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European Journal of Pharmacology 517 (2005) 68 – 73

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WIN 55,212-2-induced reduction of cocaine hyperlocomotion: Possible inhibition of 5-HT_3 receptor function

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Received 20 January 2005; received in revised form 12 May 2005; accepted 20 May 2005
Available online 14 June 2005

Abstract

We examined the effect of WIN 55,212-2 (an agonist of cannabinoid receptors) and its enantiomer WIN 55,212-3, as well as of ondansetron (an antagonist of serotonin (5-HT)$_3$ receptors) on the cocaine-induced locomotor hyperactivity in rats. WIN 55,212-2, but not WIN 55,212-3, in doses of 3 and 6 mg/kg which did not affect the basal locomotor activity, dose-dependently reduced the hyperactivation evoked by cocaine. The inhibitory effect of WIN 55,212-2 was not affected by rimonabant (an antagonist of cannabinoid receptors). Like in the case of WIN 55,212-2, the cocaine-induced hyperlocomotion was reduced in a dose-dependent manner by ondansetron (0.03–0.3 mg/kg). The obtained results indicate that the inhibitory effect of WIN 55,212-2 on cocaine hyperactivation is stereoselective and is not mediated by cannabinoid receptors. Moreover, together with the literature data they may suggest that this effect of WIN 55,212-2 involves inhibition of the 5-HT_3 receptor function.

Keywords: 5-HT_3 receptor; Cannabinoid receptor ligand; Cocaine; Locomotor activity

1. Introduction

Cannabinoid receptor agonists resemble the serotonin (5-HT)$_3$ receptor antagonists in terms of some of their pharmacological activities like antiemetic and nonopioid analgetic effects (Noyes et al., 1975; Dewey, 1986; Howlett et al., 1990; Karim et al., 1996; Martin et al., 1999; Simpson et al., 2000; Voog et al., 2000; Darmani, 2001). Interestingly, electrophysiological studies have demonstrated that cannabinoid CB_1 receptor agonists stereoselectively inhibit 5-HT-induced, 5-HT_3 receptor-mediated currents in rat nodose ganglion neurons (Fan, 1995), in excised outside-out patches of HEK 293 cells expressing recombinant human (h) 5-HT_{3A} receptors (Barann et al., 2002) and in *Xenopus* oocytes expressing cloned mouse 5-HT_3 receptors (Oz et al., 2002). Moreover it has also been shown that cannabinoids inhibit the phenylbiguanide-induced 5-HT_3 receptor-mediated, but not the vanilloid receptor-mediated von Bezold–Jarisch reflex in rats (Godlewski et al., 2003). The inhibitory effects of the cannabinoid receptor agonists in HEK 293 cells, in *Xenopus* oocytes and in the von Bezold–Jarisch reflex model were not affected by the cannabinoid receptor antagonist, rimonabant (SR 141716A) (Barann et al., 2002; Oz et al., 2002; Godlewski et al., 2003). In agreement with this, radioligand binding experiments revealed that HEK 293 cells do not express CB_1 (or CB_2) receptors (Barann et al., 2002). On the other hand, cannabinoids in contrast to 5-HT, did not modify specific [^{3}H]GR65630 binding to recombinant h5-HT_{3A} receptors in HEK 293 cells, indicating that these drugs do not act at the 5-HT recognition site of the 5-HT_{3A} receptor (Barann et al., 2002). The most plausible explanation of the cannabinoid receptor-independent cannabinoid-induced inhibition of 5-HT_3 receptor function is that these drugs act at an allosteric modulatory site of this receptor (Barann et al., 2002).

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doi:10.1016/j.ejphar.2005.05.014

Table 1
Effects of cannabinoid receptor ligands and ondansetron on the basal locomotor activity in rats

Treatment	Dose (mg/kg)	Horizontal distance traveled (cm)/60 min
WIN 55,212-2	0	316±66
	3	359±102
	6	311±63
WIN 55,212-3	0	386±46
	3	411±68
	6	390±92
Rimonabant	0	347±77
	5	386±66
Ondansetron	0	316±66
	0.03	336±49
	0.1	264±56
	0.3	387±68

Mean±S.E.M. $N=7-8$ rats/group.

In the present paper we examined whether cannabinoids resemble the effects of 5-HT_3 receptor antagonists at the behavioral level. To this end we used the model of locomotor hyperactivity induced by cocaine, an effect which is blocked by 5-HT_3 receptor antagonists (Reith, 1990; Svingos and Hitzemann, 1992; Kankaanpaa et al., 2002). In this study we compared the effect of WIN 55,212-2, an agonist of cannabinoid receptors (D'Ambra et al., 1992) and ondansetron, an antagonist of 5-HT_3 receptors (Butler et al., 1988; Hoyer et al., 2002) on the cocaine-induced hyperlocomotion in rats. In some experiments WIN 55,212-3, an enantiomer of WIN 55,212-2 (Felder et al., 1992), and rimonabant, an antagonist of the cannabinoid receptors (Rinaldi-Carmona et al., 1994), were also used.

2. Materials and methods

2.1. Animals

The experiment was performed on male Wistar rats (240–260 g). The rats were housed in a colony room maintained at 21±1 °C and 40–50% humidity on a 12-h light–dark cycle (the lights on at 06:00 h). Rodent chow and water were available ad libitum. All the experiments were conducted in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals and the approval of the Bioethics Commission (compliant with the Polish Law of 21 August 1997).

2.2. Drugs

The following drugs were used (supplier): cocaine hydrochloride (Merck, Darmstradt, Germany), ondansetron hydrochloride (GlaxoWellcome, Greenford, UK), rimonabant (=SR 141716A hydrochloride; Sanofi Recherche, Montpellier, France), WIN 55,212-2 mesylate (*R*-(+)-[2,3-dihydro-5-methyl-3-(4-morpholinylmethyl)pyrrolo[1,2,3-de]-1,4-benzoxazin-6-yl]-1-naphthalenylmethanone mesylate; Tocris, Bristol, UK) and WIN 55,212-3 mesylate (*S*-(-)-[2,3-dihydro-5-methyl-3-(4-morpholinylmethyl)-pyrrolo[1,2,3-de]-1,4-benzoxazin-6-yl]-1-naphthalenylmethanone mesylate; Tocris, Bristol, UK). Cocaine was dissolved in saline, ondansetron (from original ampoules containing 2 mg/ml) was diluted in distilled water, WIN 55,212-2 and WIN 55,212-3 were dissolved in a 19% solution of β-cyclodextrin, while rimonabant was prepared in a mixture of 95% ethanol, Cremophor El and 19% β-cyclodextrin (1:1:10). All the drugs were injected intraperitoneally (i.p.) in a volume of 1 ml/kg.

2.3. Locomotor activity measurements

Behavioral measurement was carried out between 8:30 and 13:30 h. The locomotor activity of rats was recorded for each animal as described previously (Przegaliński et al., 2001). Briefly, the locomotor activity was monitored and quantified in clear plexiglass chambers (43×43×25 cm) housed inside Optovarimex® activity monitors surrounded with a 15×15 array of photocell beams located 3 cm from the floor surface (Columbus Instruments, USA). Interruptions of these photobeams resulted in horizontal activity defined as distance traveled (expressed in cm). Records of horizontal activity were made by the control software (Columbus Instruments) for subsequent statistical evaluation.

Rats were habituated to the test environment (experimental chambers) for 2 h 2 days before the start of the experiment, and on each test day for 1 h before the start of the test session. Ondansetron, WIN 55,212-2 or WIN 55-212,3 were given 30 min, while rimonabant was given 45 min, before saline or cocaine (10 mg/kg). In additional experiments the effects of WIN 55,212-2 (6 mg/kg) on the dose–response curve for hyperlocomotion induced by cocaine (5–15 mg/kg) were evaluated. Locomotor activity was recorded for 60 min. Animals were tested only one time, and each separate group of rats consisted of 7–8 animals.

2.4. Statistical analysis

The data are expressed as the mean total distance traveled (± S.E.M.) during a 60-min observation period. A one-way analysis of variance (ANOVA), followed by post hoc Dunnett's test, were applied to evaluate the treatment group effect in locomotor activity studies. A two-way ANOVA, followed by post hoc Newman–

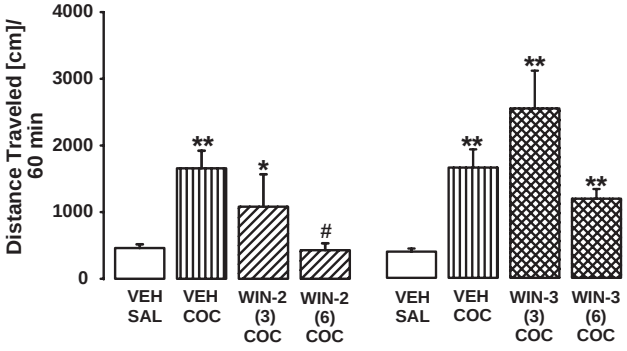

Fig. 1. Effect of WIN 55,212-2 (WIN-2) and WIN 55,212-3 (WIN-3) on the cocaine (COC; 10 mg/kg)-stimulated locomotor activity in rats. Doses are expressed in mg/kg. Means±S.E.M. *$P<0.05$, **$P<0.01$ vs. vehicle (VEH)+saline (SAL); $^{\#}P<0.01$ vs. vehicle+cocaine. $N=7-8$ rats/group.

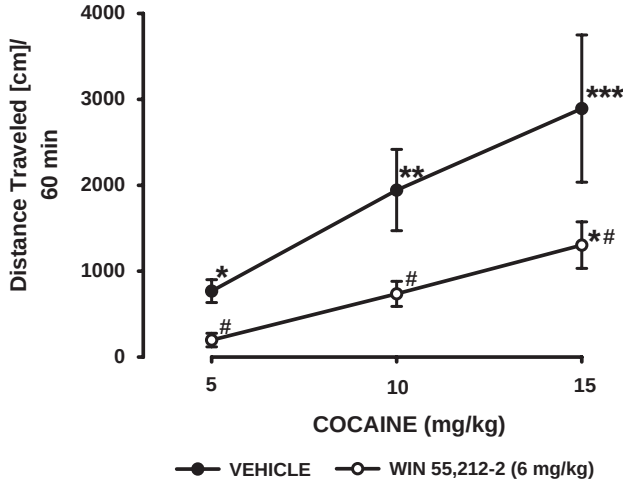

Fig. 2. Effect of WIN 55,212-2 (6 mg/kg) on the cocaine (5–15 mg/kg)-stimulated locomotor activity in rats. Means±S.E.M. The mean values for control group (vehicle+saline)=407±54. $^{*}P<0.05$, $^{**}P<0.01$, $^{***}P<0.001$ vs. control group; $^{\#}P<0.01$ vs. vehicle+a respective dose of cocaine. $N=7–8$ rats/group.

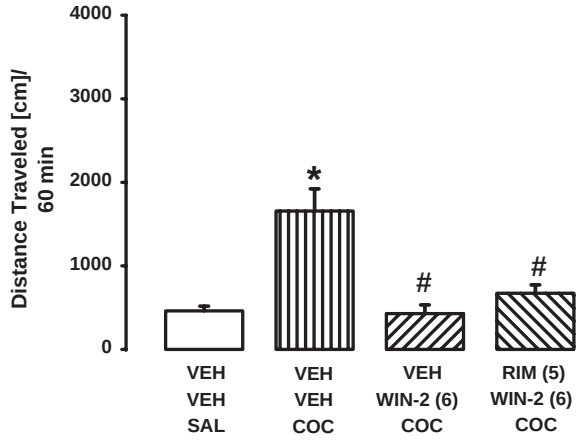

Fig. 4. Effect of rimonabant (RIM) on the WIN 55,212-2 (WIN-2)-mediated decrease of cocaine (COC; 10 mg/kg) hyperactivation in rats. Doses are expressed in mg/kg. Means±S.E.M. $^{*}P<0.001$ vs. vehicle (VEH)+vehicle+saline (SAL); $^{\#}P<0.001$ vs. vehicle+vehicle+cocaine. No significant difference between rimonabant+WIN 55,212-2+cocaine and vehicle+WIN 55,212-2+cocaine. $N=7–8$ rats/group.

Keuls test, were applied to evaluate the effects of WIN 55,212-2 on the various doses of cocaine.

3. Results

3.1. Basal locomotor activity

Basal locomotor activity was not affected in animals treated with WIN 55,212-2 (3–6 mg/kg; $F(2,19)=0.334$), WIN 55,212-3 (3–6 mg/kg; $F(2,21)=0.099$), rimonabant (5 mg/kg; $F(1,14)=0.129$) or ondansetron (0.03–0.3 mg/kg; $F(3,24)=0.766$; Table 1).

3.2. Cocaine-induced hyperactivation

Cocaine (10 mg/kg) significantly increased the rats' basal locomotor activity compared to saline (Figs. 1–5).

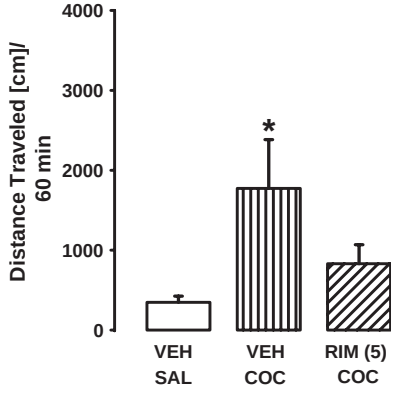

Fig. 3. Effect of rimonabant (RIM) on the cocaine (COC; 10 mg/kg)-stimulated locomotor activity in rats. Doses are expressed in mg/kg. Means±S.E.M. $^{*}P<0.01$ vs. vehicle (VEH)+saline (SAL). No significant difference between rimonabant+cocaine and vehicle+cocaine. $N=7–8$ rats/group.

A main effect of treatment was observed for rats which received injection of WIN 55,212-2 followed by cocaine ($F(3,27)=5.178$, $P<0.01$). Locomotor hyperactivation to cocaine (10 mg/kg) was dose-dependently reduced in animals treated with WIN 55,212-2 (3–6 mg/kg); a significant effect was observed after a dose of 6 mg/kg (Figs. 1, 2 and 4). Furthermore, WIN 55,212-2 (6 mg/kg) shifted to the right the dose–response curve for hyperlocomotion induced by cocaine (5–15 mg/kg) ($F(3,38)=7.46$, $P<0.001$; Fig. 2).

A main effect of treatment was observed for rats which received injection of WIN 55,212-3 followed by cocaine ($F(3,26)=11.334$, $P<0.001$). When the rats were given cocaine in combination with WIN 55,212-3 (3–6 mg/kg) no differences in locomotor activity compared to vehicle+cocaine-treated animals were found (Fig. 1).

A main effect of treatment was observed for rats which received injection of rimonabant followed by cocaine ($F(2,20)=3.667$, $P<0.05$). Rimonabant (5 mg/kg) did not alter significantly the cocaine-induced hyperactivation; however a trend to attenuate cocaine response was observed (Fig. 3).

A main effect of treatment was observed for rats which received injection of rimonabant followed by WIN 55,212-2+cocaine

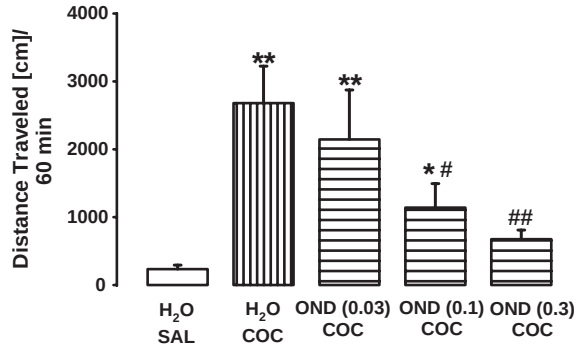

Fig. 5. Effect of ondansetron (OND) on the cocaine (COC; 10 mg/kg)-stimulated locomotor activity in rats. Doses are expressed in mg/kg. Means±S.E.M. $^{*}P<0.01$, $^{**}P<0.001$ vs. water (H_2O)+saline (SAL); $^{\#}P<0.05$, $^{\#\#}P<0.01$ vs. water+cocaine. $N=7–8$ rats/group.

($F(3,26)=13.601$, $P<0.001$). Injection of rimonabant (5 mg/kg) did not alter the reduction of cocaine hyperactivation induced by 6 mg/kg of WIN 55,212-2 (Fig. 4).

A main effect of treatment was observed for rats which received injection of ondansetron followed by cocaine ($F(3,27)=15.768$, $P<0.01$). When given in combination with cocaine (10 mg/kg), ondansetron (0.03–0.3 mg/kg) dose-dependently reduced the locomotor effect of cocaine (Fig. 5).

4. Discussion

The present study demonstrates that WIN 55,212-2, an agonist of the cannabinoid CB_1 and CB_2 receptors without affinity for numerous other neuroreceptors (D'Ambra et al., 1992; Iwamura et al., 2001), administered in doses (3 and 6 mg/kg) which did not affect the basal locomotor activity in rats, dose-dependently reduced hyperlocomotion evoked by cocaine (10 mg/kg) in the animals. Moreover, the agonist administered in a dose of 6 mg/kg inhibited hyperlocomotion induced by cocaine given in doses of 5–15 mg/kg, shifting its dose–response curve to the right. This inhibitory effect is not due to an unspecific interaction with hydrophobic regions of functional proteins or their lipid surroundings in the cell membrane of neurons, since WIN 55,212-3, an enantiomer of WIN 55,212-2, did not affect the cocaine-evoked hyperlocomotion. Rather, WIN 55,212-2, i.e. the active enantiomer, seems to produce the inhibition by an action at a certain recognition site of a protein, e.g. an ion channel or a receptor. The most obvious candidate for such an interaction is the brain cannabinoid CB_1 receptor, rather than the CB_2 one expressed by immune cells (Herkenham et al., 1990; Matsuda et al., 1992; Munro et al., 1993). However, the doses of WIN 55,212-2 which were necessary to produce the inhibition were much higher than those which induce typical CB_1 receptor-mediated effects in rats in vivo (see Rinaldi-Carmona et al., 1995; Malinowska et al., 1997). Furthermore, the selective cannabinoid CB_1 receptor antagonist rimonabant (displaying >500 times higher affinity for CB_1 than CB_2 receptors; Rinaldi-Carmona et al., 1994) at the high dose of 5 mg/kg (2–5 times higher than those necessary to block WIN 55,212-2-induced, CB_1 receptor-mediated, hypothermia and analgesia in mice; Rinaldi-Carmona et al., 1994,1995), which had per se no effect on basal locomotion, tended to mimic the inhibitory effect of the agonist WIN 55,212-2. Whereas this effect of rimonabant alone (putatively related to its extremely high lipophilicity) was not statistically significant, WIN 55,212-2 at a dose of 6 mg/kg, administered 15 min after 5 mg/kg of rimonabant, still highly significantly inhibited the cocaine-evoked locomotion in spite of the presence of the cannabinoid receptor antagonist. These results do not conform to an involvement of CB_1 receptors in the inhibitory action of WIN 55,212-2.

Basically, the inhibitory effect of WIN 55,212-2 on cocaine hyperlocomotion is in agreement with earlier results of Ferrari et al. (1999) who observed an analogous effect after HU 210, another cannabinoid agonist, but these authors did not study whether this effect of HU 210 is dependent on activation of cannabinoid receptors. Anti-cocaine effects of cannabinoids, including WIN 55,212-2, were also shown in another experiment in which convulsions and toxic effects of the psychostimulant were assessed (Hayase et al., 2001). In contrast, an investigation of the influence of WIN 55,212-2 on the reinforcing properties of cocaine revealed that the cannabinoid acted synergistically with cocaine in a manner sensitive to blockade by rimonabant (Fattore et al., 1999). Hence, the synergism, unlike the functional antagonism of cocaine-evoked hyperlocomotion found in this study, is compatible with an involvement of cannabinoid receptors (Fattore et al., 1999).

Cocaine hyperlocomotion depends on activation of the mesoaccumbens dopamine system (Kuczenski and Segal, 1992; Woolverton and Johnson, 1992) resulting from inhibition of the dopamine transporter, produced by the psychostimulant. Accordingly, this behavioral effect of cocaine is blocked by antidopaminergic agents acting presynaptically or postsynaptically, e.g. dopamine neurotoxins or dopamine receptor antagonists, respectively (Kelly and Iversen, 1976; Costall et al., 1980; Cabib et al., 1991; Ushijima et al., 1995). However, the possible involvement of such a mechanism in the antihyperlocomotion effect of WIN 55,212-2 seems doubtful, since cannabinoids, including WIN 55,212-2, facilitate rather than inhibit dopamine neurotransmission (Chen et al., 1991; French et al., 1997; Tanda et al., 1997; Gessa et al., 1998).

In contrast to the lack of a role of cannabinoid receptors in the WIN 55,212-2-induced inhibition of cocaine hyperlocomotion or of a more direct interaction of WIN 55,212-2 with the dopaminergic neurotransmission, the present data are compatible with an involvement of 5-HT_3 receptors in the inhibitory effect of the cannabinoid. Thus, the dose range of WIN 55,212-2 at which this effect occurred was identical to that at which in another in vivo study, the 5-HT-induced 5-HT_3 receptor-mediated von Bezold–Jarisch reflex was inhibited (Godlewski et al., 2003). Furthermore, the inhibition by WIN 55,212-2 observed in the present study resembles the effect of ondansetron as we have also shown that this 5-HT_3 receptor antagonist (Butler et al., 1988) administered in doses (0.03–0.3 mg/kg; sufficient to block brain 5-HT_3 receptors; Higgins et al., 1993; Consolo et al., 1994), inactive on basal locomotion, dose-dependently reduced cocaine-induced locomotor hyperactivity. Such an inhibitory effect of ondansetron was also observed in previous studies in which ondansetron and other 5-HT_3 receptor blockers were used (Reith, 1990; Svingos and Hitzemann, 1992; Herges and Taylor, 2000; Kankaanpaa et al., 2002).

Involvement of inhibition of 5-HT_3 receptor function in the interaction between WIN 55,212-2 and cocaine is also supported by the following data: 1) 5-HT_3 receptors have been identified in basal ganglia of the brain (Barnes and

Sharp, 1999); 2) activation of 5-HT_3 receptors leads to an increase in dopamine neurotransmission in the mesoaccumbens system (Jiang et al., 1990); 3) 5-HT_3 receptor antagonists reduce the cocaine-induced increase in extracellular dopamine levels in the nucleus accumbens (McNeish et al., 1993; Kankaanpaa et al., 1996).

The mechanism underlying the stereoselective inhibition of 5-HT_3 receptor function by WIN 55,212-2 and other cannabinoids has been investigated in a combined patch-clamp and radioligand binding studies on excised outside-out patches and membrane preparations, respectively (Barann et al., 2002). As already outlined in more detail in the Introduction, that study revealed that cannabinoid receptor ligands directly act at the 5-HT_3 receptor, probably by binding to an allosteric modulatory site (Barann et al., 2002).

In conclusion, the present data provide evidence that the cannabinoid receptor agonist WIN 55,212-2 stereoselectively inhibits the cocaine-evoked hyperlocomotion in a cannabinoid receptor-independent manner. Since the cannabinoid resembles the 5-HT_3 receptor antagonist in this respect and since such an analogy has been found in other models which allow a more direct investigation of the participation of 5-HT_3 receptors, it is tempting to hypothesize that the effect of WIN 55,212-2 involves an inhibition of 5-HT_3 receptor function. This hypothesis is further supported by the occurrence of 5-HT_3 receptors in the relevant brain regions and by the ability of 5-HT_3 receptor ligands to influence dopaminergic neurotransmission in these brain areas in a manner compatible with the present results.

Acknowledgement

We thank Sanofi for the gift of rimonabant. This study was supported by the Institute of Pharmacology and the Deutsche Forschungsgemeinschaft.

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