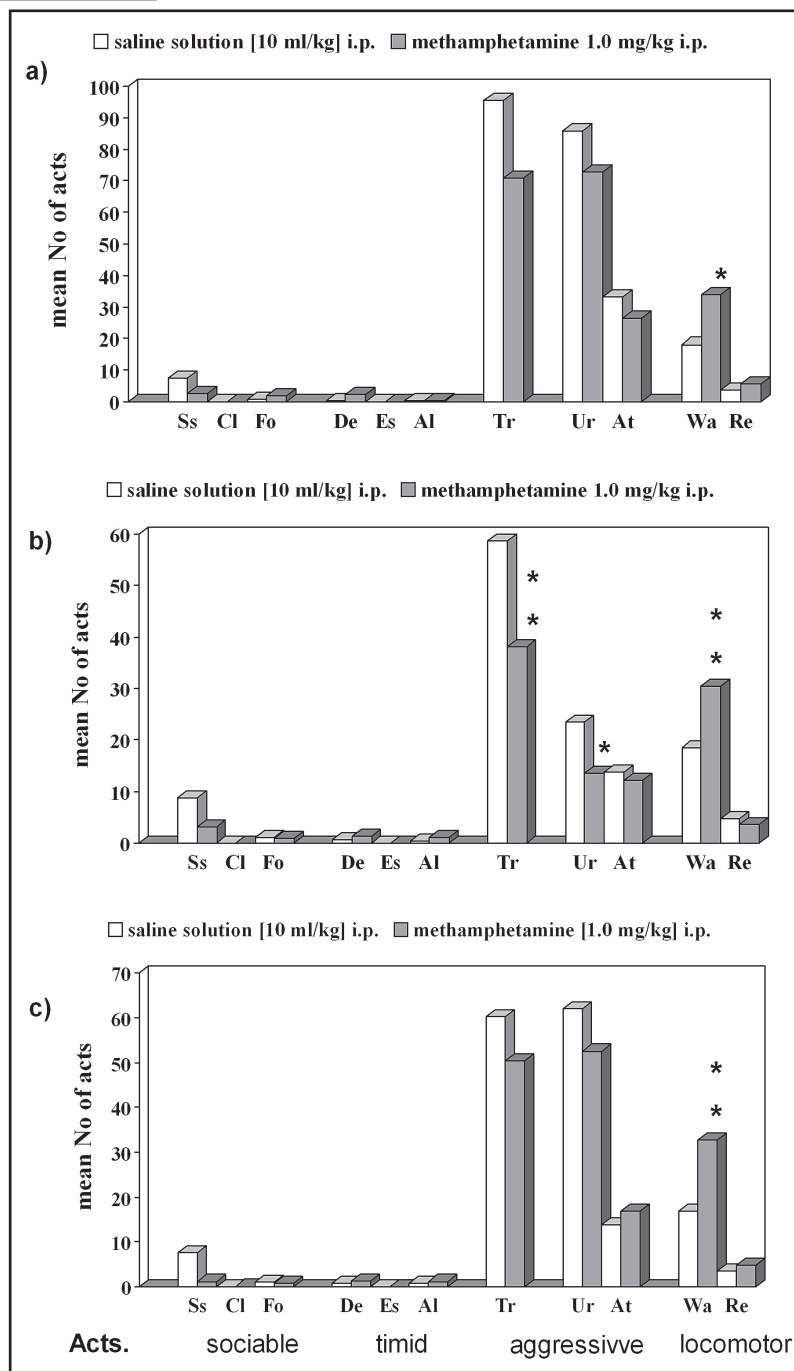


Figure 2: The effect of methamphetamine “challenge dose” in singly-housed aggressive mice on agonistic interactions with non-aggressive group-housed partners: **a)** repeatedly pre-treated with saline solution ($n_1=8$), **b)** repeatedly pre-treated with methamphetamine ($n_2=9$), **c)** repeatedly pre-treated with JWH 015 ($n_3=11$). Behavioural acts: Sociable – Ss (social sniffing), Cl (climbing over the partner), Fo (following the partner); Timid: De (defensive posture), Es (escape), Al (alert posture); Aggressive: Tr (tail rattling), Ur (aggressive unrest), At (attack); Locomotor: Wa (walking), Re (rearing). i.p. – intraperitoneally, * = $p < 0.05$, ** = $p < 0.01$, the nonparametric Wilcoxon matched pairs test.

mals in a volume of 10 ml/kg; vehicle therefore contained an adequate part of ethanol (a final concentration in the injection below 1%) to make effects of placebo and the drug comparable.

JWH 015, (1 propyl-2-methyl-3-(1-naphthoyl)indole), (Tocris Cookson Ltd., UK), dissolved in ethanol+saline – 1:19; vehicle treatment as a control in this case contained an adequate part of ethanol to make effects of placebo and the drug comparable.

AM 251, (N-(Piperidin-1-yl)-5-(4-iodophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxamide), (Tocris Cookson Ltd., UK), ultrasonically suspended in Tween 80 (1 drop in 10 ml saline); vehicle treatment as a control in this case contained an adequate part of Tween 80.

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

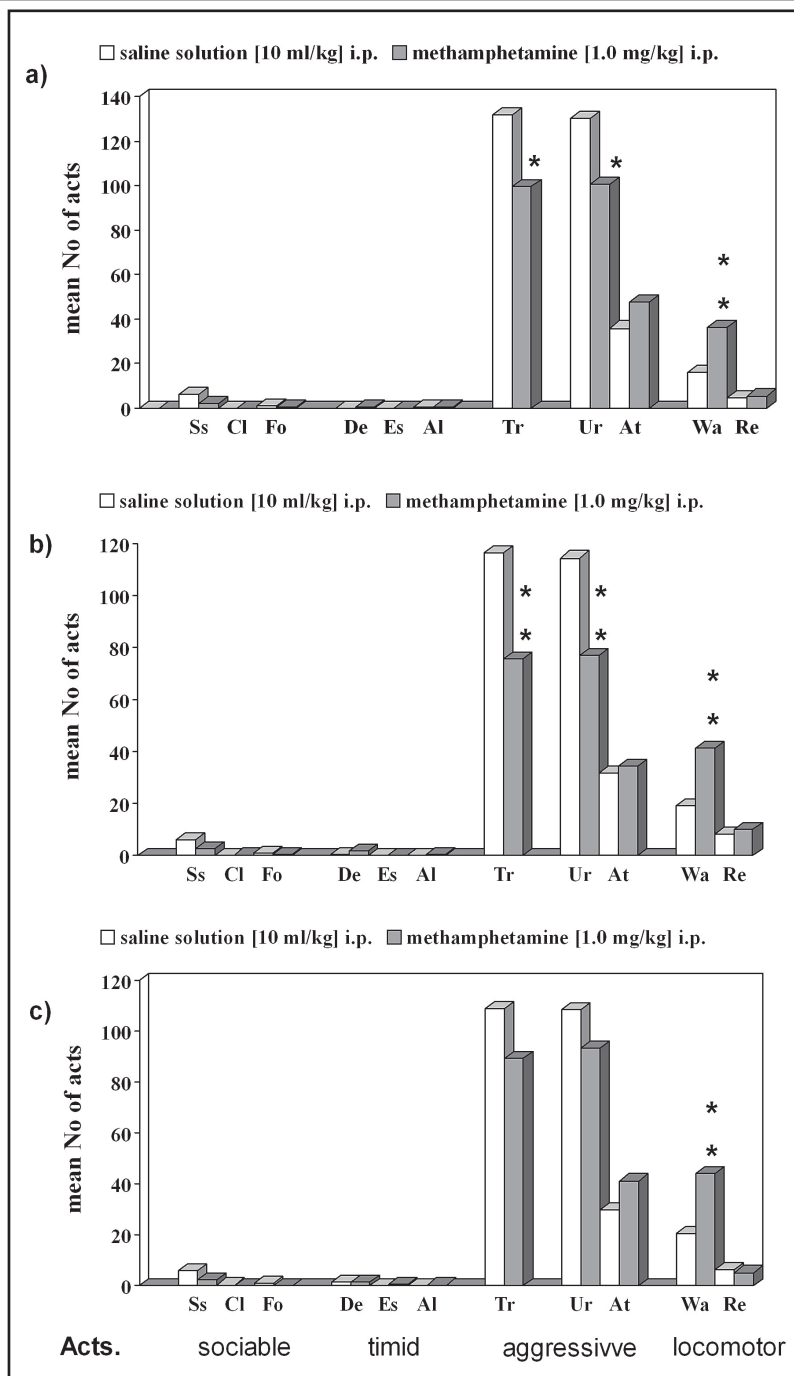


Figure 3: The effect of methamphetamine “challenge dose” in singly-housed aggressive mice on agonistic interactions with non-aggressive group-housed partners: **a)** repeatedly pre-treated with saline solution ($n_1=11$), **b)** repeatedly pre-treated with methamphetamine ($n_2=12$), **c)** repeatedly pre-treated with methamphetamine+AM 251 ($n_3=14$). Behavioural acts: Sociable – Ss (social sniffing), Cl (climbing over the partner), Fo (following the partner); Timid: De (defensive posture), Es (escape), Al (alert posture); Aggressive: Tr (tail rattling), Ur (aggressive unrest), At (attack); Locomotor: Wa (walking), Re (rearing). i.p. – intraperitoneally, * = $p < 0.05$, ** = $p < 0.01$, the nonparametric Wilcoxon matched pairs test.

Procedures

Singly-housed mice were randomly allocated into 3 groups in each of three experiments for the following 5 day drug pre-treatment given intraperitoneally: the Experiment I) $n_1=11$: saline solution 10 ml/kg/day, $n_2=18$: methamphetamine 1 mg/kg/day, $n_3=19$: methanandamide 0.5 mg/kg/day; the Experiment II) $n_1=8$: saline solution at the dose of 10 ml/kg/day, $n_2=9$:

methamphetamine at the dose of 1 mg/kg/day, $n_3=11$: JWH 015 at the dose of 10 mg/kg/day; the Experiment III) $n_1=11$: saline solution at the dose of 10 ml/kg/day, $n_2=12$: methamphetamine at the dose of 1 mg/kg/day, $n_3=14$: methamphetamine+AM 251 at the doses of 1 mg/kg/day and 5 mg/kg/day, respectively. There was a wash-out period on the Days 6–10, and on the Day

11 agonistic interactions were performed 15 min after the administration of saline solution to all subjects (10 ml/kg). The "challenge doses" of methamphetamine (1 mg/kg) were given to all subjects 15 min prior to second agonistic interactions on the Day 15 while Days 12–14 present a wash-out.

Statistical data analysis

As the data did not show normal distribution (analysed by Kolmogorov-Smirnov test of normality), the differences between the occurrence of behavioural acts in control and experimental interactions were evaluated by the non-parametric Wilcoxon test, two tailed.

Results

In the Experiment I, administration of the methamphetamine "challenge dose" elicited:

- a) non-significant changes in sociable and timid behavioural acts in mice pre-treated with saline solution (group n_1); changes in aggressive acts were also non-significant ($p > 0.05$), however there was an apparent trend of decrease in tail rattling, aggressive unrest and attack; there was a significant ($p < 0.05$) increase in walking, which represents one of two locomotor behavioural elements (see Figure 1a).
- b) non-significant changes in sociable and timid behavioural acts in mice pre-treated with methamphetamine (group n_2), highly significant ($p < 0.01$) decrease in tail rattling and aggressive unrest, significant ($p < 0.05$) decrease in attack, significant ($p < 0.05$) increase in walking – (see Figure 1b).
- c) non-significant changes in sociable and timid behavioural acts in mice pre-treated with methanandamide (group n_3), highly significant ($p < 0.01$) decrease in tail rattling and aggressive unrest, significant ($p < 0.05$) increase in walking (see Figure 1c).

In the Experiment II, administration of the methamphetamine "challenge dose" elicited:

- a) in mice pre-treated with saline solution (group n_1) non-significant changes in sociable and timid behavioural acts, as well as in all aggressive acts (tail rattling, aggressive unrest and attack), these, however, showed an apparent trend of decrease; there was a significant ($p < 0.05$) increase in walking (see Figure 2a).
- b) in mice pre-treated with methamphetamine (group n_2) non-significant changes in sociable and timid behavioural acts, highly significant ($p < 0.01$) decrease in tail rattling, significant ($p < 0.05$) decrease in aggressive unrest, highly significant ($p < 0.01$) increase in walking (see Figure 2b).
- c) in mice pre-treated with JWH 015 (group n_3) non-significant changes in sociable, aggressive and timid behavioural acts, highly significant ($p < 0.01$) increase in walking (see Figure 2c).

In the Experiment III administration of the methamphetamine "challenge dose" elicited:

- a) in mice pre-treated with saline solution (group n_1) non-significant ($p > 0.05$) changes in sociable and timid behavioural acts, significant ($p > 0.05$) decrease in tail rattling, aggressive unrest and a highly significant ($p < 0.01$) increase in walking (see Figure 3a).
- b) in mice pre-treated with methamphetamine (group n_2) non-significant changes in sociable and timid behavioural acts, highly significant ($p < 0.01$) decrease in tail rattling and aggressive unrest, highly significant ($p < 0.01$) increase in walking (see Figure 3b).
- c) in mice pre-treated with methamphetamine+AM 251 (group n_3) non-significant changes in sociable, aggressive and timid behavioural acts and highly significant ($p < 0.01$) increase in walking (see Figure 3c).

Discussion

Presented results confirmed with methamphetamine the well known effects of amphetamine and its derivatives disrupting aggressive behaviour in various animal species including male mice on agonistic interactions [20, 21, 22]. The behavioural sensitization developed not only to stimulatory effects on locomotion, but also to the inhibitory antiaggressive effects after repeated methamphetamine administration in the present study. Behavioural sensitization to psychostimulant effects of amphetamines and opioids has been already described [for review see 23, 24], however, according to literature available, there is far less evidence on behavioural sensitization to inhibitory effects of substances. It has been described for instance sensitization to catalepsy in rats [25] and also sensitization to suppression of defensive-escape behaviour in mice [8]. Our present experiments showed the development of behavioural sensitization to methamphetamine inhibitory influences on naturally motivated behaviour – male mouse aggression. The results obtained from our study concerning impact of cannabinoid receptor ligands on sensitization to antiaggressive methamphetamine effects confirmed the working hypothesis that it is possible to elicit cross-sensitization to both stimulatory and inhibitory effects of methamphetamine conditioned by repeated pre-treatment with cannabinoid CB_1 receptor agonist methanandamide. The data obtained from these our experiments confirmed an assumption published elsewhere of existing functional interaction between the activity of cannabinoid CB_1 receptors and amphetamine [6, 26, 27, 28, 29] or methamphetamine [11, 30, 31] mechanisms in the CNS.

Despite of the fact that the CB_2 receptor agonist JWH 015 has been shown earlier to produce at the acute dose of 10 mg/kg significant antiaggressive effect in our model of agonistic behaviour in singly-housed male mice on paired interactions with non-aggressive group-housed partners, the repeated pre-treatment with this compound however did not produce the cross-sensitization to these effects of methamphetamine given as a „challenge dose”

after the withdrawal of repeated treatment in the present study. Interestingly, some sign of cross-sensitization was registered in the case of methamphetamine stimulation of locomotion (walking) which occurred on a higher level of significance in JWH 015 pre-treated mice comparing to controls. The presence of CB₂ receptors has been already reported not only in the immune system, but also in the CNS in mice [14] and rats [15], and using specific polyclonal antibodies they were detected in hippocampus and cortex of Alzheimer's disease patients, too [32]. Thus, our findings suggest, that at least some cross-sensitizing processes during combined administration of CB₂ receptor agonist JWH 015 and methamphetamine can exist due to cross-talks between not only CB₁ but also CB₂ receptors and methamphetamine pathways.

The CB₁ receptor blockade attenuates the behavioural manifestations of methamphetamine sensitization in mice pre-treated repeatedly with methamphetamine+AM 251(cannabinoid CB₁ receptor antagonist) in the present study. Just the significant increase of walking was apparent after methamphetamine „challenge dose”. Our findings obtained from the model of agonistic interactions are to a large extent in accordance with some other papers. For instance, we have found [10], that AM 251 decreased methamphetamine self-administration under a FR schedule in rats, and similarly the suppression of behavioural sensitization to morphine in the rodent model of drug-seeking behaviour was shown after pre-treatment with another CB₁ antagonist SR141716A [33]. On the other hand there is also a contradictory report available suggesting that endogenous cannabinoids and CB₁ receptors are not involved in behavioural sensitization to psychostimulants, namely cocaine [34].

The endocannabinoid system is thought to be the primary site of action for the rewarding and pharmacological responses induced by cannabinoids [31, 35]. Despite the statement of above mentioned publication of Lescher et al. [34], there are multiple studies supporting that the common neurobiological mechanisms of most drugs of abuse participated in their addictive properties interact in bidirectional manner with the endocannabinoid system involvement in regulation of drug rewarding effects [31].

The main principle of behavioural sensitization to methamphetamine and also of cross-sensitization with cannabinoid CB₁ receptor agonist methanandamide is probably based on the potency of these substances to release dopamine in the nucleus accumbens [36], which is a property common to many drugs that can elicit sensitization, and dopamine activation of endogenous cannabinoid signalling in the CNS has been confirmed [37]. Although not all neurobiological bases of behavioural sensitization are fully clear yet, there are studies indicating that behavioural sensitization has a neural basis and that the neuronal circuit important for behavioural sensitization consists of various structures in the CNS. It involves not only dopaminergic, but also glutamatergic and GABAergic projections between ventral tegmental area, nucleus accumbens, prefrontal

cortex, hippocampus and amygdala. The mesolimbic dopaminergic projection from the ventral tegmental area to the nucleus accumbens seems to be of crucial importance for reward-related effects of drugs of abuse [38]. Furthermore, the mesolimbic and nigrostriatal dopamine systems also participate at the reinforcing and locomotor-stimulating effects of psychostimulant drugs [39].

In conclusion, the present study can be summarized as follows: 1) repeated administration of methamphetamine produces behavioural sensitization to its stimulatory effects on locomotion and antiaggressive effects in the mouse model of agonistic behaviour. 2) pre-treatment with cannabinoid CB₁ receptor agonist methanandamide elicited cross-sensitization to methamphetamine, whereas blocking of these receptors with antagonist AM 251 inhibited this process; 3) pre-treatment with cannabinoid CB₂ receptor agonist JWH 015 did not provoke cross-sensitization to methamphetamine antiaggressive effects in this study.

All presented findings received in the model testing antiaggressive drug effects in mice confirmed in fact the similar suggestion on interaction of methamphetamine mechanisms and endocannabinoid system activity we have published earlier [11, 40] using a differential behavioural model, the open field test as a tool for registration of behavioural sensitization to methamphetamine psychostimulant effects.

Acknowledgements

This work was supported by the Czech Ministry of Education Project: VZ SM0021622404.

REFERENCES

- 1 Robinson TE, Berridge KC. The neural basis of drug craving: an incentive-sensitization theory of addiction. *Brain Res Rev* 1993; **18**:247–291.
- 2 Cadoni C, Pisanu A, Solinas M, Acquas E, Di Chiara G. Behavioural sensitization after repeated exposure to 9-tetrahydrocannabinol and cross-sensitization with morphine. *Psychopharmacology* 2001; **158**:259–266.
- 3 De Vries TJ, Schoffelmeer AN, Binnekade R, Vanderschuren LJ. Dopaminergic mechanisms mediating the incentive to seek cocaine and heroin following long-term withdrawal of IV drug self-administration. *Psychopharmacology* 1999; **143**:254–260.
- 4 Costa FG, Frussa-Filho R, Felício FL. The neurotensin receptor antagonist, SR48692, attenuates the expression of amphetamine – induced behavioural sensitisation in mice. *Eur J Pharmacol* 2001; **428**:97–103.
- 5 Elliot EE. Cocaine sensitization in the mouse using a cumulative dosing regime. *Behav Pharmacol* 2002; **13**:407–415.
- 6 Lamarque S, Taghzouti K, Simon H. Chronic treatment with Delta(9) – tetrahydrocannabinol enhances the locomotor response to amphetamine and heroin. Implications for vulnerability to drug addiction. *Neuropharmacology* 2001; **41**:118–129.
- 7 Celik E, Uzbay IT, Karakas S. Caffeine and amphetamine produce cross-sensitization to nicotine-induced locomotor activity in mice. *Prog Neuropsychopharmacol Biol Psychiatry* 2006; **30**:50–55.

- 8 Votava M, Krsiak M. Morphine increases duration of a walking bout and timidity signs after its acute and challenge administration in mice. *Behav Pharmacol* 2003; **14**, Suppl. 1:549.
- 9 Lanis A, Schmidt WJ. NMDA receptor antagonists do not block the development of sensitization of catalepsy, but make its expression state-dependent. *Behav Pharmacol* 2001; **12**:143–149.
- 10 Vinklerova J, Novakova J, Sulcova A. Inhibition of methamphetamine self-administration in rats by cannabinoid receptor antagonist AM 251. *J Psychopharmacol* 2002; **16**:139–143.
- 11 Landa L, Slais K, Sulcova A. Involvement of cannabinoid CB1 and CB2 receptor activity in the development of behavioural sensitization to methamphetamine effects in mice. *Neuro Endocrinol Lett* 2006; **27**:63–69.
- 12 LeFoll B, Goldberg SR. Cannabinoid CB₁ receptor antagonists as promising new medications for drug dependence. *J Pharmacol Exp Ther* 2005; **312**:875–883.
- 13 Vinklerova J, Novakova J, Sulcova A. Acute and chronic methamphetamine effects on agonistic behaviour in mice. Abstract of neurochemistry winter conference; April 2–11 2002 Solden, Austria, University of Innsbruck, p. 55.
- 14 Skaper SD, Buriani A, Dal Toso R, Petrelli L, Romanello S, Facci L, Leon A. The ALIamide palmitoylethanolamide and cannabinoids, but not anandamide, are protective in a delayed postglutamate paradigm of excitotoxic death in cerebellar granule neurons. *Proc Natl Acad Sci USA* 1996; **93**:3984–3989.
- 15 Carlisle SJ, Marciano-Cabral F, Staab A, Ludwick C, Cabral GA. Differential expression of the CB2 cannabinoid receptor by rodent macrophages and macrophage-like cells in relation to cell activation. *Int Immunopharmacol* 2002; **2**:69–82.
- 16 Nunez E, Benito C, Pazos MR, Barbachano A, Fajardo O, Gonzalez S, Tolon RM, Romero J. Cannabinoid CB₂ receptors are expressed by perivascular microglial cells in the human brain: An immunohistochemical study. *Synapse* 2004; **53**:208–213.
- 17 Sulcová A, Landa L, Slais K. Impact of cannabinoid CB2 receptor activity on aggressive behaviour in mice and sensitization to methamphetamine antiaggressive effects. FENS Forum Abstracts, Lisbon, Portugal, July 10–14, 2004, 2, A217.16.
- 18 Krsiak M. Timid singly-housed mice: Their value in prediction of psychotropic activity of drugs. *Brit J Pharmacol* 1975; **55**:141–150.
- 19 Donat P. Uvod do etofarmakologie. PF UK, 1992, Praha.
- 20 Miczek KA, Haney M. Psychomotor stimulant effects of d-amphetamine, MDMA and PCP: aggressive and schedule-controlled behavior in mice. *Psychopharmacology* 1994; **115**:358–365.
- 21 Moro M, Salvador A, Simon VM. Effects of repeated administration of d-amphetamine on agonistic behaviour of isolated male mice. *Behav Pharmacol* 1997; **8**:309–318.
- 22 Navarro JF, Maldonado E. Behavioral profile of quinpirole in agonistic encounters between male mice. *Methods Find Exp Clin Pharmacol* 1999; **21**:477–480.
- 23 Novakova J, Sulcova A. K teorii sensitizace u látek vyvolávajících závislost. *Adiktologie* 2003; **2**:24–32.
- 24 Tzschentke TM. The role of sensitization in drug addiction. *Adiktologie* 2003; **2**:34–48.
- 25 Schmidt WJ. Mechanisms of behavioural sensitization. *Adiktologie* 2004; **1**:21–27.
- 26 Gorriti MA, Rodriguez de Fonseca F, Navarro M, Palomo T. Chronic (-)-delta9-tetrahydrocannabinol treatment induces sensitization to the psychomotor effects of amphetamine on rats. *Eur J Pharmacol* 1999; **365**:133–142.
- 27 Di Marzo V, Berrendero F, Bisogno T, Gonzales S, Cavaliere P, Romero J, Cebeira M, Ramos JA, Fernandez Ruiz JJ. Enhancement of anandamide formation in the limbic forebrain and reduction of endocannabinoid contents in the striatum of Δ9-tetrahydrocannabinol-tolerant rats. *J Neurochim* 2000; **74**:1627–1635.
- 28 Vezina P, Lorrain DS, Austin, JD. Locomotor responding to amphetamine is enhanced following exposure to delta-9-THC. 6th Internet World Congress for Biomedical Sciences INABIS, 2000.
- 29 Muschamp JW, Siviuy SM. Behavioral sensitization to amphetamine follows chronic administration of the CB1 agonist WIN 55,212–2 in Lewis rats. *Pharmacol Biochem Behav* 2002; **73**:835–842.
- 30 Anggadiredja K, Nakamichi M, Hiranita T, Tanaka H, Shoyama Y, Watanabe S, Yamamoto T. Endocannabinoid system modulates relapse to methamphetamine seeking: Possible mediation by the arachidonic acid cascade. *Neuropsychopharmacol* 2004; **29**:1470–1478.
- 31 Maldonado R, Valverde O, Berrendero F. Involvement of the endocannabinoid system in drug addiction. *Trends Neurosci* 2006; **29**:225–232.
- 32 Benito C, Nunez E, Tolon RM, Carrier EJ, Rabano A, Hillard CJ, Romero J. Cannabinoid CB2 Receptors and Fatty Acid Amide Hydrolase Are Selectively Overexpressed in Neuritic Plaque-Associated Glia in Alzheimer's Disease Brains. *J Neurosci* 2003; **23**:11136–11141.
- 33 Vigano D, Valenti M, Cascio MG, Di Marzo V, Parolaro D, Rubino T. Changes in endocannabinoid levels in a rat model of behavioural sensitization to morphine. *Eur J Neurosci* 2004; **20**:1849–1857.
- 34 Lesscher HM, Hoogveld E, Burbach JP, van Ree JM, Gerrits MA. Endogenous cannabinoids are not involved in cocaine reinforcement and development of cocaine-induced behavioural sensitization. *Eur Neuropsychopharmacol* 2005; **15**:31–37.
- 35 Ledent C, Valverde O, Cossu G, Petitet F, Aubert JF, Beslot F, Bohme GA, Imperato A, Pedrazzini T, Roques BP, Vassart G, Fratta W, Parmentier M. Unresponsiveness to cannabinoids and reduced addictive effects of opiates in CB1 receptor knockout mice. *Science* 1999; **283**:401–404.
- 36 Uhl GR, Volkow N. Perspectives on reward circuitry, neurobiology, genetics and pathology: Dopamine and addiction. *Mol Psychiatr* 2001; **6**, Suppl. 1:S1.
- 37 Giuffrida A, Parsons LH, Kerr TM, de Fonseca FR, Navarro M, Piomelli D. Dopamine activation of endogenous cannabinoid signaling in dorsal striatum. *Nat Neurosci* 1999; **2**:358–363.
- 38 Kalivas PW, Sorg BA, Holka MS. The pharmacology and neural circuitry of sensitization to psychostimulants. *Behav Pharmacol* 1993; **4**:315–334.
- 39 Wise RA, Bozarth MA. A psychomotor stimulant theory of addiction. *Psychological Rev* 1987; **94**:469–492.
- 40 Landa L, Slais K, Hanesova M., Sulcova A. Interspecies comparison of sensitization to methamphetamine effects on locomotion in mice and rats. *Homeostasis* 2005; **43**:146–147.