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ACTIVATION OF ENDOCANNABINOID TRANSMISSION INDUCES ANTIDEPRESSANT-LIKE EFFECTS IN RATS

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Recent reports indicate that endocannabinoid (eCB) system may be involved in depression and in the antidepressant-like activity demonstrated in experimental models. The present study examined the effects of the eCB uptake inhibitor 4-hydroxyphenyl-5Z,8Z,11Z,14Z-eicosatetraenamide (AM404; 0.1-3 mg/kg), the fatty acid amide hydrolase (FAAH) inhibitor cyclohexylcarbamic acid 3-carbamoylbiphenyl-3-yl ester (URB597; 0.03-0.3 mg/kg), the cannabinoid CB₁ receptor agonist (–)-cis-3-[2-hydroxy-4-(1,1-dimethylheptyl) phenyl]-trans-4-(3-hydroxypropyl)-cyclohexanol (CP55,940; 0.03-0.3 mg/kg) and the CB₁ receptor antagonist rimonabant (0.3-3 mg/kg) on immobility time in the forced swim test (FST) in rats. Moreover, the effects of AM404, CP55,940 and URB597 on the antidepressant-like activity of imipramine and citalopram in the FST were also examined. We found that AM404 (0.3-3 mg/kg), CP55,940 (0.1 mg/kg) and URB597 (0.1-0.3 mg/kg) reduced the immobility time of rats, while rimonabant (0.3-3 mg/kg) was inactive in this respect. We also observed that the anti-immobility effects of AM404 (1 mg/kg), CP55,940 (0.1 mg/kg) and URB597 (0.3 mg/kg), but not of imipramine (30 mg/kg), were blocked by rimonabant (3 mg/kg). In another set of experiments we showed that the inactive dose of AM404 (0.1 mg/kg) potentiated the effects of the inactive doses of imipramine (15 mg/kg) or citalopram (30 mg/kg), while CP55,940 (0.03 mg/kg) and URB597 (0.03 mg/kg) enhanced the effect of imipramine only. None of the drugs studied, given alone or in combination, increased the basal locomotor activity of rats. Our results indicate that activation of the eCB system induces antidepressant-like effects in the FST in rats, and that these effects are mediated by CB₁ receptors. Moreover, they also indicate that agents activating eCB transmission enhance the anti-immobility responses to antidepressant drugs.

Key words: CB₁ receptor, depression, endocannabinoid system, forced swim test, rats
INTRODUCTION

The endocannabinoid (eCB) system consists of the arachidonic acid derivatives anandamide, 2-arachidonyleglycerol and 2-arachidonyleglyceryl ether which have potent, but differential, actions at both cannabinoid (CB) CB₁ and CB₂ receptors. Anandamide and 2-arachidonyleglycerol are present in the brain and other tissues, they are synthesized and released locally on demand and rapidly inactivated by transporter mechanism and by the enzymes fatty acid amide hydrolase (FAAH), and monoacylglycerol lipase, respectively. CB₁ receptors are known to be expressed in the brain, while CB₂ receptors are expressed mainly in peripheral tissues (1).

The eCB system in the brain is also responsive to Δ⁹-tetrahydrocannabinol (THC), the major psychoactive constituent from the plant Cannabis sativa recreationally used by humans (1). Interestingly, consumption of cannabis in humans results in an elevation in mood, the induction of euphoria and a reduction in stress, anxiety and depressive symptoms (2 - 4).

In line with the above observations, some authors have reported that agents activating eCB transmission exert anxiolytic (after low doses) or anxiogenic (after high doses) effects in animal models (5 - 10). Activation of the eCB system produces also antidepressant-like effects in the behavioural forced swim test (11 - 13) or in the chronic mild stress (14). Moreover, chronic treatment with antidepressant drugs has been found to increase the density of CB₁ receptors in the hippocampus and hypothalamus (15). The eCB system has been found to be engaged in the ability of long-term antidepressant treatment to block stress-induced activation of the hypothalamic-pituitary-adrenal axis (15). To extend our knowledge on the antidepressant-like activity of agents affecting eCB transmission, in the present studies we examined the effect of the eCB uptake inhibitor 4-hydroxyphenyl-5Z,8Z,11Z,14Z-eicosatetraenamide (AM404) (16), the FAAH inhibitor cyclohexylcarbamic acid 3-carbamoylphenyl-3-yl ester (URB597) (17-18) and the selective CB₁ receptor agonist (−)-cis-3-[2-hydroxy-4-(1,1-dimethylheptyl)phenyl]-trans-4-(3-hydroxypropyl)-cyclohexanol (CP55,940) (19) in an animal model of depression, the forced swim test (FST) in rats. The effect of the selective CB₁ receptor antagonist rimonabant (20) was tested alone as well as its influence on the anti-immobility activity of AM404, URB597, CP55,940 and imipramine was investigated. Finally, we also studied the antidepressant-like activity of combination of inactive doses of AM404, URB597 or CP55,940 given with inactive doses of imipramine or citalopram.

MATERIALS AND METHODS

Animals

Male Wistar rats (sourced from a licensed animal breeder T. Górkowska, Warszawa, Poland) weighing 250-300 g were used in this study. Animals were housed 6-8 rats/cage in standard plastic
rodent cages (57x35x20 cm) with free access to food (Labofeed pellets) and water, at a room temperature of 20 ± 1 °C under 12-h light-dark cycle (lights on at 6:00). All experiments were conducted between 08:00-15:00 h and were carried out in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals and with approval of the Animal Care and Use Committee at the Institute of Pharmacology, Polish Academy of Sciences in Krakow.

Drugs

The following drugs were used: (4-hydroxyphenyl)-5Z,8Z,11Z,14Z-eicosatetraenamide (AM404); (−)-cis-3-[2-hydroxy-4-(1,1-dimethylheptyl)phenyl]-trans-4-(3-hydroxypropyl)-cyclohexanol (CP55,940; Tocris, UK); rimonabant (SR141617A); cyclohexylcarbamic acid 3-carbamoylbiphenyl-3-yl ester (URB597); citalopram hydrochloride (Polfa, Starogard Gdański, Poland) and imipramine hydrochloride (Polfa, Kraków, Poland). AM404 was dissolved in Tocrisolve 100 (Tocris, UK) and diluted as required in distilled water. CP55,940 was dissolved in 15% 2-hydroxypropyl-β-cyclodextrin (Sigma-Aldrich, USA). Rimonabant was dissolved in a mixture of 1:1:10 ethanol, cremophor and 19% 2-hydroxypropyl-β-cyclodextrin. URB597 was dissolved in 2-3 drops of ethanol and diluted as required in a 1% aqueous solution Tween 80. Citalopram and imipramine were dissolved in 0.9% saline. All drugs were injected intraperitoneally (i.p.) in a volume of 1 ml/kg and were prepared before behavioral tests. Rimonabant was given at 70 min, AM404, citalopram and imipramine were given at 60 min, CP55,940 was given at 45 min, and URB597 was given at 40 min before the tests.

Forced swim test

We used the forced swim test (FST) as described previously by Porsolt (21) with small modification by Detke and colleagues (22). The experiment consisted of two sessions during which animals were forced to swim. On the first day (pretest day) rats were individually placed in the testing cylinder (44 cm × 23 cm diameter) filled to a 30 cm depth with water (25°C) for 15 min, and then were removed from the water, dried with towels in a warmer environment and then returned back to their home cages. On the second day (test day), 24 h after the first swim session, animals were placed in the cylinders for 5 min to measure time of immobility. The cylinders were emptied and cleaned between rats. A rat was said to be immobile if it was making only movements necessary for the animal to keep its head above water. The animals were drug- and test-naïve. N= 6-8 rats/group.

Locomotor activity

The locomotor activity of rats was recorded for each animal as described previously by Przegalinski et al. (23). Briefly, the locomotor activity was measured in Opto-Varimex cages surrounded with a 15 x 15 array of photocell beams located 3 cm from the floor surface (Columbus Instruments, Columbus, USA). Interruptions of these photobeams resulted in horizontal activity defined as distance traveled and expressed in cm. Locomotor activity was defined as a break of three consecutive photo-beams. Animals were placed individually into the locomotor activity cages for 30 min, their locomotion was recorded after 5 min and at the end of the 30-min test session and analyzed using Auto-track software (Columbus Instruments, USA). The animals were drug- and test-naïve. N=6-8 rats/group.

Statistical analyses

The data in the FST are expressed as the mean immobility time (±S.E.M.) during 5-min (300 s) observation period. Comparisons between groups were carried out by a one-way analysis of
variance (ANOVA), followed by intergroup comparisons using the Dunnett’s test (when only one drug was given) or by the Newman-Keuls test (when two drugs were administered).

The locomotor activity data are expressed as the mean horizontal distance traveled in cm (± S.E.M.) for the first 5 min and the entire 30-min test session. Comparisons between groups were carried out by a one-way analysis of variance (ANOVA), followed by intergroup comparisons using the Dunnett’s test (when only one drug was given) or by the Newman-Keuls test (when two drugs were administered).

RESULTS

Effects of eCB agents on immobility time in the FST

Administration of AM404 (0.1, 0.3, 1 or 3 mg/kg) significantly reduced immobility time \((F(4,30)=14.59, P<0.001)\), with post-hoc analysis revealing that the reduction in immobility time was significant at 0.3, 1 and 3 mg/kg of AM404 (Fig. 1).

After administration of URB597 (0.03, 0.1 or 0.3 mg/kg) a significant, dose-dependent reduction of immobility time was observed \((F(3,23)=6.56, P<0.002)\), and post-hoc analysis showed that 0.1 and 0.3 mg/kg of URB597 significantly reduced immobility time (Fig. 1).

CP55,940 (0.03, 0.1 or 0.3 mg/kg) significantly decreased immobility time \((F(3,22)=4.03, P<0.01)\), with post-hoc analysis demonstrating that CP55,940 in a single dose of 0.1 mg/kg significantly reduced immobility time (Fig. 1).

Rimonabant given alone in doses of 0.3, 1 or 3 mg/kg did not affect immobility time \((F(3,25)=0.42)\) (Fig. 2).

At the same time, rimonabant administered in a dose of 3 mg/kg significantly reduced or fully blocked the anti-immobility effect of AM404 (1 mg/kg) \((F(2,17)=16.95, P<0.001)\), URB597 (0.3 mg/kg) \((F(2,18)=12.12, P<0.001)\) or CP55,940 (0.1 mg/kg) \((F(2,16)=7.34, P<0.005)\) (Fig. 3). Groups of rats pretreated with rimonabant (3 mg/kg) in combination with AM404 (1 mg/kg),

![Graph](image-url)

*Fig. 1. Effects of AM404 (AM; 0.1-3 mg/kg), URB597 (URB; 0.03-0.3 mg/kg) and CP55,940 (CP; 0.03-0.3 mg/kg) on the immobility time in the FST. Data are presented as means ± S.E.M. * \(P<0.01\), ** \(P<0.001\) vs vehicle (VEH).
Fig. 2. Effect of rimonabant (RIM; 0.3-3 mg/kg) on immobility time in the FST. Data are presented as means ± S.E.M. There were no significant differences between groups.

Fig. 3. Inhibitory effects of rimonabant (RIM; 3 mg/kg) pretreatment on the anti-immobility effects of AM404 (AM; 1 mg/kg), URB597 (URB; 0.3 mg/kg) or CP55,940 (CP; 0.1 mg/kg). Data are presented as means ± S.E.M. * P<0.01 vs respective vehicle (VEH)+vehicle groups; † P<0.01 vs vehicle+AM (1); ‡ P<0.01 vs vehicle+URB (0.3); ^P <0.01 vs vehicle+CP (0.1).

URB597 (0.3 mg/kg) or CP55,940 (0.1 mg/kg) did not differ from their respective control groups (Fig. 3).

Effects of combination of eCB agents, CB₁ receptor agonist, or CB₁ receptor antagonist and antidepressant drugs on the immobility time in the FST

Imipramine (15-30 mg/kg) induced dose-dependent reduction of immobility time in the FST (F(2,21)=6.22, P<0.007), and post-hoc analysis showed that 30 mg/kg of imipramine induced significant reduction of immobility. Citalopram (30-60 mg/kg) did not show any significant antidepressant-like effects (F(2,20)=1.08) (Fig. 4).

Combination of AM404 (0.1 mg/kg) with imipramine (15 mg/kg) (F(2,21)=17.42, P<0.001) (Fig. 5) or with citalopram (30 mg/kg) (F(2,19)=7.17, P<0.004) (Fig. 6), significantly reduced immobility time.
**Immobility**

Imipramine (15 mg/kg) significantly shortened immobility time also in rats treated with URB597 (0.03 mg/kg) \((F(2,16)=6.28, P<0.009)\) or CP55,940 (0.03 mg/kg) \((F(2,18)=3.86, P<0.05)\) (Fig. 5).

Neither URB597 (0.03 mg/kg) \((F(2,18)=0.02)\) nor CP55,940 (0.03 mg/kg) \((F(2,18)=0.06)\) combined with citalopram (30 mg/kg) reduced immobility time (Fig. 6).

Rimonabant (3 mg/kg) did not alter significantly the anti-immobility effects of imipramine, 30 mg/kg \((F(1,21)=17.42, P<0.001)\) (Fig. 7).

**Locomotor activity**

AM404 (0.1-3 mg/kg), URB597 (0.03-0.3 mg/kg) and CP55,940 (0.1-0.3 mg/kg) did not affect locomotor activity of rats during the first 5-min or the entire 30-min test sessions (Table 1).
Fig. 6. Effects of citalopram (CIT; 30 mg/kg) combined with AM404 (AM; 0.1 mg/kg), URB597 (URB; 0.03 mg/kg) or CP55,940 (CP; 0.03 mg/kg) on the immobility time in the FST. Data are presented as means ± S.E.M. * P < 0.05 vs vehicle (VEH)+vehicle.

Fig. 7. Effects of imipramine (IMI; 30 mg/kg) combined with rimonabant (RIM; 3 mg/kg) on the immobility time in the FST. Data are presented as means ± S.E.M. * P < 0.01 vs vehicle (VEH)+vehicle.

A significant reduction of locomotor activity was observed in animals treated with imipramine (15 mg/kg) or citalopram (30 mg/kg) given alone and in animals treated with combinations of AM404 (0.1 mg/kg) + imipramine (15 mg/kg), AM404 (0.1 mg/kg) + citalopram (30 mg/kg), or imipramine (15 mg/kg) + URB597 (0.03 mg/kg) (Table 1).

DISCUSSION

Our results extend the knowledge on antidepressant-like activity of pharmacologically stimulated eCB transmission and indicate that antidepressant-like responses to classical antidepressant drugs are augmented by agents activating this eCB system.

In fact, we observed that AM404, an eCB re-uptake inhibitor (16) as well as URB597, a FAAH inhibitor (17 - 18), and CP55,940, an agonist at CB₁ receptors
Table 1. Effects of citalopram and imipramine given alone or AM404, URB597, CP55,940, given alone and in combination with antidepressant drugs on the rat's basal horizontal locomotor activity expressed as a distance traveled in cm during the first 5 min or the entire 30-min test sessions.

<table>
<thead>
<tr>
<th>Drugs (mg/kg)</th>
<th>Locomotor activity (mean ± S.E.M.)</th>
<th>5 min</th>
<th>30 min</th>
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<td>VEH</td>
<td>871.3 ± 91.2</td>
<td>1494.8 ± 250.1</td>
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<td>AM (0.1)</td>
<td>618.9 ± 140.9</td>
<td>1258.9 ± 291.3</td>
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<tr>
<td>AM (0.3)</td>
<td>1064.4 ± 70.2</td>
<td>2034.1 ± 189.7</td>
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<td>AM (1)</td>
<td>818.6 ± 87.7</td>
<td>1440.0 ± 312.7</td>
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<td>AM (3)</td>
<td>865.9 ± 89.9</td>
<td>1413.4 ± 158.8</td>
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<td>ANOVA F(4,34)=1.41</td>
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<tr>
<td>VEH</td>
<td>580.8 ± 71.7</td>
<td>946.6 ± 146.7</td>
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<tr>
<td>URB (0.03)</td>
<td>831.1 ± 104.8</td>
<td>1444.0 ± 266.5</td>
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<td>URB (0.1)</td>
<td>746.1 ± 61.7</td>
<td>1130.9 ± 157.6</td>
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<td>URB (0.3)</td>
<td>579.5 ± 61.4</td>
<td>869.0 ± 103.9</td>
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<td>ANOVA F(3,28)=2.65</td>
<td>ANOVA F(3,28)=2.04</td>
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<td>VEH</td>
<td>890.4 ± 95.0</td>
<td>1488.0 ± 183.3</td>
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<td>CP (0.1)</td>
<td>870.0 ± 74.7</td>
<td>1588.4 ± 202.7</td>
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<td>CP (0.3)</td>
<td>770.2 ± 61.4</td>
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<td>ANOVA F(2,17)=0.98</td>
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<tr>
<td>VEH + VEH</td>
<td>1081.4 ± 79.3</td>
<td>2344.6 ± 174.1</td>
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<td>CIT (30) + VEH</td>
<td>564.3 ± 91.8 b</td>
<td>1218.6 ± 112.7 b</td>
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<td>CIT (30) + AM (0.1)</td>
<td>563.2 ± 87.9 b</td>
<td>1307.4 ± 301.2 b</td>
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<td>VEH + VEH</td>
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<td>2344.6 ± 174.1</td>
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<td>IMI (15) + VEH</td>
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<td>VEH + VEH</td>
<td>806.8 ± 127.0</td>
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<td>IMI (15) + VEH</td>
<td>569.0 ± 76.7</td>
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<td>IMI (15) + CP (0.03)</td>
<td>586.7 ± 61.9</td>
<td>999.6 ± 115.1 b</td>
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<tr>
<td>ANOVA F(2,18)=2.12</td>
<td>ANOVA F(2,18)=6.01, P&lt;0.01</td>
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*P<0.05, b P<0.01 vs respective control groups

(19) administered in single doses significantly reduced immobility time in the FST in rats. Concerning this effect the following comments should be raised:
- the ability of AM404, URB597 and CP55,940 to reduce immobility time was comparable to that seen after single dose of tricyclic antidepressant imipramine;
- the reduction in immobility time was a dose-dependent effect, particularly observed after AM404 and URB597;
- the anti-immobility effect of the above agents activating eCB transmission is likely not mediated by increases in motor activity because the doses effective in the FST did not affect rats’ locomotor activity;
- since rimonabant, a selective CB₁ receptor antagonist (20), administered at a dose inactive in the FST, significantly reduced or even totally blocked the antidepressant-like effect of eCB agents, CB₁ receptors seem to be engaged in the anti-immobility effects of these drugs.

The above results and conclusions are in line with other recently reported data. Thus, the anti-immobility effects of AM404, oleamide (a competitive FAAH inhibitor and CB₁ receptor agonist; 24-25) and 1,1-dimethylheptyl-11-hydroxytetrahydrocannabinol (HU-210; a CB₁ receptor agonist; 19) were previously described by Hill and Gorzalka (12) who also found that antidepressant-like effects of these agents were potently reduced by the CB₁ receptor antagonist 1-(2,4-dichlorophenyl)-5-(4-iodophenyl]-4-methyl-N-(1-piperidyl)pyrazole-3-carboxamide (AM251; 26). Similarly, in mice, an anti-immobility effect of URB597 and its reduction by rimonabant in the FST and tail suspension test in mice was reported by Gobbi et al. (11). Finally, the anti-immobility effect in the FST was also observed after arachidonyl-2-chloroethylamide (ACEA), a CB₁ receptor agonist (13).

In contrast to the observations that rimonabant (present study) and AM251 (12) are inactive in the FST in rats and yet antagonize the anti-immobility effect of agents activating the eCB transmission, Shearman et al. (27) and Tzavara et al. (28) reported that in mice these CB₁ receptor antagonists produced antidepressant-like responses in the FST and tail suspension test. In other words the effect of CB₁ receptor antagonists in experimental models predictive of an antidepressant activity could be a species-dependent phenomenon. However, in contrast to these studies, the recent description of the lack of effect of rimonabant in the FST and in the tail suspension test in mice (11) should also be underlined.

The activation of the eCB transmission producing antidepressant-like activity leads also to several neurochemical effects – including increased synaptic levels of classical neurotransmitters (29) resembling effects produced by antidepressant drugs. However, since similar effects have been found after CB₁ receptor antagonists (29), further studies are necessary to shed light on the mechanism(s) for the anti-immobility effects of agents activating eCB transmission. At the same time activation of serotonergic and noradrenergic neurons – reminiscent of that produced by anti-depressant drugs – has been shown in electrophysiological studies after URB597. Actually, Gobbi et al. (11) have demonstrated that the drug administered acutely or repeatedly increases firing activity of serotonergic neurons in the dorsal raphe nucleus and noradrenergic neurons in the nucleus locus coeruleus, either effect being mediated via CB₁ receptors, as it was prevented by rimonabant.

Another important finding of the present studies is the potentiation by AM404, URB597 and CP55,940 of the anti-immobility effects of antidepressant drugs. In fact, inactive doses of these eCB transmission-activating agents combined with an
inactive dose of imipramine (15 mg/kg) produced antidepressant-like effects comparable to those observed after a two-fold larger dose of the tricyclic antidepressant (30 mg/kg). Likewise, an anti-immobility effect was observed after the combination of inactive doses of citalopram (30 mg/kg) and AM404 (0.1 mg/kg), whereas URB597 or CP55,940 were inactive in this respect. The lower susceptibility of citalopram to the potentiating effect of the eCB transmission-activating agents may be connected with the observation that this selective serotonin uptake inhibitor administered alone even at doses as high as 60 mg/kg was ineffective in the FST in rats, supporting earlier findings (30-31). Interestingly enhancement the anti-immobility effect of another selective serotonin uptake inhibitor fluoxetine by the CB1 receptor agonist arachidonyl-2-chloroethylamide (ACEA) in the FST in mice has been recently described (13).

Anti-immobility effects of concomitant administration of agents which enhance the eCB transmission and antidepressants seem to be specific since they are not related to increased locomotor activity. On the contrary all the combinations producing antidepressant-like effects reduce locomotion in rats. Moreover, potentiation of antidepressant drugs effect does not seem to result from pharmacokinetic interaction, since at least in the case of imipramine it was observed after three chemically different agents (AM404, URB597, CP55,940). This phenomenon also does not seem to be connected with antidepressant drug-induced increased signalling abilities of CB1 receptors since such an effect appears only after chronic treatment with these drugs (12) and since anti-immobility effect of antidepressant drugs, or at least of imipramine, is not mediated via CB1 receptors, as it was not affected by rimonabant (present study). Whether cannabinoid enhancer-induced activation of serotonergic and/or noradrenergic neurons (see above; 32) is responsible for the potentiation of anti-immobility effect of antidepressant drugs remains to be elucidated.

The above observations may be important from the clinical point of view since concomitant administration of the eCB transmission-activating agents and antidepressant drugs may produce more beneficial effects than antidepressants given alone (reduction of antidepressant drug dose leading to potential reduced side-effects). It is also interesting to speculate that there would be a reduction of antidepressant-latency, but further studies need to confirm this hypothesis.

In conclusion, our results bring further evidence that activation of the eCB transmission induces antidepressant-like activity in rats and that the CB1 receptors appear to be critically involved in this phenomenon. Moreover, they also indicate that agents activating the eCB transmission enhance antidepressant-like responses to antidepressant drugs.

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