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Short communication

Antidepressant-like effect of the selective 5-HT_{1B} receptor agonist CP 94253: A possible mechanism of action

Ewa Tatarczyńska, Lucyna Antkiewicz-Michaluk, Aleksandra Kłodzińska, Katarzyna Stachowicz, Ewa Chojnacka-Wójcik*

Institute of Pharmacology, Polish Academy of Sciences, 12 Smętna Street, Cracow PL 31-343, Poland

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Abstract

The mechanism of the antidepressant-like activity of the selective 5-hydroxytryptamine$_{1B}$ (5-HT_{1B}) receptor agonist 5-propoxy-3-(1,2,3,6-tetrahydro-4-pyridinyl)-1*H*-pyrrolo[3,2-*b*]pyridine (CP 94253) was studied in the forced swimming test in mice. CP 94253 administered intraperitoneally at a single dose of 5 mg/kg potently shortened the immobility time of mice. The anti-immobility effect of CP 94253 was wholly blocked by the selective 5-HT_{1B} receptor antagonist *N*-[3-(2-dimethylamino)ethoxy-4-methoxyphenyl]-2′-methyl-4′-(5-methyl-1,2,4-oxadiazol-3-yl)-(1,1′-biphenyl)-4-carboxamide (SB 216641, 5 mg/kg), the dopamine D2-like receptor antagonist sulpiride (50 mg/kg) and the α_2-adrenoceptor antagonist idazoxan (2 mg/kg), but was not modified in animals with a lesion of the 5-HT system produced by *p*-chlorophenylalanine (*p*-CPA, 3 × 300 mg/kg). The obtained results suggest that the anti-immobility effect of CP 94253 is mediated by activation of 5-HT_{1B} receptors—most probably located postsynaptically and/or as heteroreceptors, and that the dopamine and the noradrenaline systems are involved in this action.

Keywords: 5-HT_{1B} receptor ligand; *p*-Chlorophenylalanine; Idazoxan; Sulpiride; Forced swimming test in mice

1. Introduction

5-Hydroxytryptamine$_{1B}$ (5-HT_{1B}) receptors, widely expressed throughout the mammalian central nervous system, are predominantly located on axon terminals of serotonergic neurons where they act as inhibitory autoreceptors, or on non-serotonergic terminals as heteroreceptors modulating the release of other neurotransmitters, including dopamine and noradrenaline (see Barnes and Sharp, 1999). 5-HT_{1B} receptors also exist as postsynaptic sites on cell bodies of non-serotonergic neurons (see Barnes and Sharp, 1999). Studies into the potential antidepressant effect of 5-HT_{1B} receptor ligands are sparse, and the actual role of 5-HT_{1B} receptors in depression is still far from being clarified. Our recent studies showed that the selective 5-HT_{1B} receptor agonist 5-propoxy-3-(1,2,3,6-tetrahydro-4-pyridinyl)-1*H*-pyrrolo[3,2-*b*]pyridine (CP 94253) exerted antidepressant-like activity in the forced swimming test in mice (Tatarczyńska et al., 2004). Although the mechanism underlying this effect of CP 94253 is unknown, it most probably results from the stimulation of 5-HT_{1B} receptors, since CP 94253 is a selective 5-HT_{1B} receptor agonist. In fact, the drug in question shows a high affinity for 5-HT_{1B} receptors in rats, a substantially lower affinity for other 5-HT receptors and little or no affinity for other receptors including dopamine D1 and D2 receptors and α_1-, α_2-, β-adrenoceptors; CP 94253 is neither a monoamine oxidase inhibitor nor a significant 5-HT, dopamine and noradrenaline uptake blocker (Koe et al., 1992). The 5-HT_{1B} receptor agonistic activity of CP 94253 has been demonstrated in functional in vivo and in vitro experiments (Fish et al., 1999; Knobelman et al., 2000; Koe et al., 1992; Lee et al., 2002).

* Corresponding author. Tel.: +48 12 6623323; fax: +48 12 6374500.
E-mail address: wojcik@if-pan.krakow.pl (E. Chojnacka-Wójcik).

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It has been well established that the shortening of the immobility time in the forced swimming test depends primarily on the enhancement of central catecholamine and – to a lesser extent – on 5-HT neurotransmission (Borsini, 1995; Borsini and Meli, 1990; Porsolt et al., 1977, 1979). Hence, the aim of the present study was to ascertain whether the antidepressant-like action of CP 94253 depended, firstly, on the stimulation of 5-HT_{1B} receptors, and secondly, on the enhancement of dopamine or noradrenaline neurotransmission. To this end, we examined, the effect of the selective 5-HT_{1B} receptor antagonist *N*-[3-(2-dimethylamino)ethoxy-4-methoxyphenyl]-2′-methyl-4′-(5-methyl-1,2,4-oxadiazol-3-yl)-(1,1′-biphenyl)-4-carboxamide (SB 216641) (Hagan et al., 1997; Price et al., 1997), the dopamine D2-like receptor antagonist sulpiride (Seeman and Van Tol, 1994) and the α_2-adrenoceptor antagonist idazoxan (Doxey et al., 1983) on the anti-immobility action of CP 94253. CP 94253 was investigated at a dose in which it produced an antidepressant-like effect in the forced swimming test in mice, without altering the locomotor activity of mice (Tatarczyńska et al., 2004). SB 216641 was used in a dose producing effects related to the blockade of 5-HT_{1B} receptors (Hagan et al., 1997). Sulpiride and idazoxan were used in a dose in which they antagonized the anti-immobility effect of antidepressants (Cervo et al., 1990; Cesana et al., 1995; Rénéric et al., 2001). Moreover, in order to determine whether the integrity of the 5-HT neural system was indispensable, the antidepressant-like effect of CP 94253 was also studied in mice pretreated with an inhibitor of 5-HT synthesis *p*-chlorophenylalanine (*p*-CPA).

2. Materials and methods

2.1. Animals and housing

The experiments were performed on male Albino Swiss mice (24–26 g; purchased from a licensed dealer Staniszewska, Ilkowice, Poland). The animals were kept in groups of 20 to a cage (60 × 38 × 20 cm) at a temperature of 20 ± 1 °C, and had free access to food (standard laboratory pellets) and tap water before the experiment. All the investigations were conducted in the light phase, on a natural light/dark cycle (May to September), between 9 AM and 2 PM. Each experimental group consisted of 8–10 animals per drug dose. Animals were tested in a counterbalanced order and were used only once in each test. The experiments were performed by an observer unaware of the treatment. All the experimental procedures were approved by the Local Bioethics Commission at the Institute of Pharmacology, Polish Academy of Sciences in Kraków.

2.2. Drug treatment

The following drugs were used: *p*-chlorophenylalanine (hydrochloride, *p*-CPA, Sigma, USA), *N*-[3-(2-dimethylamino)ethoxy-4-methoxyphenyl]-2′-methyl-4′-(5-methyl-1,2,4-oxadiazol-3-yl)-(1,1′-biphenyl)-4-carboxamide (hydrochloride, SB 216641; Tocris, Cookson Ltd., UK), idazoxan (hydrochloride, RBI, USA), 5-propoxy-3-(1,2,3,6-tetrahydro-4-pyridinyl)-1*H*-pyrrolo[3,2-*b*]pyridine (hydrochloride, CP 94253; Tocris, Cookson Ltd., UK), sulpiride (Sigma, USA). CP 94253, SB 216641 and idazoxan were used as aqueous solutions, *p*-chlorophenylalanine and sulpiride were suspended in a 1% aqueous solution of Tween 80. Idazoxan was injected subcutaneously (s.c.), the remaining compounds were administered intraperitoneally (i.p.). CP 94253 was given 30 min, while SB 216641, idazoxan and sulpiride were given 60 min before the test. *p*-Chlorophenylalanine was given on three consecutive days (at 72, 48 and 24 h) before the test. Control mice received a vehicle according to the same schedule.

2.3. Forced swimming test in mice

The experiment was carried out according to the method of Porsolt et al. (1977). Briefly, the mice were individually placed in a glass cylinder (25 cm high, 10 cm in diameter) containing 6 cm of water maintained at 23–25 °C, and were left therein for 6 min. A mouse was regarded as immobile when it remained floating on water, making only small movements to keep its head above it. The total duration of immobility was measured by an experimenter during the final 4 min of a 6-min test session, after a 2-min habituation period.

2.4. Locomotor activity in mice

The spontaneous locomotor activity of mice was recorded in photoresistor actometers (24 cm in diameter, illuminated by two light beams), which were connected to a counter for the recording of light-beam interruptions. The mice were placed individually in the actometers, and the number of crossings of the light beams was counted during a 6-min experimental session (i.e. for the time equivalent to the observation period in the forced swimming test).

2.5. Biochemical determinations

The brains were removed on an ice-chilled glass plate and dissected into three regions: the frontal cortex, striatum and brain stem. The content of serotonin (5-HT) and its metabolite 5-hydroxyindoleacetic acid (5-HIAA) and dopamine and its metabolites: homovanillic acid, 3,4-dihydroxyphenylacetic acid and 3-methoxytyramine were assayed by means of a high-performance liquid chromatography with electrochemical detection. Tissue samples were weighed and homogenized in an ice-cold 0.1 M trichloroacetic acid containing 0.05 mM ascorbic acid. After centrifugation (10,000 ×*g*, 5 min), the supernatants were filtered through RC 58 0.2 μM cellulose membranes (Bioanalytical Systems, West Lafayette, IN, USA). The chromatograph (Hewlett-Packard 1050) was equipped with C18 columns. The mobile phase consisted of 0.05 M citrate-phosphate buffer, pH 3.5, 0.1 mM EDTA, 1 mM sodium octyl sulfonate and 3.5% methanol. The flow rate was maintained at 0.8 ml/min. Biogenic amines and their metabolites were quantified by peak height comparisons with standards, run on the day of analysis by the HP ChemStation programme (Antkiewicz-Michaluk et al., 2000).

2.6. Statistical analysis

All the data are given as the mean±S.E.M. The data obtained in behavioural experiments were analyzed by a two-way analysis of variance with comparison between individual groups by the Newman–Keuls multiple comparison test (forced swimming test), or by a one-way analysis of variance followed by Student's *t*-test (locomotor activity test). The results derived from biochemical studies were analyzed by a one-way analysis of variance, followed – when appropriate – by Fisher's Least Significant Difference test for individual tissue samples.

3. Results

As shown in Table 1, CP 94253 (5 mg/kg) given alone significantly shortened (by 43%) the immobility time of mice in the forced swimming test. The anti-immobility effect of CP 94253 was wholly blocked by the 5-HT_{1B} receptor antagonist SB 216641 (5 mg/kg), the dopamine D2-like receptor antagonist sulpiride (50 mg/kg) and the α_2-adrenoceptor antagonist idazoxan (2 mg/kg). The effect of CP 94253 was not changed in animals pretreated with *p*-chlorophenylalanine (3×300 mg/kg) (Table 1). SB 216641, sulpiride, idazoxan or *p*-chlorophenylalanine given alone did not modify the immobility time of mice (Table 1).

As was demonstrated in an earlier study, neither CP 94253 (5 mg/kg) nor SB 216641 (5 mg/kg) affected the spontaneous locomotor activity of mice during 6-min experimental sessions (i.e. for the time equivalent to the observation period in the forced swimming test) (Tatarczyńska et al., 2004). Similarly, sulpiride (50 mg/kg) and idazoxan (2 mg/kg) had practically no effect on the activity of mice during 6-min experimental sessions (the mean±S.E.M. values for the number of crossings were: control 107.0±4.4; sulpiride-treated 83.4±8.8 and idazoxan-treated 91.5±6.2 ($F(1,18)=4.271$, $P>0.05$ and $F(1,18)=3.985$, $P>0.05$, respectively; $n=10$).

Administration of *p*-chlorophenylalanine (3×300 mg/kg) reduced the concentrations of 5-HT and 5-HIAA in the frontal cortex, striatum and brain stem by 75–92% (Table 2), while the levels of dopamine and its metabolites in those brain areas were not changed (data not shown).

Table 1
Effects of SB 216641, sulpiride, idazoxan and *p*-chlorophenylalanine (*p*-CPA) on the anti-immobility action of CP 94253 in the forced swimming test in mice

Treatment and dose (mg/kg)	Immobility time (s)
Vehicle+vehicle	187.1±6.3
Vehicle+CP 94253 (5)	107.1±12.0[a]
SB 216641 (5)+vehicle	172.8±5.3
SB 216641 (5)+CP 94253 (5)	204.4±8.7[b]
	$F(1,28)=43.396$
	$P<0.001$
Vehicle+vehicle	187.1±6.3
Vehicle+CP 94253 (5)	107.1±12.0[a]
Sulpiride (50)+vehicle	201.4±7.7
Sulpiride (50)+CP 94253 (5)	203.1±10.3[b]
	$F(1,29)=17.899$
	$P<0.001$
Vehicle+vehicle	187.1±6.3
Vehicle+CP 94253 (5)	107.1±12.0[a]
Idazoxan (2)+vehicle	182.1±8.4
Idazoxan (2)+CP 94253 (5)	161.3±8.1[b]
	$F(1,29)=10.063$
	$P<0.01$
Vehicle+vehicle	176.8±7.8
Vehicle+CP 94253 (5)	101.0±10.8[a]
p-CPA (3×300)+vehicle	169.2±7.1
p-CPA (3×300)+CP 94253 (5)	78.9±7.6[a]
	$F(1,32)=0.740$
	n.s.

CP 94253 was given 30 min, while SB 216641, sulpiride and idazoxan were given 60 min before the test. *p*-CPA was administered on three consecutive days (at 72, 48 and 24 h) before the test. The values shown are the mean±S.E.M. for $n=8–9$. n.s. means not significant.

[a] $P<0.001$ compared to the respective vehicle+vehicle.

[b] $P<0.001$ compared to the respective vehicle+CP 94253 (Newman–Keuls multiple comparison test).

Table 2
Effects of *p*-chlorophenylalanine (*p*-CPA, 3×300 mg/kg) on the concentrations of serotonin (5-HT) and 5-hydroxyindoleacetic acid (5-HIAA) in the frontal cortex, striatum and brain stem of mice

Treatment	Frontal cortex		Striatum		Brain stem	
	5-HT	5-HIAA	5-HT	5-HIAA	5-HT	5-HIAA
Vehicle	460±30	121±10	233±23	197±21	705±25	314±18
p-CPA	67±8[a]	10±0.6[a]	33±3[a]	16±2[a]	177±15[a]	88±10[a]

p-CPA was injected on three consecutive days (at 72, 48 and 24 h) before the test. The levels of 5-HT and 5-HIAA are given in units of ng/g tissue; the values shown are the mean±S.E.M. for $n=8$.

[a] $P<0.01$ compared to the respective vehicle (Fisher's test).

4. Discussion

In line with our earlier study (Tatarczyńska et al., 2004), the presently described results indicate that the selective 5-HT_{1B} receptor agonist CP 94253 (Koe et al., 1992), at a dose of 5 mg/kg that does not affect the locomotor activity of mice, exerts an antidepressant-like activity in mice by shortening the immobility time in the forced swimming test. To the best of our knowledge, there exist no other data on the effect of selective 5-HT_{1B} receptor agonists in animal models used for detecting antidepressant-like action. The present results clearly demonstrate that the antidepressant-like effect of CP 94253 in the test used depends primarily on stimulation of 5-HT_{1B} receptors. Such a conclusion is based on the finding that the anti-immobility effect of CP 94253 is blocked by the selective 5-HT_{1B} receptor antagonist SB 216641, used at a dose producing effects related to the in vivo blockade of these receptors (Hagan et al., 1997) and not affecting mouse locomotor activity (Tatarczyńska et al., 2004). At the same time, like in our previous study (Tatarczyńska et al., 2004), SB 216641 given alone did not evoke any effect characteristic of antidepressants in the forced swimming test in mice. Direct involvement of other receptors in the effect of CP 94253 should be excluded, as this compound is a selective ligand of 5-HT_{1B} receptors

(Koe et al., 1992). Moreover, SB 216641 shows high affinity for h5-HT_{1B} receptors, approximately 25-fold selectivity over h5-HT_{1D} and little or no affinity for a range of other h5-HT receptors (Price et al., 1997).

As has been mentioned in the Introduction, the shortening of immobility time in the forced swimming test induced by antidepressants depends on the enhancement of central catecholamine and 5-HT neurotransmission (Borsini, 1995; Borsini and Meli, 1990; Porsolt et al., 1977, 1979). CP 94253 causes a decrease in 5-HT release in different brain structures in mice and rats (Adell et al., 2001; Knobelman et al., 2000); thus, it seems, that the anti-immobility effect of this compound does not result from its interaction with terminal 5-HT_{1B} autoreceptors. Most probably, stimulation of 5-HT_{1B} receptors located postsynaptically or as heteroreceptors may be responsible for the effect of CP 94253. The successive results obtained in our experiment demonstrate that the antidepressant-like effect of CP 94253 does not actually require integrity of 5-HT neurons. Indeed, administration of *p*-chlorophenylalanine – which dramatically reduces the concentration of 5-HT and 5-HIAA in mouse frontal cortex, striatum and brain stem – does not modify the effect of CP 94253. It is noteworthy that also the anxiolytic-like (Chojnacka-Wójcik et al., 2005) and the anti-aggressive (de Almeida et al., 2001) effects of CP 94253 do not seem to be connected with 5-HT_{1B} autoreceptors, since they are unaltered by lesions of 5-HT neurons.

We have also found that catecholamine systems play some role in the anti-immobility effect of CP 94253, since it is abolished by the selective dopamine D2-like receptor antagonist sulpiride and the α_2-adrenoceptor antagonist idazoxan, which by themselves do not induce any antidepressant-like effect. It is noteworthy that neither sulpiride nor idazoxan in the doses used modifies spontaneous locomotor activity in mice, hence their antagonism towards CP 94253 in the forced swimming test cannot be attributed to the competing behaviour such as, e.g. locomotor activity. Other data also indicate that a dopaminergic mechanism may be involved in the functional effects of CP 94253. In fact, although CP 94253 does not bind to dopamine receptors (Koe et al., 1992), it increases basal extracellular dopamine concentration in rat prefrontal cortex (Iyer and Bradberry, 1996) and enhances the amphetamine-evoked locomotor hyperactivity under in vivo conditions (Przegaliński et al., 2001). It has been also shown that CP 94253 is devoid of any affinity for adrenergic receptors (Koe et al., 1992); moreover, so far there has been no available information about its effect on noradrenaline level and function in animal brain.

The importance of dopamine and noradrenaline systems for the antidepressant-induced anti-immobility effect has been extensively discussed. Among others, it has been shown that dopamine D2 receptor antagonists including sulpiride abolish the anti-immobility effect of various antidepressants (see Borsini and Meli, 1990), and that the idazoxan-induced α_2-adrenoceptors blockade prevents the antidepressant-like activity of the noradrenaline reuptake inhibitor desipramine (Cervo et al., 1990; Rénéric et al., 2001). On the other hand, idazoxan potentiates the anti-immobility effect evoked by combined administration of desipramine and the selective serotonin reuptake inhibitor fluoxetine or the dual serotonin/noradrenaline reuptake inhibitor milnacipran (Rénéric et al., 2001). It is noteworthy that antagonists of dopamine D2 receptors and α_2-adrenoceptors reduce the anti-immobility effect of 5-HT_{1A} receptor agonists (Cervo et al., 1988; Cervo and Samanin, 1987; Chojnacka-Wójcik et al., 1991).

In conclusion, our results indicate that the antidepressant-like effect of CP 94253 in the forced swimming test in mice is due to stimulation of 5-HT_{1B} receptors, most likely those located postsynaptically and/or as heteroreceptors. Moreover, dopamine and noradrenaline neurotransmission is involved in the anti-immobility effect of this 5-HT_{1B} receptor agonist.

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