

# Interaction of CB<sub>1</sub> receptor agonist arachidonylcyclopropylamide with behavioural sensitisation to morphine in mice

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**ABSTRACT:** Activities of the endocannabinoid system are believed to be substantially involved in psychostimulant and opioid addiction. Nevertheless, interactions between cannabinoid and opioid systems are not yet fully understood. Thus, the aim of the present study was to investigate the interaction between morphine and the cannabinoid CB<sub>1</sub> receptor agonist arachidonylcyclopropylamide (ACPA) in behavioural sensitisation. Sensitisation occurs after repeated exposure to drugs of abuse including morphine and cannabinomimetics and it has been suggested to mediate craving and relapses. Male mice were randomly allocated into three groups and were seven times (from the 7<sup>th</sup> to 13<sup>th</sup> day of the experiment) administered drugs as follows: (a) n<sub>1</sub>: vehicle at the dose of 10 ml/kg/day; (b) n<sub>2</sub>: morphine at the dose of 10.0 mg/kg/day; (c) n<sub>3</sub>: ACPA at the dose of 1.0 mg/kg/day. Changes in locomotor behaviour were measured in the Open Field Test: (a) after administration of vehicle on the 1<sup>st</sup> experimental day, (b) after the 1<sup>st</sup> dose of drugs given on the 7<sup>th</sup> day, and (c) on the 14<sup>th</sup> day after “challenge doses” given in the following way: n<sub>1</sub>: saline at the dose of 10 ml/kg, n<sub>2,3</sub>: morphine at the dose of 10.0 mg/kg. Registered behavioural changes unambiguously showed the development of behavioural sensitisation to the stimulatory effects of morphine on locomotion after its repeated administration ( $P < 0.05$ ). However, surprisingly, taking into account reports on synergistic effects of opioids and cannabinoid receptor stimulation, a significant decrease ( $P < 0.05$ ) in behavioural sensitisation to morphine occurred when the drug challenge dose was given following repeated pre-treatment with the CB<sub>1</sub> receptor agonist ACPA, i.e. suppression of cross-sensitisation to morphine.

**Keywords:** behavioural sensitisation; morphine; cannabinoids; ACPA; mice

## List of abbreviations

**ACPA** = *N*-(cyclopropyl)-5*Z*,8*Z*,11*Z*,14*Z*-eicosatetraenamide (alternative name: arachidonylcyclopropylamide, selective CB<sub>1</sub> receptor agonist), **AM 251** = *N*-(piperidin-1-yl)-5-(4-iodophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxamide (synthetic CB<sub>1</sub> receptor antagonist/inverse agonist), **CP 55,940** = (-)-cis-3-[2-Hydroxy-4-(1,1-dimethylheptyl)phenyl]-trans-4-(3-hydroxypropyl)cyclohexanol (mixed CB<sub>1,2</sub> receptor agonist), **CPP** = conditioned place preference, **HU 210** = (6*a*R)-trans-3-(1,1-Dimethylheptyl)-6*a*,7,10,10*a*-tetrahydro-1-hydroxy-6,6-dimethyl-6*H*-dibenzo[*b*,*d*]pyran-9-methanol (synthetic mixed CB<sub>1,2</sub> receptor agonist), **JWH 015** = 1-propyl-2-methyl-3-(1-naphthoyl)indole (selective CB<sub>2</sub> receptor agonist), **Met** = methamphetamine, **Mo** = morphine, **Sal** = saline, **THC** = delta 9-tetrahydrocannabinol (mixed CB<sub>1,2</sub> receptor agonist), **V** = vehicle, **WIN 55,212-2** = (R)-(+)-[2,3-dihydro-5-methyl-3-(4-morpholinylmethyl)pyrrolo[1,2,3-*de*]-1,4-benzoxazin-6-yl]-1-naphthalenylmethanone (synthetic CB<sub>1,2</sub> receptor agonist)

Repeated administration of various psychotropic substances may result in an increasing behavioural response to their effects, which has been termed

as behavioural sensitisation. This phenomenon can for example develop to amphetamines (Landa et al. 2006; Slamberova et al. 2011; Enman and Unterwald

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2012; Herrera et al. 2013; Hutchinson et al. 2014; Jing et al. 2014), cannabinoids (Rubino et al. 2001; Rubino et al. 2003; Cadoni et al. 2008), opioids (Vanderschuren and Kalivas 2000; Farahmandfar et al. 2011a; Hofford et al. 2012), caffeine (Hu et al. 2014), nicotine (Lee et al. 2012) or ethanol (Bahi and Dreyer 2012). It has also been described that an increased response to a drug may be elicited by previous repeated administration of a drug different from the drug tested - so called cross-sensitisation. This was reported for heroin after pre-treatment with THC (Singh et al. 2005) or for morphine after pre-treatment with the cannabinoid agonist WIN 55,212-2 (Manzanedo et al. 2004). Similar results were observed even across generations. Adolescent female rats were exposed to the cannabinoid agonist WIN 55,212-2 and as adults mated with drug-naïve males. Their adult female offspring were tested for behavioural sensitisation to the effects of morphine and showed cross-sensitisation development and a significantly higher density of mu opioid receptors in the nucleus accumbens (Vassoler et al. 2013).

After its development, behavioural sensitisation lasts for a long period of time (Coelhoso et al. 2013). Its neurobiological background consists in drug-induced neuroadaptive changes in a circuit involving dopaminergic and glutamatergic interconnections between the ventral tegmental area, the nucleus accumbens, prefrontal cortex and amygdala (Vanderschuren and Kalivas 2000; Nestler 2001; Landa et al. 2014a). A simultaneous impact of both endogenous opioid and cannabinoid systems on the development of behavioural sensitisation can be the result of a cross-talk between opioid and cannabinoid receptors (Robledo et al. 2008).

Despite increasing evidence for functional synergistic interactions between the endocannabinoid and opioid systems (Braida et al. 2008; Robledo et al. 2008; Zarrindast et al. 2008; Lopez-Moreno et al. 2010; Parolaro et al. 2010), our pilot study using the model of agonistic behaviour in singly housed male mice on paired interactions with non-aggressive group-housed partners showed no cross-sensitisation to the anti-aggressive effects of morphine after repeated pre-treatment with the cannabinoid methanandamide (Sulcova et al. 2004). As behavioural sensitisation and cross-sensitisation are suggested to play a role in relapses in drug abusers (De Vries et al. 2002) the aim of the present study was to further investigate functional interactions between morphine and the selective CB<sub>1</sub> receptor

agonist arachidonylcyclopropylamide (ACPA) in a model of behavioural sensitisation using the mouse Open Field Test.

## MATERIAL AND METHODS

**Animals.** Thirty one male mice (strain ICR, TOP-VELAZ s.r.o., Prague, Czech Republic) with an initial weight of 18–21 g were used. The mice were randomly allocated into three experimental groups and 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 between 1:00 p.m. and 3:00 p.m. in order to minimise possible variability due to circadian rhythms.

**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 and evaluates the locomotor activity of the animal by registering the beam interruptions caused by movements of the body. Using this equipment we have determined trajectory in cm per 3 min (Distance Travelled).

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

Morphine hydrochloride (Tamda a.s., Czech Republic) was dissolved in saline.

Arachidonylcyclopropylamide, *N*-(cyclopropyl)-5*Z*,8*Z*,11*Z*,14*Z*-eicosatetraenamide was supplied pre-dissolved in anhydrous ethanol at a concentration of 5 mg/ml (Tocris Cookson Ltd., UK) and was diluted in saline to a concentration that allowed administration of the drug in a volume of 10 ml/kg; therefore, the vehicle contained an adequate amount of ethanol (a final concentration in the injection of 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.** Animals were randomly divided into three 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)  $n_2$ : morphine at the dose of 10.0 mg/kg/day; (c)  $n_3$ : ACPA at the dose of 1.0 mg/kg/day. On Day 14 all mice received challenge doses in the following way:  $n_1$ : saline at the dose of 10 ml/kg,  $n_2$ ,  $n_3$ : morphine at the dose of 10.0 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 and cross-sensitising phenomenon, respectively.

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) and the following parametric

statistics were used: unpaired *t*-test, two tailed for comparison across the individual groups and paired *t*-test, two tailed for comparison within the individual groups (statistical analysis package Statistica – StatSoft, Inc., Tulsa, USA).

## RESULTS

No significant differences were found in Distance Travelled across the groups that were given vehicle for the first time (see Figure 1; vehicle1 versus vehicle2, vehicle2 versus vehicle3, vehicle1 versus vehicle3).

The first doses of saline, morphine and ACPA, respectively, did not elicit any significant behavioural changes among the three experimental groups (see Figure 1; saline versus morphine, morphine versus ACPA, saline versus ACPA).

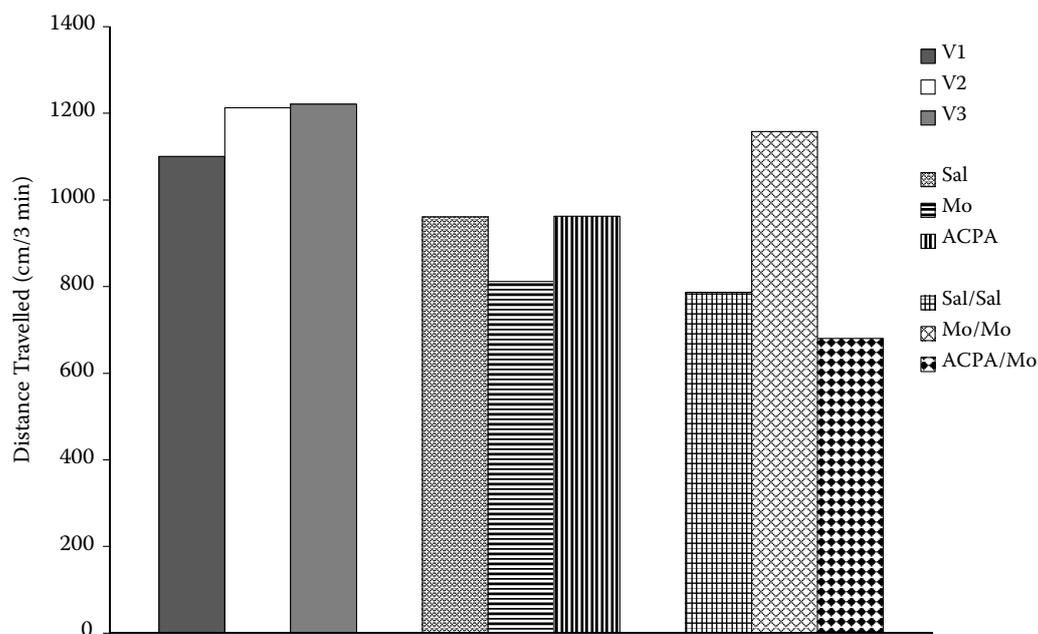


Figure 1. Effects of drug treatments on Distance Travelled (cm/3 min) in the mouse open field test shown as mean values with standard deviation (SD): vehicle1 = mice in the group  $n_1$  after the 1<sup>st</sup> dose of vehicle, (SD = 145.4); vehicle2 = mice in the group  $n_2$  after the 1<sup>st</sup> dose of vehicle, (SD = 182.2); vehicle3 = mice in the group  $n_3$  after the 1<sup>st</sup> dose of vehicle, (SD = 241.1); saline = mice in the group  $n_1$  after the 1<sup>st</sup> dose of saline, (SD = 379.0); morphine = mice in the group  $n_2$  after the 1<sup>st</sup> dose of morphine (10.0 mg/kg), (SD = 431.0); ACPA = mice in the group  $n_3$  after the 1<sup>st</sup> dose of arachidonylcyclopropylamide (1.0 mg/kg), (SD = 301.9); saline/saline = mice in the group  $n_1$  after the challenge dose of saline, (SD = 157.9); morphine/morphine = mice in the group  $n_2$  repeatedly pre-treated with morphine after the challenge dose of morphine (10.0 mg/kg), (SD = 486.0); ACPA/morphine = mice in the group  $n_3$  repeatedly pre-treated with ACPA after the challenge dose of morphine (1.0 mg/kg + 10.0 mg/kg), (SD = 266.9). Statistical significances are as follows: vehicle1 : vehicle2 (non-significant), vehicle2 : vehicle3 (non-significant), vehicle1 : vehicle3 (non-significant); saline : morphine (non-significant), morphine : ACPA (non-significant), saline : ACPA (non-significant); saline/saline : morphine/morphine ( $P < 0.05$ ), morphine/morphine : ACPA/morphine ( $P < 0.05$ ), saline/saline : ACPA/morphine (non-significant); unpaired *t*-test, two tailed, vehicle3 : ACPA ( $P < 0.05$ ); paired *t*-test, two tailed

The challenge dose of morphine evoked a significant increase in Distance Travelled ( $P < 0.05$ ) in animals pre-treated repeatedly with morphine when compared to animals pre-treated with saline after the saline challenge dose (see Figure 1; saline/saline versus morphine/morphine). The challenge dose of morphine administered to animals repeatedly pre-treated with ACPA led to a significant decrease ( $P < 0.05$ ) in Distance Travelled compared to mice pre-treated with morphine after the morphine challenge dose (see Figure 1; morphine/morphine versus ACPA/morphine). No significant difference was found between mice pre-treated repeatedly with saline after the saline challenge dose and mice pre-treated repeatedly with ACPA after the morphine challenge dose (see Figure 1; saline/saline versus ACPA/morphine).

## DISCUSSION

Based on results from studies in different animal models and from clinical trials, the existence of functional interactions between endogenous opioid and cannabinoid systems is generally accepted. It is important to determine the conditions, under which these interactions lead to synergistic or antagonistic outcomes because of their consequences for both therapy and addiction.

In the present study we observed the development of behavioural sensitisation to the effects of morphine on mouse locomotor behaviour in the Open Field test after its repeated administration. This corresponds to previously published results (Vanderschuren and Kalivas 2000; Serrano et al. 2002; Singh et al. 2004; Zarrindast et al. 2007; Contet et al. 2008; Azizi et al. 2009; Farahmandfar et al. 2011b; Hofford et al. 2012). We then studied the impact of a possible functional interaction between the behavioural effects of morphine on mouse locomotion and cannabinoid CB<sub>1</sub> receptor activity using administration of ACPA and morphine.

The first dose of ACPA elicited a significant decrease in locomotor behaviour in the present study which is consistent with the results of a previous experiment using the same dose of this substance for evaluation of its influence on the development of amphetamine behavioural sensitisation (Landa et al. 2014b). However, these findings to some extent run counter to the results of another of our previous studies in which the less selective CB<sub>1</sub> receptor agonist methanandamide (the syn-

thetic analogue of endocannabinoid anandamide) did not elicit any changes in mouse locomotion (Landa et al. 2006). It has to be taken into account that in a series of physiological and behavioural assays anandamide was shown to evoke biphasic activity with stimulatory and inhibitory effects at low and high doses, respectively (Sulcova et al. 1998; Katsidoni et al. 2013). It was also suggested that depending on the local concentration of cannabinomimetic agents cannabinoid CB<sub>1</sub> receptors are modulated presynaptically at different neurotransmitter pathways, e.g. glutamatergic terminals at low doses and GABAergic at high doses. This explanation is supported by a study in which the CB<sub>1</sub> receptor agonist CP-55,940 elicited anxiolytic-like effects at a low dosing regimen and anxiogenic-like effects after high doses in wild-type mice, but not in mice with brain region-specific CB<sub>1</sub> receptor knockout (Rey et al. 2012). Furthermore, there can be differences in endocannabinoid signalling in different animal lines and between males and females (Keeney et al. 2012) as well as in pharmacokinetic and pharmacodynamic profiles of various cannabinoid receptor agonists. This was reported for example from a comparison of the effects of the cannabinomimetics HU 210 and CP 55,940 on rat locomotor activities (Bosier et al. 2010). Low doses (0.1 mg/kg) of the herbal cannabinoid THC have also been shown to lead to hyperactivity in the Open Field Test and increase intracranial self-stimulation thresholds, while higher doses (1 mg/kg) elicited hypoactivity and anhedonia. These effects were mediated by stimulation of the CB<sub>1</sub> receptors as they were abolished by co-administration of CB<sub>1</sub> receptor antagonist/inverse agonist rimonabant (Katsidoni 2013).

After repeated administration both cannabinoids and opioids are known to evoke locomotor sensitisation or cross-sensitisation between these two systems; however, in some species differences or discrepancies between pharmacological models are also reported (Robledo et al. 2008). Although the majority of reports speak in favour of cross-sensitisation to opioids after repeated CB<sub>1</sub> receptor agonist administration (Cadoni et al. 2001; Lamarque et al. 2001; Manzanedo et al. 2004) the results presented in this paper suggest inhibition of this phenomenon. In fact, the data obtained in the present study with morphine mirror the results from our previous investigation in which repeated pretreatment with the cannabinoid CB<sub>1</sub> receptor agonist methanandamide elicited cross-sensitisation to the stimulatory drug methamphetamine (Landa

et al. 2006; Landa et al. 2011), whereas the more selective CB<sub>1</sub> receptor agonist ACPA suppressed this phenomenon (Landa et al. 2014b).

On the other hand there are also reports supporting the results we describe in this paper. Valverde et al. (2001) treated mice repeatedly over a period of 21 days with THC (10 mg/kg/day, *i.p.*). There were no applications for the next three days and finally, the conditioned place preference produced by different doses of morphine (0.5 or 2 mg/kg, *s.c.*) was evaluated. Administration of morphine after chronic THC treatment did not evoke rewarding responses in the conditioned place preference paradigm and thus Valverde et al. (2001) concluded that chronic use of high doses of cannabinoids presumably does not stimulate psychic dependence on opioids.

Controversial results are also reported from various other studies dealing with the modulatory influence of the endocannabinoid system on the effects of opioids as well as other drugs of abuse. A study on cross-sensitisation between THC and morphine characterised by stereotyped activity in male Sprague-Dawley rats (Cadoni et al. 2001) showed sensitisation to a challenge dose of THC as well as to the synthetic cannabinoid receptor agonist WIN55,212-2; both effects were antagonised by the CB<sub>1</sub> antagonist/inverse agonist rimonabant (SR141716A). Interactions between cannabinoid agonists and antagonists with morphine activity were also demonstrated in another work (Norwood et al. 2003). Hypoactivity during the first hour following morphine administration changed to hyperactivity 14 days after drug administration. An increase in morphine hyperactivity was measured in rats pre-treated with the cannabinoid receptor agonist CP 55,940 or the combination of morphine + CP 55,940, but not in rats administered the antagonist/inverse agonist rimonabant + morphine. These results were believed to support the “gateway theory” of cannabinoid effects for intake of other drugs of abuse in humans.

CB<sub>1</sub> receptor modulation was suggested to be involved in the rewarding effects of morphine which were attenuated in the rat model of conditioned place preference by the antagonist/inverse agonist rimonabant (SR141716). Cannabinoid and opioid cross-sensitisation was also observed in a further study in which heroin increased rat locomotor response after pre-treatment with THC (Singh et al. 2005). On the other hand rats pre-treated with THC (5 mg/kg/day for seven days) did not show any

sensitisation to morphine intake under a progressive-ratio schedule in the model of *i.v.* drug self-administration (Gonzales et al. 2005) and in mice THC also reduced the reinforcing effects of morphine in the conditioned place preference test (Jardinaud et al. 2006). These findings resemble to some extent the results of the present study in which we measured a decrease in behavioural sensitisation to the effects of morphine on mouse locomotor behaviour instead of augmentation after pre-treatment with the selective CB<sub>1</sub> receptor agonist ACPA.

Similarly, the motor stimulatory effects measured in mice after acute and repeated low doses of morphine (5 or 7.5 mg/kg) were antagonised by the cannabinoid agonist HU 210 and enhanced by the antagonist/inverse agonist rimonabant (Hagues et al. 2007). Differential neurochemical changes within the brain endocannabinoid system were reported during induction and expression of morphine sensitisation in the rat model of drug-seeking behaviour (Vigano et al. 2004). The levels of endocannabinoids anandamide and 2-arachidonoylglycerol were altered in the brain differentially in these two phases and moreover in opposite ways in specific brain regions. Changes in the activity of CB<sub>1</sub> receptors in the nucleus accumbens were shown to be important for processing of behavioural sensitisation to morphine (Haghparast et al. 2009). Bilateral sub-chronic administration of the CB<sub>1</sub> receptor antagonist/inverse agonist AM 251 into this region caused the development of sensitisation to doses of morphine (0.5 mg/kg) which in intact rats did not produce sensitisation in the conditioned place preference model. Neither saline nor DMSO (dimethyl sulfoxide) used as the solvent led to a similar influence on the sensitising effects of morphine. Later, it was reported (Rezayof et al. 2011) that microinjection of AM 251 into the central amygdala is sufficient to induce the phenomenon of conditioned place preference but inhibits the place preference to morphine. On the other hand, microinjection of ACPA into the central amygdala increased the extent of morphine-induced conditioned place preference. This finding runs counter to our present results where pre-treatment with ACPA led to an inhibition of morphine sensitisation to locomotor effects.

Although the majority of previous reports describe the development of cross-sensitisation to opioids after repeated CB<sub>1</sub> receptor agonist administration, the results presented in this paper suggest an inhibition of this phenomenon. Nevertheless,

these data resemble to some extent our previous results showing a suppression of cross-sensitisation to methamphetamine with the CB<sub>1</sub> receptor agonist ACPA. These discrepancies in results on the involvement of the endocannabinoid signalling system in addiction to cannabis, and also to other drugs of abuse including opioids, require further research because more detailed information on the neurobiological basis of cannabinoid-opioid interactions may help to develop novel pharmacotherapeutic interventions in the management of opioid dependence and withdrawal (Gonzales al. 2005; Scavone at al. 2013).

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