Interaction of CB_1 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_1 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 7th to 13th day of the experiment) administered drugs as follows: (a) n_1: vehicle 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. Changes in locomotor behaviour were measured in the Open Field Test: (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 "challenge doses" given in the following way: n_1: saline at the dose of 10 ml/kg, $n_{2,3}$: 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_1 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_1 receptor agonist), **AM 251** = *N*-(piperidin-1-yl)-5-(4-iodophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxamide (synthetic CB_1 receptor antagonist/inverse agonist), **CP 55,940** = (−)-cis-3-[2-Hydroxy-4-(1,1-dimethylheptyl)phenyl]-trans-4-(3-hydroxypropyl)cyclohexanol (mixed $CB_{1,2}$ receptor agonist), **CPP** = conditioned place preference, **HU 210** = (6aR)-trans-3-(1,1-Dimethylheptyl)-6a,7,10,10a-tetrahydro-1-hydroxy-6,6-dimethyl-6*H*-dibenzo[b,d]pyran-9-methanol (synthetic mixed $CB_{1,2}$ receptor agonist), **JWH 015** = 1 propyl-2-methyl-3-(1-naphthoyl)indole (selective CB_2 receptor agonist), **Met** = methamphetamine, **Mo** = morphine, **Sal** = saline, **THC** = delta 9-tetrahydrocannabinol (mixed $CB_{1,2}$ 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-napthalenylmethanone (synthetic $CB_{1,2}$ 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

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_1 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.
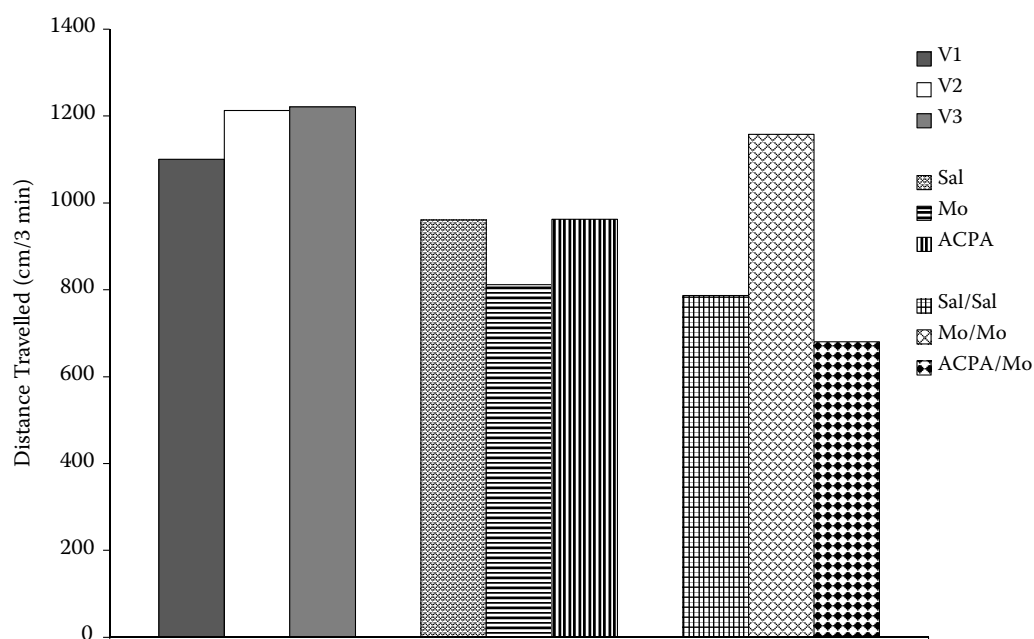

Figure 1. Effects of drug treatments on Distance Travelled (cm/3 min) in the mouse open field test shown as mean values with standard deviation (SD): vehicle1 = mice in the group n_1 after the 1st dose of vehicle, (SD = 145.4); vehicle2 = mice in the group n_2 after the 1st dose of vehicle, (SD = 182.2); vehicle3 = mice in the group n_3 after the 1st dose of vehicle, (SD = 241.1); saline = mice in the group n_1 after the 1st dose of saline, (SD = 379.0); morphine = mice in the group n_2 after the 1st dose of morphine (10.0 mg/kg), (SD = 431.0); ACPA = mice in the group n_3 after the 1st 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_1 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 metamphetamine 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_1 receptor agonist methanandamide (the synthetic analogue of endocannabioid 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 cannabimimetic agents cannabinoid CB_1 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_1 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_1 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 cannabimetics 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_1 receptors as they were abolished by co-administration of CB_1 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_1 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 pre-treatment with the cannabinoid CB_1 receptor agonist methanandamide elicited cross-sensitisation to the stimulatory drug methamphetamine (Landa

et al. 2006; Landa et al. 2011), whereas the more selective CB$_1$ receptor agonist ACPA supressed 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$_1$ 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$_1$ 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 locomotory 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$_1$ 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$_1$ 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$_1$ 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$_1$ 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_1 receptor agonist ACPA. These discrepancies in results on the involvement 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).

REFERENCES

Azizi P, Haghparast A, Hassanpour-Ezatti M (2009): Effects of CB1 receptor antagonist within the nucleus accumbens on the acquisition and expression of morphine-induced conditioned place preference in morphine-sensitized rats. Behavioural Brain Research 197, 119–124.

Bahi A, Dreyer JL (2012): Involvement of nucleus accumbens dopamine D1 receptors in ethanol drinking, ethanol-induced conditioned place preference, and ethanol-induced psychomotor sensitization in mice. Psychopharmacology 222, 141–153.

Bosier B, Sarre S, Smolders I, Michotte Y, Hermans E, Lambert DM (2010): Revisiting the complex influences of cannabinoids on motor functions unravels pharmacodynamic differences between cannabinoid agonists. Neuropharmacology 59, 503–510.

Braida D, Limonta V, Capurro V, Fadda P, Rubino T, Mascia P, Zani A, Gori E, Fratta W, Parolaro D, Sala M (2008): Involvement of κ-opioid and endocannabinoid system on salvinorin a-induced reward. Biological Psychiatry 63, 286–292.

Cadoni C, Pisanu A, Solinas M, Acquas E, Di Chiara G (2001): Behavioural sensitization after repeated exposure to Δ9-tetrahydrocannabinol and cross-sensitization with morphine. Psychopharmacology 158, 259–266.

Cadoni C. Valentini V, Di Chiara G (2008): Behavioral sensitization to Delta(9)-tetrahydrocannabinol and cross-sensitization with morphine: differential changes in accumbal shell and core dopamine transmission. Journal of Neurochemistry 106, 1586–1593.

Coelhoso CC, Engelke DS, Filev R, Silveira DX, Mello LE, Santos JG (2013): Temporal and behavioral variability in cannabinoid receptor expression in outbred mice submitted to ethanol-induced locomotor sensitization paradigm. Alcoholism – Clinical and Experimental Research 37, 1516–1526.

Contet C, Filliol D, Matifas A, Kieffer BL (2008): Morphine-induced analgesic tolerance, locomotor sensitization and physical dependence do not require modification of mu opioid receptor, cdk5 and adenylate cyclase activity. Neuropharmacology 54, 475–486.

De Vries TJ, Schoffelmeer AN, Binnekade R, Raaso H, Vanderschuren LJ (2002): Relapse to cocaine- and heroin-seeking behavior mediated by dopamine D2 receptors is time-dependent and associated with behavioral sensitization. Neuropsychopharmacology 26, 18–26.

Enman NM, Unterwald EM (2012): Inhibition of GSK3 attenuates amphetamine-induced hyperactivity and sensitization in the mouse. Behavioural Brain Research 231, 217–225.

Farahmandfar M, Zarrindast MR, Kadivar M, Karimian SM, Naghdi N (2011a): The effect of morphine sensitization on extracellular concentrations of GABA in dorsal hippocampus of male rats. European Journal of Pharmacology 669, 66–70.

Farahmandfar M, Karimian SM, Zarrindast MR, Kadivar M, Afrouzi H, Naghdi N (2011b): Morphine sensitization increases the extracellular level of glutamate in CA1 of rat hippocampus via mu-opioid receptor. Neuroscience Letters 494, 130–134.

Gonzalez S, Cebeira M, Fernandez-Ruiz J (2005): Cannabinoid tolerance and dependence: A review of studies in laboratory animals. Pharmacology Biochemistry and Behavior 81, 300–318.

Haghparast A, Azizi P, Hassanpour-Ezatti M, Khorrami H, Naderi N (2009): Sub-chronic administration of AM251, CB1 receptor antagonist, within the nucleus accumbens induced sensitisation to morphine in the rat. Neuroscience Letters 467, 43–47.

Hagues G, Costentin J, Duterte-Boucher D (2007): Modulation of morphine and alcohol motor stimulant effects by cannabinoid receptors ligands. Behavioural Brain Research 178, 274–282.

Herrera AS, Casanova JP, Gatica RI, Escobar F, Fuentealba JA (2013): Clozapine pre-treatment has a protracted hypolocomotor effect on the induction and expression of amphetamine sensitization. Progress in Neuropsychpharmacology & Biological Psychiatry 47, 1–6.

Hofford RS, Schul DL, Wellman PJ, Eitan S (2012): Social influences on morphine sensitization in adolescent rats. Addiction Biology 17, 547–556.

Hu Z, Lee CI, Han JY, Oh EH, Ryu JH, Hong JT, Kim Y, Oh KW (2014): Caffeine induces behavioural sensitization and overexpression of cocaine-regulated and amphetamine-regulated transcript peptides in mice. Behavioural Pharmacology 25, 32–43.

Hutchinson AJ, Ma JS, Liu JB, Hudson RL, Dubocovich ML (2014): Role of MT1 melatonin receptors in meth-

amphetamine-induced locomotor sensitization in C57BL/6 mice. Psychopharmacology 231, 257–267.

Jardinaud F, Roques BP, Noble F (2006): Tolerance to the reinforcing effects of morphine in delta9-tetrahydrocannabinol treated mice. Behavioural Brain Research 173, 255–261.

Jing L, Zhang M, Li JX, Huang P, Liu Q, Li YL, Liang H, Liang JH (2014): Comparison of single versus repeated methamphetamine injection induced behavioral sensitization in mice. Neuroscience Letters 560, 103–106.

Katsidoni V, Kastellakis A, Panagis G (2013): Biphasic effects of Delta(9)-tetrahydrocannabinol on brain stimulation reward and motor activity. International Journal of Neuropsychopharmacology 16, 2273–2284.

Keeney BK, Meek TH, Middleton KM, Holness LF, Garland T (2012): Sex differences in cannabinoid receptor-1 (CB1) pharmacology in mice selectively bred for high voluntary wheel-running behavior. Pharmacology Biochemistry and Behavior 101, 528–537.

Lamarque S, Taghzouti K, Simon H (2001): Chronic treatment with Delta(9) – tetrahydrocannabinol enhances the locomotor response to amphetamine and heroin. Implications for vulnerability to drug addiction. Neuropharmacology 41, 118–129.

Landa L, Slais K, Sulcova A (2006): Involvement of cannabinoid CB_1 and CB_2 receptor activity in the development of behavioural sensitization to methamphetamine effects in mice. Neuroendocrinology Letters 27, 63–69.

Landa L, Jurajda M, Sulcova A (2011): Altered cannabinoid CB_1 receptor mRNA expression in mesencephalon from mice exposed to repeated methamphetamine and methanandamide treatments. Neuroendocrinology Letters 32, 841–846.

Landa L, Machalova A, Sulcova A (2014a): Implication of N-methyl-D-aspartate mechanisms in behavioural sensitization to psychostimulants: a short review. European Journal of Pharmacology 730, 77–81.

Landa L, Slais K, Machalova A, Sulcova A (2014b): The effect of cannabinoid CB_1 receptor agonist arachidonylcyclopropylamide (ACPA) on behavioural sensitisation to methamphetamine in mice. Veterinarni Medicina 59, 88–94.

Lee B, Park J, Kwon S, Yeom M, Sur B, Shim I, Lee H, Yoon SH, Jeong DM, Hahm DH (2012): Inhibitory effect of sowthistle (Ixeris dentata) on development and expression of behavioral locomotor sensitization to nicotine in rats. Food Science and Biotechnology 21, 723–729.

Lopez-Moreno JA, Lopez-Jimenez A, Gorriti MA, de Fonseca FR (2010): Functional interactions between endogenous cannabinoid and opioid systems: focus on alcohol, genetics and drug-addicted behaviors. Current Drug Targets 11, 406–428.

Manzanedo C, Aguilar MA, Rodriguez-Arias M, Navarro M, Minarro J (2004): Cannabinoid agonist-induced sensitisation to morphine place preference in mice. Neuroreport 15, 1373–1377.

Nestler EJ (2001): Molecular basis of long-term plasticity underlying addiction. Nature Reviews Neuroscience 2, 119–128.

Norwood CS, Cornish JL, Mallet PE, McGregor IS (2003): Pre-exposure to the cannabinoid receptor agonist CP 55,940 enhances morphine behavioral sensitisationand alters morphine self-administration in Lewis rats. European Journal of Pharmacology 465, 105–114.

Parolaro D, Rubino T, Vigano D, Massi P, Guidali C, Realini N (2010): Cellular mechanisms underlying the interaction between cannabinoid and opioid system. Current Drug Targets 11, 393–405.

Rey AA, Purrio M, Viveros MP, Lutz B (2012): Biphasic effects of cannabinoids in anxiety responses: CB1 and GABA(B) receptors in the balance of GABAergic and glutamatergic neurotransmission. Neuropsychopharmacology 37, 2624–2634.

Rezayof A, Sardari M, Zarrindast MR, Nayer-Nouri T (2011): Functional interaction between morphine and central amygdala cannabinoid CB1 receptors in the acquisition and expression of conditioned place preference. Behavioural Brain Research 220, 1–8.

Robledo P, Berrendero F, Ozaita A, Maldonado R (2008): Advances in the field of cannabinoid-opioid cross-talk. Addiction Biology 13, 213–224.

Rubino T, Vigano, Massi P, Parolaro D (2001): The psychoactive ingredient of marijuana induces behavioural sensitization. European Journal of Neuroscience 14, 884–886.

Rubino T, Vigano D, Massi P, Parolaro D (2003): Cellular mechanisms of Delta(9)-tetrahydrocannabinol behavioural sensitization. European Journal of Neuroscience 17, 325–330.

Scavone JL, Sterling RC, Van Bockstaele EJ (2013): Cannabinoid and opioid interactions: Implications for opiate dependence and withdrawal. Neuroscience 248, 637–654.

Serrano A, Aguilar MA, Manzanedo C, Rodriguez-Arias M, Minarro J (2002): Effects of DA D1 and D2 antagonists on the sensitisation to the motor effects of morphine in mice. Progress in Neuro-Psychopharmacology & Biological Psychiatry 26, 1263–1271.

Singh ME, Verty ANA, McGregor IS, Mallet PE (2004): A cannabinoid receptor antagonist attenuates conditioned place preference but not behavioural sensitisationto morphine. Brain Research 1026, 244–253.

Singh ME, McGregor IS, Naplet PE (2005): Repeated exposure to Δ9-tetrahydrocannabinol alters heroin-

induced locomotor sensitisation and Fos-immunore-activity. Neuropharmacology 49, 1189–1200.

Slamberova R, Yamamotova A, Schutova B, Hruba L, Pometlova M (2011): Impact of Prenatal Methamphetamine Exposure on the Sensitivity to the Same Drug in Adult Male Rats. Prague Medical Report 112, 102–114.

Sulcova A, Mechoulam R, Fride E (1998): Biophasic Effects of Anandamide. Pharmacology Biochemistry and Behavior 59, 347–352.

Sulcova A, Landa L, Slais K (2004): Sensitization and cannabinoid cross-sensitization to methamphetamine antiaggressive effects is not developed in morphine treatment design in mice. Fundamental & Clinical Pharmacology 18, Suppl.1, 58.

Vanderschuren LJMJ, Kalivas PW (2000): Alterations in dopaminergic and glutamatergic transmission in the induction and expression of behavioral sensitization: a critical review of preclinical studies. Psychopharmacology 151, 99–120.

Valverde O, Noble F, Beslot F, Dauge V, Fournie-Zaluski MC, Roques BP (2001): Δ9-tetrahydrocannabinol releases and facilitates the effects of endogenous enkephalins: reduction in morphine withdrawal syndrome without change in rewarding effect. European Journal of Neuroscience 13, 1816–1824.

Vassoler FM, Johnson NL, Byrnes EM (2013): Female adolescent exposure to cannabinoids causes transgenerational effects on morphine sensitisation in female offspring in the absence of in utero exposure. Journal of Psychopharmacology 27, 1015–1022.

Vigano D, Valenti M, Cascio MG, Di Marzo V, Parolaro D, Rubino T (2004): Changes in endocannabinoid levels in a rat model of behavioural sensitisation to morphine. European Journal of Neuroscience 20, 1849–1857.

Zarrindast MR, Heidari-Darvishani A, Rezayof A, Fathi-Azarbaijani F, Jafari-Sabet M, Hajizadeh-Moghaddam A (2007): Morphine-induced sensitization in mice: changes in locomotor activity by prior scheduled exposure to GABA(A) receptor agents. Behavioural Pharmacology 18, 303–310.

Zarrindast MR, Sarahroodi S, Arzi A, Khodayar MJ, Taheri-Shalmani S, Rezayof A (2008): Cannabinoid CB1 receptors of the rat central amygdala mediate anxiety-like behavior: interaction with the opioid system. Behavioural Pharmacology 19, 716–723.

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