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The Role of 5-Hydroxytryptamine$_{1A}$ (5-HT$_{1A}$) Receptors in the Anticonflict Activity of β-Adrenoceptor Antagonists

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PRZEGALIŃSKI, E., M. FILIP, E. CHOJNACKA-WÓJCIK AND E. TATARCZYŃSKA. *The role of 5-hydroxytryptamine$_{1A}$ (5-HT$_{1A}$) receptors in the anticonflict activity of β-adrenoceptor antagonists.* PHARMACOL BIOCHEM BEHAV 47(4) 873–878, 1994.—Using the conflict drinking test as a model, we studied in rats the effect of the nonselective β-adrenoceptor blockers pindolol and cyanopindolol which bind to 5-HT$_{1A}$ and 5-HT$_{1B}$ receptors, and of the selective β_1- and β_2-adrenoceptor antagonists betaxolol and ICI 118,551, respectively, which have a negligible affinity for 5-HT receptors. Both pindolol (2.0–8.0 mg/kg) and cyanopindolol (0.5–2.0 mg/kg) showed an anticonflict effect, having dose dependently increased the number of punished licks. On the other hand, neither betaxolol nor ICI 118,551—administered separately or in combination—affected the punished responding. The anticonflict effects of pindolol and cyanopindolol were completely abolished by the 5-HT$_{1A}$ receptor and α_1-adrenoceptor antagonist 1-(2-methoxyphenyl)-4-[4-(2-phtalimmido)butyl]piperazine (NAN-190), but were not modified by the selective α_{1-}-adrenoceptor antagonist prazosin. The effects of pindolol and cyanopindolol were also not modified in animals with lesions of 5-HT neurons, produced by p-chloroamphetamine (PCA). Moreover, it was also found that the anticonflict effects of pindolol and cyanopindolol in PCA-pretreated rats were antagonized by NAN-190 but not prazosin. Our results indicate that the anticonflict effects of pindolol and cyanopindolol depend on their agonist action on postsynaptic 5-HT$_{1A}$ receptors.

β-Blockers 5-HT$_{1A}$ receptors Anticonflict effect

ANTAGONISTS of β-adrenoceptors have a definite place in the treatment of situation-specific anxiety, being most effective in different stressful conditions, such as public speaking, concert performance, examination stress, etc. (17,28,49). Antianxiety effects of β-blockers, of which propranolol has been most frequently examined, have also been found in different animal models, including conflict tests (10,39,40,45).

Although the mechanism of the anxiolytic activity of propranolol and other β-adrenoceptor blockers is unclear, a peripheral β-blockade has been suggested to be responsible for their effects in patients and in experimental animals (10,32, 45). However, in addition to their adrenergic mechanism, several β-adrenoceptor antagonists have been shown to interact with the central 5-hydroxytryptamine (5-HT) system, which is involved in the modulation of anxiety and in the action of antianxiety drugs (6,23). Specifically, the following arguments indicate that 5-HT mechanisms may participate in the antianxiety effects of β-adrenoceptor antagonists: a) several drugs of this group have a high affinity for some subtypes of 5-HT receptors, particularly 5-HT$_{1A}$ and 5-HT$_{1B}$ ones (21,22); b) drugs acting on 5-HT$_{1A}$ receptors (buspirone, ipsapirone, gepirone) display a potent antianxiety activity (9,46); c) involvement of 5-HT$_{1B}$ receptors has been suggested in the anxiolytic effect of propranolol in an animal model (2); d) interaction with 5-HT$_{1A}$ receptors has been proposed to be responsible for other effects of β-adrenoceptor blockers, e.g., for their inhibitory action on male sexual behaviour (43).

In the present study, using the conflict drinking test (Vogel test) in rats, we compared the effects of β-adrenoceptor blockers (pindolol, cyanopindolol), which have a high affinity for 5-HT$_{1A}$ and 5-HT$_{1B}$ receptors, with the activity of β-adrenoceptor antagonists (betaxolol, ICI 118,551) which do not inter-

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act with these receptors (21). Moreover, the role of 5-HT_{1A} receptors in the anticonflict activity of pindolol and cyanopindolol was also examined.

METHOD

Animals

The experiments were performed on male Wistar rats weighing 180–220 g. The animals were kept at a room temperature of 19–21°C, on a natural day : night cycle (autumn); they were housed under standard laboratory conditions and had free access to food and water before the experiment.

Conflict Drinking Test (Vogel Test)

A modification of the method of Vogel et al. (51) was used. On the first day of the experiment the rats were adapted to a test chamber for 10 min. It was a Plexiglas box (27 × 27 × 50 cm), equipped with a grid floor of stainless steel bars and a drinking bottle containing tap water. After the initial adaptation period the animals were deprived of water for 24 h and were then placed in the test chamber for another 10-min adaptation period during which they had free access to the drinking bottle. Afterwards, they were allowed a 30-min free drinking session in their home cage. After another 24-h water deprivation period the rats were placed again in the test chamber and were allowed to drink for 30 s. Immediately afterwards, drinking attempts were punished with an electric shock (0.5 mA, delivered for 1 s) every 2 s (timed from the moment when a previous shock was delivered). The number of shocks accepted throughout a 5-min experimental session was recorded. The animals were used only once in this test.

Shock Threshold and Free-Drinking Tests

To control the possibility of drug-induced changes in perception of the stimulus, or in the thirst drive which might have contributed to the activity in the conflict drinking test, stimulus threshold measurements and a free-drinking experiment were also conducted. In the shock threshold test and free-drinking test the rats were treated in a manner similar to that described in the conflict drinking test, including two 24-h water deprivation periods separated by 30 min of water availability.

In the shock threshold test, the rats were placed individually in the box, and electric shocks were delivered through the grid floor. The shock threshold was determined stepwise by manually increasing the current (0.1, 0.2, 0.3, 0.4 mA) delivered through the grid floor, until the rat showed an avoiding reaction to the electrical stimulus (jump, jerk, or similar). There was a 15 s shock-free interval between the steps.

In the free-drinking test each animal was allowed to drink from a water spout. Licking was not punished. The total amount of water (ml) consumed during 5 min was recorded for each rat.

The animals were used only once in either test.

Biochemical Determination

The rats were killed by decapitation and their brains were quickly removed and dissected. The hippocampi were immediately frozen on dry ice and stored at −70°C for 5-HT and 5-hydroxyindoleacetic acid (5-HIAA) determinations. The 5-HT and 5-HIAA concentrations in tissue extracts were measured by a high pressure liquid chromatography (HPLC) method as described previously (37).

Drugs

Cyanopindolol (Sandoz), pindolol (Sandoz) and 1-(2-methoxyphenyl)-4-[4-(2-phthalimmido)]butylpiperazine hydrobromide (NAN-190; synthetized by Dr. J. Boksa, Institute of Pharmacology, Polish Academy of Sciences, Kraków) were suspended in a 1% aqueous solution of Tween 80. Betaxolol hydrochloride (Synthelabo), ICI 118,551 hydrochloride (Imperial Chemical Industries PLC) and p-chloroamphetamine hydrobromide (PCA; Regis) were dissolved in saline. Prazosin hydrochloride (Pfizer) was dissolved in distilled water. All the compounds were injected intraperitoneally (IP) in a volume of 4 ml/kg. Betaxolol, cyanopindolol, ICI 118,551 and pindolol were given at 60 min, NAN-190 and prazosin at 90 min, and PCA at 9 and 8 days before the test.

Statistical Analysis

All the data are expressed as the mean ± SEM. A statistical analysis of the each block of results (obtained on the same day) was assessed with separate one-way ANOVA. Specific comparisons were carried out with Dunnett test (when only one drug was given) or by the Newman-Keuls test (when more than one drug was given).

TABLE 1

EFFECTS OF PINDOLOL, CYANOPINDOLOL, BETAXOLOL, AND ICI 118,551 IN THE CONFLICT DRINKING TEST IN RATS

Treatment and Doses (mg/kg)	*n*	Number of Shocks Accepted/5 Min Mean ± SEM	Percent
Control	8	11.9 ± 1.8	100
Pindolol			
(1.0)	7	14.1 ± 1,6	118
(2.0)	7	22.9 ± 3.4*	192
(4.0)	7	32.3 ± 7.2*	271
(8.0)	8	40.1 ± 3.7†	337
Control	8	7.0 ± 0.9	100
Cyanopindolol			
(0.25)	7	9.9 ± 1.3	141
(0.5)	8	12.4 ± 3.2*	177
(1.0)	8	21.6 ± 7.1*	309
(2.0)	8	25.2 ± 4.1†	360
Control	8	11.3 ± 2.7	100
Betaxolol			
(4.0)	7	13.6 ± 2.4	120
(8.0)	8	15.8 ± 2.2	140
Control	8	10.0 ± 2.1	100
ICI 118,551			
(4.0)	8	11.0 ± 2.8	110
(8.0)	7	9.6 ± 3.7	96
Control	8	8.1 ± 1.2	100
Betaxolol (4.0) + ICI 118,551 (4.0)	8	7.8 ± 1.0	95
Betaxolol (8.0) + ICI 118,551 (8.0)	8	9.4 ± 1.5	115

All drugs were administered at 60 min before the test. *n* = Number of rats per group.

*$p < 0.05$, †$p < 0.01$ vs. respective control (Dunnett's test).

TABLE 2

EFFECTS OF PINDOLOL AND CYANOPINDOLOL ON THE SHOCK THRESHOLD AND THE AMOUNT OF WATER CONSUMED IN WATER-DEPRIVED RATS

Treatment and Doses (mg/kg)	n	Shock Threshold (mA)	Water Consumption (ml)
Control	8	0.3 ± 0.03	6.7 ± 1.0
Pindolol			
(2.0)	8	0.3 ± 0.03	6.0 ± 1.3
(4.0)	7	0.3 ± 0.02	7.2 ± 1.3
(8.0)	7	0.4 ± 0.02	8.7 ± 1.0
Control	8	0.3 ± 0.02	8.7 ± 1.3
Cyanopindolol			
(0.5)	7	0.3 ± 0.03	7.9 ± 1.7
(1.0)	8	0.3 ± 0.03	9.3 ± 2.0
(2.0)	8	0.3 ± 0.03	9.0 ± 1.3

All drugs were administered at 60 min before the test.
n = Number of rats per group.

RESULTS

Pindolol (2.0–8.0 mg/kg) and cyanopindolol (0.5–2.0 mg/kg) significantly increased, in a dose-dependent manner, the punished responding in the licking conflict paradigm, the strongest effect having been observed after a dose of 8.0 mg/kg of pindolol and 2.0 mg/kg of cyanopindolol. Betaxolol (4.0–8.0 mg/kg) and ICI 118,551 (4.0–8.0 mg/kg) administered separately or in combination did not produce any significant anticonflict activity (Table 1).

As shown in Table 2, the possibility that the efficacy of pindolol (2.0–8.0 mg/kg) and cyanopindolol (0.5–2.0 mg/kg) is related to the reduced perception of the stimulus or to the increased thirst drive can be excluded, because the two drugs increased neither the threshold current nor the water intake.

The anticonflict effect of pindolol (8.0 mg/kg) and cyanopindolol (2.0 mg/kg) was antagonized by NAN-190 (0.25–0.5 mg/kg), but unaffected by prazosin (0.5 mg/kg) (Table 3). The effect of pindolol (8.0 mg/kg) or cyanopindolol (8.0 mg/kg) was not modified in animals with lesion of 5-HT neurons, produced by PCA (2 × 10.0 mg/kg). Moreover, it was also found that the anticonflict effect of pindolol (8.0 mg/kg) and cyanopindolol (2.0 mg/kg) in PCA-pretreated rats was antagonized by NAN-190 (0.5 mg/kg) but not by prazosin (0.5 mg/kg) (Table 4).

Neither NAN-190 (0.25–0.5 mg/kg) nor prazosin (0.5 mg/kg) affected the punished responding in rats (Table 3). Similarly, neither NAN-190 (0.5 mg/kg) nor prazosin (0.5 mg/kg) were active in PCA-pretreated rats (Table 4).

PCA (2 × 10.0 mg/kg, 9 and 8 days before the killing of animals) reduced the hippocampal concentration of 5-HT and 5-HIAA by ca. 86 and 83%, respectively (absolute values: control—460 ± 139 and 315 ± 115 ng/g, respectively, n = 8; PCA-treated—64.4 ± 17 and 53.3 ± 16 ng/g, respectively, n = 8).

TABLE 3

EFFECTS OF NAN-190 AND PRAZOSIN ON THE ANTICONFLICT ACTION OF PINDOLOL OR CYANOPINDOLOL IN RATS

Treatment and Doses (mg/kg)	n	Number of Shocks Accepted/5 Min Mean ± SEM
Control	8	11.2 ± 1.6
Pindolol (8.0)	8	30.8 ± 2.3*
NAN-190 (0.25) + pindolol (8.0)	7	13.9 ± 3.4†
NAN-190 (0.5) + pindolol (8.0)	7	10.5 ± 2.3†
Prazosin (0.5) + pindolol (8.0)	8	24.9 ± 3.9*
Control	8	10.9 ± 1.8
Cyanopindolol (2.0)	7	32.0 ± 5.2*
NAN-190 (0.25) + cyanopindolol (2.0)	7	17.8 ± 1.9‡
NAN-190 (0.5) + cyanopindolol (2.0)	7	6.9 ± 1.0†
Prazosin (0.5) + cyanopindolol (2.0)	7	34.2 ± 3.3*
Control	8	10.0 ± 1.8
NAN-190 (0.25)	7	11.2 ± 2.0
NAN-190 (0.5)	8	8.4 ± 1.6
Prazosin (0.5)	8	9.4 ± 1.8

NAN-190 or prazosin were administered at 90 min, and pindolol or cyanopindolol at 60 min before the test.
n = Number of rats per group.
*$p < 0.01$ vs. respective control; †$p < 0.01$, ‡$p < 0.05$ vs. pindolol or cyanopindolol (Newman-Keuls test).

DISCUSSION

Our results indicate that the nonselective β-adrenoceptor antagonists pindolol and cyanopindolol exert an anticonflict activity. In fact, both those drugs dose dependently increased

TABLE 4

EFFECTS OF NAN-190 AND PRAZOSIN ON THE ANTICONFLICT ACTION OF PINDOLOL OR CYANOPINDOLOL IN P-CHLORAMPHETAMINE (PCA)-PRETREATED RATS

Treatment and Doses (mg/kg)	n	Number of Shocks Accepted/5 Min Mean ± SEM
Control	8	9.6 ± 2.1
PCA	7	10.5 ± 3.4
PCA + pindolol (8.0)	7	26.7 ± 3.2*
PCA + NAN-190 (0.5) + pindolol (8.0)	7	10.3 ± 2.1†
PCA + prazosin (0.5) + pindolol (8.0)	8	21.7 ± 3.7*
Control	7	9.1 ± 1.2
PCA	7	12.5 ± 3.4
PCA + cyanopindolol (2.0)	8	27.4 ± 5.3*
PCA + NAN-190 (0.5) + cyanopindolol (2.0)	8	12.4 ± 2.9†
PCA + prazosin (0.5) + cyanopindolol (2.0)	7	29.7 ± 3.0*
Control	7	10.6 ± 2.0
PCA	8	14.7 ± 2.9
PCA + NAN-190 (0.5)	7	13.2 ± 1.8
PCA + prazosin (0.5)	7	15.7 ± 3.8

PCA (2 × 10 mg/kg) was given 9 and 8 days before the test, NAN-190 or prazosin were administered at 90 min, and pindolol or cyanopindolol at 60 min before the test.
n = Number of rats per group.
*$p < 0.01$ vs. respective PCA; †$p < 0.05$ vs. PCA + pindolol or PCA + cyanopindolol (Newman-Keuls test).

the number of punished licks in the drinking conflict test in rats. Importantly, the anticonflict effects of pindolol and cyanopindolol seem to be specific, because these drugs—administered in doses effective in the Vogel test—affected neither the shock threshold nor the nonpunished water consumption.

Although no data are available in the literature on the effects of pindolol and cyanopindolol in the conflict animal models, a few experiments have been conducted with other β-adrenoceptor antagonists, particularly propranolol. While early results obtained with the latter drug were negative (31, 38,41), recently some positive effects have been described (10,39,40,45).

As regards the mechanism of the antianxiety action of β-blockers on punished behavior, involvement of peripheral β-blockade has been suggested (10,45). However, such a mechanism does not seem to be responsible for the anticonflict action of pindolol and cyanopindolol, observed in the present study. The main argument is that the two other β-adrenoceptor antagonists examined, betaxolol and ICI 118,551, which are selective blockers of β_1- and β_2-adrenoceptors, respectively (3), did not produce any anticonflict activity when they were administered separately or in combination. Interestingly, the latter observation is in line with clinical data which show that—in contrast to several β-adrenoceptor antagonists (17,28,49), including pindolol (1)—ICI 118,551 has no antianxiety activity in man (26).

On the other hand, our results indicate that the anticonflict effect of pindolol and cyanopindolol may result from activation of 5-HT_{1A} receptors. Actually, pindolol and cyanopindolol have a high affinity for 5-HT_{1A} and 5-HT_{1B}, but not for other subtypes of 5-HT receptors, while the affinity of betaxolol and ICI 118,551 for different subtypes of 5-HT receptors is negligible (21). Moreover, though most results of the functional studies indicate that pindolol and cyanopindolol behave like antagonists of 5-HT_{1A} and 5-HT_{1B} receptors (7,25,29,47), some other data suggest that they may also act as agonists at these receptor sites. In fact, pindolol has been found to reduce the brain 5-HT synthesis rate (19), while cyanopindolol has been reported to inhibit the potassium-evoked release of [^{3}H]5-HT from hippocampal synaptosomes (30), the effects that can be connected with stimulation of 5-HT_{1A} and/or 5-HT_{1B}receptors. Moreover, in the behavioral drug discrimination studies, pindolol has been shown to substitute for eltoprazine or TFMPP (15,52), and the stimulus generalization of pindolol has been suggested to result from its agonistic effect at 5-HT_{1A} and/or 5-HT_{1B} receptors (52).

The conclusion that the anticoflict activity of pindolol and cyanopindolol is due to stimulation of 5-HT_{1A} rather than 5-HT_{1B} receptors is based on our interaction studies with NAN-190, which dose dependently antagonized the effect of these drugs. NAN-190 has a high affinity for 5-HT_{1A}, but not for other subtypes of 5-HT receptors (14), and in the functional in vivo studies it blocks different effects of the 5-HT_{1A} receptor agonist 8-hydroxy-2-(di-n-propylamino)-tetralin (8-OH-DPAT) (14,20,36), but not these of the 5-HT_{1B} receptor agonist TFMPP (13). It should be remembered, however, that apart from 5-HT_{1A} receptors, NAN-190 shows a high affinity for α_1-adrenoceptors (14) and behaves as their antagonist (36). However, the α_1-adrenoceptor blocking activity of NAN-190 does not seem to be important for its antagonism towards the anticonflict effect of pindolol and cyanopindolol, because that response was not affected by the selective α_1-adrenoceptor antagonist prazosin.

In contrast to our conclusion, Audi et al. (2) have recently suggested that the antianxiety effect (in rats exposed to an elevated plus maze) of propranolol injected into the dorsal periaqueductal gray results from the blockade of 5-HT_{1B} autoreceptors. The reason for this discrepancy is difficult to explain, though certain differences between our experimental conditions and those of Audi et al. (2), concerning drugs under investigation (propranolol vs. pindolol and cyanopindolol), route of their administration (intracerebral vs. intraperitoneal), and experimental model (plus maze test vs. Vogel test), should be taken into account.

5-HT_{1A} receptors occur both pre- and postsynaptically, the presynaptic receptors being located on 5-HT cell bodies and/or dendrites of the raphe nuclei, whereas the postsynaptic ones are present in different brain structures and their greatest density is observed in the hippocampus (34,50). Our results suggest that the 5-HT_{1A} receptors that are involved in the anticonfict activity of pindolol and cyanopindolol are located postsynaptically. Such a suggestion is supported by our abovementioned observation that the anticonflict effect of pindolol and cyanopindolol is antagonized by NAN-190, which, in different experimental systems, acts as an antagonist of postsynaptic 5-HT_{1A} receptors, yet shows rather agonistic properties at somatodendritic presynaptic 5-HT_{1A} receptor sites (16,20). Furthermore, we have also observed that the anticonflict effect of pindolol and cyanopindolol was not altered in rats pretreated with PCA, which reduced the concentration of 5-HT and 5-HIAA in the hippocampus by about 85%. Again, the anticonflict effect of pindolol and cyanopindolol in PCA-pretreated animals was antagonized by NAN-190, but not by prazosin.

The shortcoming of our conclusion on the participation of postsynaptic 5-HT_{1A} receptors in the anticonflict activity of pindolol and cyanopindolol—based on the results of their interaction with PCA—is that PCA produces only a partial destruction of the brain 5-HT system, as it destroys axons originating from the dorsal but not median raphe nuclei (33). Moreover, we have observed that PCA itself does not induce the anticonflict effect, though such an effect was described after other 5-HT neurotoxins, such as 5,6-dihydroxy-tryptamine (44) or 5,7-dihydroxytryptamine (48). However, regarding the effect of the latter neurotoxin, negative results were also reported (4,42). Furthermore, our preliminary results from experiments that are now in progress indicate that both pindolol and cyanopindolol exert an anticonflict activity also after local injections into the dorsal hippocampus, an observation arguing in favor of involvement of postsynaptic rather than presynaptic 5-HT_{1A} receptors.

Interestingly, the role of postsynaptic 5-HT_{1A} receptors has recently been suggested in the antianxiety effect of the number of 5-HT_{1A} drugs. Actually, in our previous study we found that the anticonflict effect of ipsapirone was not reduced in rats with PCA-lesioned 5-HT neurons, and that NAN-190 antagonized the effect of ipsapirone under those experimental conditions (5,35). We also observed the anticonflict effect of ipsapirone after its intrahippocampal injection, that effect being antagonized by the local or peripheral administration of NAN-190 (in preparation). Shimizu et al. (42) reported that 5,7-dihydroxytryptamine (5,7-DHT)-induced 5-HT lesions did not alter the effect of tandospirone on the punished responding in the Vogel conflict test. Moreover, Kataoka et al. (24) observed an anticonflict effect of tandospirone administered locally into the hippocampus. Finally, participation of postsynaptic 5-HT_{1A} receptors in the effects of buspirone in other nonconflict models of anxiety has also been suggested (8, 12,27). However, as far as the effects of buspirone, ipsapirone and gepirone in different animal models of anxiety, including

conflict drinking test, are concerned, some evidence pointing to the role of presynaptic 5-HT_{1A} receptors has also been presented (4,11,18).

Summing up, our results suggest that the β-adrenoceptor antagonists pindolol and cyanopindolol act as anticonflict drugs, yet their anticonflict effects are not connected with the β-adrenoceptor blockade. On the other hand, they indicate that the anticonflict activity of these drugs is due to activation of postsynaptic 5-HT_{1A} receptors.

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