The effect of the cannabinoid CB_1 receptor agonist arachidonylcyclopropylamide (ACPA) on behavioural sensitisation to methamphetamine in mice

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ABSTRACT: The psychostimulant methamphetamine (Met), similarly to other drugs of abuse, is known to produce an increased behavioural response after its repeated application (behavioural sensitisation). It has also been described that an increased response to a drug may be elicited by previous repeated administration of another drug (cross-sensitisation). We have previously shown that the CB_1, CB_2 and TRPV (vanilloid) cannabinoid receptor agonist methanandamide, cross-sensitised to Met stimulatory effects in mice. The present study was focused on ability of the more selective and potent CB_1 receptor activator arachidonylcyclopropylamide (ACPA) to elicit cross-sensitisation to the stimulatory effects of Met on mouse locomotor behaviour in the Open field test. Male mice were randomly divided into three groups and on seven occasions (from the 7th to 13th day of the experiment) were administered drugs as follows:(a) n_1: vehicle at the dose of 10 ml/kg/day; (b) n_2: Met at the dose of 2.5 mg/kg/day; (c) n_3: ACPA at the dose of 1.0 mg/kg/day. Locomotor behaviour in the Open field test was measured (a) after administration of vehicle on the 1st experimental 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 manner: n_1: saline at a dose of 10 ml/kg, $n_{2,3}$: Met at a dose of 2.5 mg/kg. The observed behavioural changes consisted in: (a) gradual development of habituation to the open field conditions in three consecutive tests; (b) development of behavioural sensitisation to the stimulatory effects of Met after repeated treatment; (c) insignificant effect of repeated pre-treatment with ACPA on the stimulatory effects of Met challenge dose. The results of our study give rise to the question which of the cannabinoid receptor mechanisms might be most responsible for the neuroplastic changes inducing sensitisation to the stimulatory effects of Met.

Keywords: behavioural sensitisation; methamphetamine; cannabinoids; ACPA; mice

List of abbreviations

ACPA = N-(cyclopropyl)-5Z,8Z,11Z,14Z-eicosatetraenamide (alternative name: arachidonylcyclopropylamide); **AM 251** = N-(piperidin-1-yl)-5-(4-iodophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxamide; **GPR55** = G protein-coupled receptor 55; **JWH 015** = 1 propyl-2-methyl-3-(1-naphthoyl)indole; **Met** = methamphetamine; **Sal** = saline; **THC** = delta 9-tetrahydrocannabinol; **TRPV1** = transient receptor potential cation channel subfamily V member 1; **V** = vehicle

It has been consistently described that repeated administration of dependence-producing substances leads to an increased behavioural response, defined as behavioural sensitisation (Robinson and Berridge 1993). This phenomenon was observed after repeated administration of both legal and illegal drugs and has been described for ethanol (Broadbent 2013; Kim and Souza-Formigoni 2013; Linsenbardt and Boehm 2013), nicotine (Hamilton et al. 2012; Lenoir et al. 2013; Perna and Brown 2013), caffeine (Zancheta et al. 2012), cannabinoids (Rubino et al. 2003; Cadoni et al. 2008), psycho-

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stimulants (Landa et al. 2006a,b; 2011; 2012a,b; Wang et al. 2010; Ball et al. 2011; Kameda et al. 2011) or opioids (Bailey et al. 2010; Liang et al. 2010; Farahmandfar et al. 2011; Hofford et al. 2012; Rezayof et al. 2013).

When an increased response to a tested substance is elicited by previous repeated administration of a different drug, such a phenomenon is termed as cross-sensitisation. Cross-sensitisation was described (among others) after repeated treatment of nicotine to amphetamine (Adams et al. 2013) with tetrahydrocannabinol to heroin (Singh et al. 2005) or with methamphetamine (Met) to modafinil (Merhautova et al. 2012).

Vinklerova et al. (2002) reported that in animals trained to self-administer Met (rat *i.v.* drug self-administration model) the cannabinoid CB_1 receptor antagonist/inverse agonist AM 251 decreased Met intake. This finding obtained in our laboratory suggested an interaction between the endocannabionoid system and Met brain mechanisms. Thus, we then focused on interactions of cannabinoid receptor ligands with different intrinsic activities and Met. Using our original experimental design in the mouse Open Field Test and the model of agonistic behaviour we found that repeated pre-treatment with the CB_1 receptor agonist methanandamide elicited cross-sensitisation to the stimulatory effects of Met, whereas pre-treatment with the CB_2 receptor agonist JWH 015 did not (Landa et al. 2006a,b). Furthermore, combined pre-treatment with methamphetamine and CB_1 receptor antagonist/inverse agonist AM 251, suppressed sensitisation to Met, which is in accordance with the attenuation of behavioural sensitisation to amphetamine reported after co-administration with AM 251 (Thiemann et al. 2008).

Both Met and herbal cannabinoids, particularly delta 9-tetrahydrocannabinol (THC; the main psychotropic component of marijuana) are well known substances with dependence potential. Nevertheless, there are also reports on the therapeutic potential of pharmacological manipulation of the endocannabinoid system; besides addiction, this system has also been studied with respect to possible treatment of multiple sclerosis, chronic neuropathic pain, nausea and vomiting, loss of appetite, cancer or AIDS patients, psychosis, epilepsy, metabolic disorders, asthma and glaucoma (Fisar 2009; Robson 2014). In veterinary medicine attention has focused mainly on the cases of intoxication with marijuana (Donaldson 2002; Meola et al. 2012). Nevertheless, there is an increasing number of reports (as yet anecdotal) on the therapeutic use of cannabinoids in small animals. However, this issue still need to be investigated thoroughly.

In the present experiment we examined the possible influence of the selective cannabinoid CB_1 receptor agonist arachidonylcyclopropylamide (ACPA) on behavioural sensitisation to Met. Repeated use of cannabinoid CB_1 receptor agonists is believed to facilitate consumption of other dependency producing substances (Lamarque et al. 2001). On the other hand, the use of CB_1 receptor antagonists was described as a possible approach for treatment of drug dependence (LeFoll and Goldberg 2005; Thiemann et al. 2008). We believe that our study may contribute to better understanding of the mutual relationship between cannabinoids and Met interactions in the processes of behavioural sensitisation.

MATERIAL AND METHODS

Animals. Mice (males, strain ICR, TOP-VELAZ s.r.o., Prague, Czech Republic) weighing 18–21 g at the beginning of the experiment were used. Animals were randomly allocated into three equal 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. The animals were maintained under a 12-h light/dark cycle.

Apparatus. Locomotor activity was measured in an open-field arena using the Actitrack instrument (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 and it acts 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 its body. Using this equipment we 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.

Arachidonylcyclopropylamide, *N*-(cyclopropyl)-5*Z*,8*Z*,11*Z*,14*Z*-eicosatetraenamide was supplied

pre-dissolved in anhydrous ethanol 5 mg/ml (Tocris Cookson Ltd., UK) and was further diluted in saline to the appropriate concentration; the vehicle contained an adequate part of ethanol (final concentration in the injection below 1%) to make the effects of the placebo and the drug comparable.

The adjustment of all drug doses was based on both literature data and results obtained in our earlier behavioural experiments.

Procedure. Mice were randomly divided into three treatment groups (n_1 = 10, n_2 = 11, n_3 = 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: saline at the dose of 10 ml/kg/day; (b) n_2: Met at the dose of 2.5 mg/kg/day; (c) n_3: ACPA at the dose of 1.0 mg/kg/day. On Day 14 animals were given challenge doses in the following manner: n_1: saline at the dose of 10 ml/kg, $n_{2, 3}$: Met at the dose of 2.5 mg/kg. All substances were administered intraperitoneally. Changes in horizontal locomotion were measured for a period of 3 min in the open field on Days 1, 7 and 14 to evaluate 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 normally distributed (according to the Kolmogorov-Smirnov test of normality), parametric statistics were used: paired *t*-test, two tailed for comparison within the individual groups and unpaired *t*-test, two tailed for comparison across the individual groups (statistical analysis package Statistica – StatSoft, Inc., Tulsa, USA).

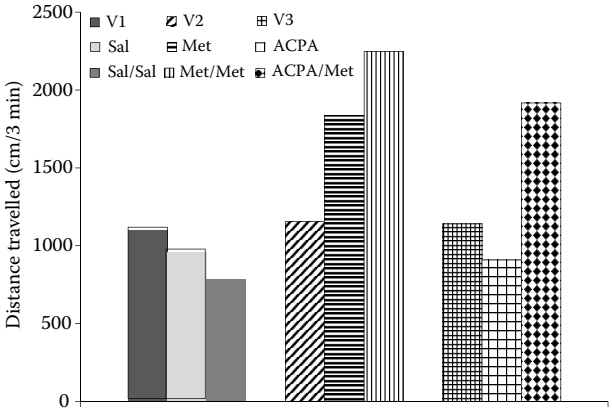

Figure 1. Effects of drug treatments on Distance Travelled (cm/3 min) in the mouse open field test shown as mean values with standard deviation (SD): V1 = mice in the group n_1 after the 1st dose of vehicle, (SD = 145.4); Sal = mice in the group n_1 after the 1st dose of saline, (SD = 379.0); Sal/Sal = mice in the group n_1 after the last dose of saline, (SD = 157.9); V2 = mice in the group n_2 after the 1st dose of vehicle, (SD = 207.2); Met = mice in the group n_2 after the 1st dose of methamphetamine (2.5 mg/kg), (SD = 413.0); Met/Met = mice in the group n_2 repeatedly pre-treated with methamphetamine after the challenge dose of methamphetamine (2.5 mg/kg), (SD = 491.0); V3 = mice in the group n_3 after the 1st dose of vehicle, (SD = 283.9); ACPA = mice in the group n_3 after the 1st dose of arachidonylcyclopropylamide (1.0 mg/kg), (SD = 228.2); ACPA/Met = mice in the group n_3 repeatedly pre-treated with ACPA (1.0 mg/kg) after the challenge dose of methamphetamine (2.5 mg/kg), (SD = 396.0). Statistical significances are as follows: V1 : Sal (non-significant), Sal : Sal/Sal (non-significant), V1 : Sal/Sal ($P < 0.01$), V2 : Met ($P < 0.01$), Met : Met/Met ($P < 0.01$), V2 : Met/Met ($P < 0.01$); V3 : ACPA ($P < 0.05$), ACPA : ACPA/Met ($P < 0.01$), V3 : ACPA/Met ($P < 0.01$); paired *t*-test, two tailed. ACPA/Met : Met/Met (non-significant), ACPA/Met : Met (non-significant); unpaired *t*-test, two tailed

RESULTS

The applications in the group n_1 induced highly significant decreases ($P < 0.01$) in locomotion after the last application of saline (Sal/Sal) compared to the 1st application (V1) (see Figure 1; V1 versus Sal/Sal).

The applications in group n_2 led to highly significant increases ($P < 0.01$) in locomotion after the 1st application of methamphetamine (Met) compared to the application of vehicle (V2) (see Figure 1; V2 versus Met). The challenge dose of Met produced a further highly significant increase in Distance Travelled ($P < 0.01$) in animals that were repeatedly given Met (see Figure 1; Met versus Met/Met). Highly significant increases ($P < 0.01$) in locomotion were also observed between the group of mice after the administration of V2 and the group that received the Met challenge dose (see Figure 1; V2 versus Met/Met).

In group n_3 the 1st administration of ACPA caused a significant decrease ($P < 0.05$) in Distance Travelled compared to the application of V3 (see Figure 1; V3 versus ACPA). In contrast, the challenge of Met caused a highly significant increase ($P < 0.01$) in locomotion in animals pre-treated repeatedly with

ACPA (see Figure 1; ACPA versus ACPA/Met). A highly significant increase in Distance Travelled ($P < 0.01$) was also found between animals after the application of V3 and animals that were given a Met challenge dose following repeated ACPA administration (see Figure 1; V3 versus ACPA/Met).

There was no statistically significant difference between animals pre-treated repeatedly with Met after the Met challenge dose and animals repeatedly pre-treated with ACPA after the Met challenge dose (see Figure 1; Met/Met versus ACPA/Met). No significant difference was found between the group that was given Met for the 1st time and the group repeatedly pre-treated with ACPA after the Met challenge dose (see Figure 1; Met versus ACPA/Met).

DISCUSSION

The robust development of behavioural sensitisation to the stimulatory effects of Met on locomotion observed in the present study is fully in accordance with results obtained earlier (Landa et al. 2006a,b; 2011; 2012a,b,c).

In the current study the first dose of the CB_1 receptor selective agonist ACPA led to a significant decrease in locomotor behaviour. This, to some extent runs counter to the results of our previous experiments using the CB_1 receptor agonist methanandamide, which did not change mouse locomotor behaviour (Landa et al. 2006a).

Cannabinoids delta-9-THC, ACPA, methanandamide, and endocannabinoid anandamide were reported to produce comparable discriminative stimulus effects (McMahon 2009). The modulatory effects of the cannabinoid CB_1 receptor-selective agonist ACPA on brain reward systems were described many times. For example, ACPA influences conditioned place preference and conditioned place aversion (Rezayof et al. 2011, 2012). Rezayof et al. (2011) found that microinjection of ACPA into the central amygdala of rats (0.5, 2.5 and 5 ng/rat) potentiated morphine-induced (2 mg/kg) conditioned place preference in a dose-dependent manner. In addition, the application of ACPA alone (5 ng/rat) led to a significant conditioned place preference. In their more recent experiments Rezayof et al. (2012) observed significant conditioned place preference after bilateral injection of ACPA into basolateral amygdala whereas co-administration of ACPA with ethanol produced conditioned place aversion. Rezayof et al. (2011) also reported that microinjection of the cannabinoid CB_1 antagonist/inverse agonist AM 251 (90 and 120 ng/animal) into central amygdala suppressed morphine-induced place preference. These results are similar to our previously published data obtained with AM 251 and Met (Landa et al. 2006a,b), where AM 251 (5.0 mg/kg) given together with Met inhibited behavioural sensitisation to this psychostimulant drug in the Open Field Test and in the model of agonistic behaviour in mice.

In the present study the locomotor activity of mice treated repeatedly with saline for three consecutive exposures in the Open Field Test decreased significantly which clearly shows the development of habituation to exploration of the open field arena. Despite that, the stimulatory effects of Met were significantly increased in the third Open Field Test in mice repeatedly pre-treated with either Met or ACPA, with no significant difference between them. However, the cross-sensitisation phenomenon was not fully confirmed with ACPA pre-treatment as there was no significant difference between the stimulatory effects of a single Met dose administered after the vehicle and Met challenge dose after repeated ACPA pre-treatment. This finding is also in contradiction with our earlier experiments using the less selective CB_1 receptor agonist methanandamide which also activates other cannabinoid receptor subtypes such as TRPV1 (vanilloid) receptors (Malinowska et al. 2001) and GPR55 receptors (Pertwee 2010).

Both ACPA and methanandamide are CB_1 receptor agonists with very low affinity for the cannabinoid CB_2 receptor subtype, with ACPA exhibiting a potency ratio of CB_2/CB_1 325 (Hillard et al. 1999) whereas the value for methanandamide is 41 (Khanolkar et al. 1996). The development of cross-sensitisation to Met by methanandamide pre-treatment was clearly observed in our previous studies (Landa et al. 2006a,b). On the other hand, methanandamide was reported to produce no changes in locomotor activities and to block amphetamine-induced behavioural sensitisation in rats (Rasmussen 2010). A decrease in locomotion after acute methanandamide treatment was observed in rats (Landa et al. 2008) while in mice the drug did not change locomotor behaviour (Landa 2006a). These results might speak in favour of possible interspecific differences in sensitivity to modulation of cannabinoid CB_1 receptor mechanisms.

Important distinctions which may underlie the different pharmacological actions of these sub-

stances also include susceptibility to hydrolytic enzymes, namely FAAH (fatty amino acid hydrolase). ACPA, similarly to ananadamide, is more susceptible, while methanandamide is more resistant probably because of the presence of a methyl substituent in its molecular stucture (Pertwee 2006). Methanandamide exhibits enhanced biological stability when compared to endocannabinoid anadamide and although the metabolic rate of ACPA has not so far been directly compared with anandamide, it is thought that the rate of metabolism is similar in primates (McMahon 2009). Thus, it is possible to speculate that different behavioural actions can be explained by faster elimination of ACPA compared to methanandamide and also by other differences. Jarbe et al. (1998) suggested that agonists of cannabinoid receptors may have various mechanisms of action. Indeed, it has been shown that both methanandamide and ACPA also possess other activities. Stimulation of CB_1 receptors in the basal ganglia and cerebellum-induced motor deficits and sedative effects of ACPA have been reported (Patel and Hillard 2001).

Our present results with the CB_1 receptor agonist ACPA diverge from those acquired earlier with methanandamide, an analogue of the endocannabinoid anandamide. However, it is clear that the endocannabinoid system is involved in modulating the brain reward pathway induced by Met and thus exploration of functional interactions with CB_1 cannabinoid receptor ligands might be a promising approach to discover potential treatments for addiction to psychostimulants (Oliere et al. 2013).

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