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Behavioral Effect of Beta-Blocking Drugs Resulting From the Stimulation or the Blockade of Serotonergic 5-HT_{1B} Receptors

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FRANCES, H., C. MONIER AND M. DEBRAY. *Behavioral effect of beta-blocking drugs resulting from the stimulation or the blockade of serotonergic 5-HT_{1B} receptors.* PHARMACOL BIOCHEM BEHAV **48**(4) 965–969, 1994. – The present study was aimed at determining the relative potency of various beta-blocking drugs as agonists or antagonists at 5-HT_{1B} receptors. The behavioral model used (increase in escape attempts of isolated mice) has been previously shown to be exclusively responsive to 5-HT_{1B} agonists such as 1-3-(trifluoromethyl) phenylpiperazine (TFMPP). Beta-blocking drugs acted in three different ways: they were either inactive, or acted as agonists or as antagonists at 5-HT_{1B} receptors. The specific beta-blocking drugs: atenolol and betaxolol (beta-1) and ICI 118 551 (beta-2) were inactive by themselves and in interaction with TFMPP. The mixed beta-1 beta-2 blocking drug l-penbutolol, (but not *d*-penbutolol), inactive alone, behaved as an antagonist: it impaired in a dose-dependent way the effect of TFMPP. (±)Pindolol and (−)pindolol acted as agonists; (+)pindolol was inactive. None of the (−), (+), or (±)pindolol was able to impair TFMPP effect. The increase in escape attempts induced by (±)pindolol was antagonized with l-penbutolol or after a specific desensitization. Cyanopindolol and S-tertatolol (but not R-tertatolol) acted as agonists. SDZ 21009 was inactive as agonist or antagonist. It may be concluded that all beta-blocking drugs are not equivalent regarding their effect at 5-HT_{1B} receptors. L-penbutolol was the only drug acting as an antagonist.

Beta-blocking drugs Serotonergic 5-HT_{1B} agonist Social isolation Mouse

SINCE the work of Green and Grahame-Smith (11), numerous biochemical (15) or behavioral (4) reports have shown that some beta-blocking drugs act as antagonists at some serotonergic receptors. Recent biochemical results (13) define pindolol, cyanopindolol, and SDZ 21009 as 5-HT_{1B} antagonists. However, the beta-blocking drug pindolol has also been reported to act as an agonist-antagonist at central 5-HT receptors (12). Schoeffter and Hoyer (21) reported that (−)pindolol, (−)propranolol, cyanopindolol, and SDZ 21009 mimic the effect of 5-HT at 5-HT_{1D} receptors which are reported as the functional equivalents in nonrodents of the 5-HT_{1B} receptors in rodents.

To clarify the role of beta-blocking drugs regarding the function of 5-HT_{1B} receptors, a test previously elaborated in this laboratory: the isolation-induced social behavioral deficit, has been used.

A brief isolation period (7 days) alters the behavior of mice. An isolated mouse and a nonisolated mouse observed together under an inverted beaker attempt to escape, but the number of escape attempts of the isolated mouse is half that of the nonisolated one over 2 min of observation. This difference has been called "the isolation-induced social behavioral deficit" (5). This deficit has been explained as an hyperreactivity with a behavioral inhibition (6). The pharmacology of this deficit has been studied. The number of escape attempts of isolated mice was increased up to the level of nonisolated mice only with the serotonergic drugs: RU 24969 (5-methoxy-3(1,2,3,6-tetrahydropyridin-4-yl) 1-H indole), TFMPP, m-CPP and CGS 120 66B. On the contrary, the specific serotonergic 5-HT_{1A} agonist 8-OH-DPAT decreased the number of escape attempts (7). The effect of TFMPP in this model is impaired by neither of the following drugs: ritanserine (5-HT_2 antagonist), mianserine, or cyproheptadine (5-HT_{1C} antagonists), ICS 205 930 (5-HT_3 antagonist), but is antagonized by

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penbutolol (5-HT_{1A} and 5-HT_{1B} antagonist). In the same way, the increase in escape attempts induced by m-CPP, RU 24969, or CGS 120 66B is also antagonized by penbutolol. So, regarding the serotonergic system, these results have led to the proposal that the effect of serotonergic agonists in this model is to affect the behavioral deficit through the stimulation of 5-HT_{1B} receptors (8). In an attempt to exclude false positive, the effect of drugs increasing the locomotor activity through different mechanisms has also been tested on the number of escape attempts of isolated mice. The results (9) show that at doses increasing significantly the locomotor activity, the number of escape attempts was unchanged with atropine and oxolinic acid, reduced with cafeine and amphetamine; it was then concluded that no relation exists between the effect of a drug on locomotor activity on one hand and the isolation-induced social behavioral deficit on the other hand. Taken together, these results strengthen the proposal that 5-HT_{1B} receptors are involved in the TFMPP-induced increase in escape attempts.

Therefore, we proposed that the antagonism of the TFMPP effect in the isolation-induced social behavioral deficit may be a valuable tool for the screening of antagonists of the 5-HT_{1B} receptors. There exists no drug exclusively acting as a 5-HT_{1B} antagonist. The drugs used by biochemists are beta-blocking drugs or metitepine, which antagonizes all but 5-HT_3 and 5-HT_4 subtypes of serotonin receptors (14). The aim of the present experiments was to compare different beta-blocking drugs as potential antagonists of the 5-HT_{1B} receptors implicated in this behavioral model.

METHOD

Animals

Male NMRI mice (20–24 g at the beginning of the experiments) from CERJ, Genest St Isle 53940 (France), were either housed in groups of six in home cages of 30 × 20 × 8 cm or isolated in home cages of 24 × 10 × 8 cm. Mice were 4–5 weeks old at the beginning of isolation. The room was thermostatically maintained at 21 ± 1°C, with a 12L : 12D schedule (lights on from 0800–2000 h). Food and water were freely available. The duration of isolation was 7 days. The weight of the isolated mice did not differ from the weight of the group-housed mice. The isolated mice were allocated to the different drugs or doses at random.

Experimental Procedures

Mice were tested in pairs (one isolated and one nonisolated mouse), under a transparent beaker (height: 14 cm, diameter: 10 cm), inverted on a rough surface glass plate. The number of attempts at escape was counted for the first 2 min of observation. It must be noted that only the performances of the isolated mice were taken into account. The presence of the nonisolated mouse is, however, a necessity because, as described in a previous paper (6), the isolated mouse observed alone has a greater number of escape attempts than the nonisolated mouse observed alone. So, the decrease in escape attempts of the isolated mice observed in pairs with nonisolated mice is a social phenomenon because it requires the presence of another mouse.

An attempt at escape was defined as any one of the following: 1—the two forepaws were leant against the wall of the beaker, 2—the mouse was sniffing, its nose into the spout of the beaker, 3—the mouse was scratching the glass floor. There was no minimal duration for one attempt. For a long-lasting attempt, a new attempt was counted for each period of 3 s [detailed comments about this experimental procedure are indicated in an earlier paper (7)]. All mice were used only once. Behavioral observations were made by an observer blind to the treatments received by the mice.

Drugs were administered intraperitoneally (0.2 ml/20 g body weight) only to the isolated mice. Tests were performed 30 min after the last injection. In the tolerance experiment, RU 24969 was administered on 3 consecutive days, once a day at 5 mg/kg (IP); the test was performed the fourth day. Isolated mice in the control group received demineralized water (0.2 ml/20 g). All experiments were performed during the light phase of the light : dark schedule.

Drugs

The drugs used were: racemic betaxolol HCl (Synthelabo, Paris, France), racemic ICI 118551 (DL-erythro-3-isopropylamino-1-(7-methyl-4-indamyloxy)-2-butanol hydrochloride), ICI, Macclesfield, England), 1- and *d*-penbutolol sulfates (Hoechst, Paris-la-Défense, France), (±)cyanopindolol, (−), (+), (±)pindolol, and SDZ 21 009 (Sandoz, Basle, Switzerland), atenolol (base; Sigma, La Verpillière, France), S- and R-tertatolol HCl (IRIS, Courbevoie, France), 1-3-(trifluoromethyl) phenylpiperazine (TFMPP; Aldrich Chemical Co., Strasbourg, France), 5-methoxy-3 (1,2,3,6-tetrahydropyridin-4-yl) 1-H indole (RU 24969; Roussel-Uclaf, Paris-la-Défense, France).

Statistical Analysis

Results were analysed using a two-way analysis of variance followed by a Bonferroni or a Tukey test; in Fig.1, the Student's *t*-test was used. For Tertatolol (Table 2) a one-way ANOVA followed by a Dunnett test was used.

RESULTS

TFMPP increased the number of escape attempts of isolated mice; different comparative values are shown in the Tables 1 and 2. The effect of TFMPP is highly significant ($p < 0.001$).

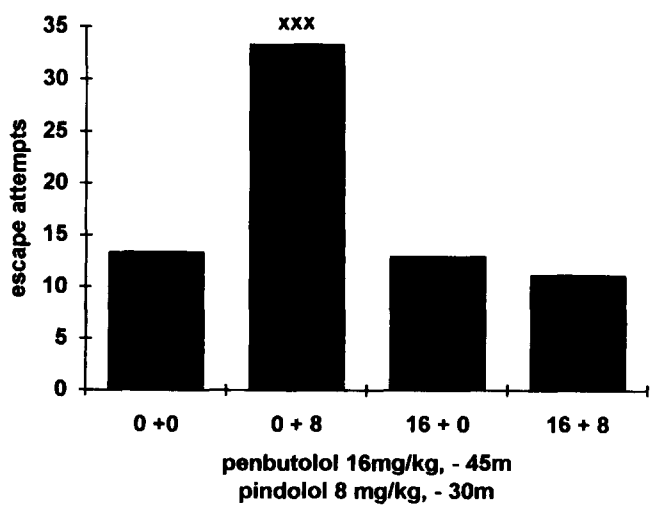

FIG. 1. Antagonism by 1-penbutolol of (±)pindolol-induced increase in escape attempts. Results are the mean number (±SEM) of 10 values in each group. Student's *t*-test: ***$p < 0.001$ (corresponding controls: water ± water).

TABLE 1

EFFECT OF SPECIFIC BETA-BLOCKING DRUGS ALONE AND IN INTERACTION WITH TFMPP ON THE NUMBER OF ESCAPE ATTEMPTS OF ISOLATED MICE

Drugs mg/kg −45 m	TFMPP 2 mg/kg −30 m	*n*	Escape Attempts mean ± SEM
Atenolol			
0	0	10	13.4 ± 3.2
4	0	9	10.9 ± 1.6
16	0	9	12.6 ± 3.3
0	2	9	24.6 ± 4.6
4	2	9	23.3 ± 2.6
16	2	8	28.0 ± 2.5
Betaxolol			
0	0	10	11.2 ± 2.2
1	0	10	14.9 ± 2.9
4	0	10	13.0 ± 2.2
16	0	10	12.5 ± 1.9
0	2	9	28.7 ± 3.8
1	2	9	25.0 ± 2.7
4	2	9	27.0 ± 4.9
16	2	9	23.3 ± 3.6
ICI 118 551			
0	0	10	9.9 ± 2.3
1	0	10	11.6 ± 1.5
4	0	10	10.6 ± 2.7
16	0	10	9.1 ± 2.2
0	2	11	24.3 ± 2.3
1	2	11	20.9 ± 2.4
4	2	12	28.1 ± 4.3
16	2	11	25.2 ± 3.6

Interaction Between Specific Beta-Blocking Drugs and TFMPP (Table 1)

Betaxolol and atenolol, two specific beta-1 adrenergic blocking drugs were administered at the doses of 1, 4, and 16 mg/kg for the former, and 4 and 16 mg/kg for the latter. ICI 118 551, a specific beta-2 adrenergic blocking drug, was studied at the doses of 1, 4, and 16 mg/kg. Statistical analysis for each of these three drugs did not show any significant effect either of the doses or of the interaction.

Interaction Between Nonspecific Beta-Blocking Drugs and TFMPP (Table 2)

1-Penbutolol is a mixed beta-1 beta-2 adrenergic blocking drug. A significant TFMPP by dose interaction was observed ($p < 0.001$) for 1-penbutolol. The Bonferroni test showed that there was no dose effect without TFMPP, but in interaction with TFMPP the number of escape attempts decreased with penbutolol ($p < 0.01$). The dextro-isomer of penbutolol was inactive at the dose of 16 mg/kg.

(±)Pindolol is also a mixed beta-1 beta-2 adrenergic blocking drug. Statistical analysis of the data shows no TFMPP by dose interaction ($p = 0.162$). With the Bonferroni test a marginally significant dose effect without TFMPP is observed ($p = 0.061$). In two other experiments described in Fig. 1 and Table 3 (±)pindolol, at the dose of 8 mg/kg, increased highly significantly the number of escape attempts.

The isomers of pindolol were also studied as well as SDZ 21009. The analysis of variance shows no TFMPP by dose interaction ($p = 0.258$); the Tukey test indicates that (−)pindolol (8 mg/kg) increased significantly itself the number of escape attempts ($p = 0.048$) but that (+)pindolol (8 mg/kg) was inactive. For cyanopindolol, the statistical analysis showed a significant TFMPP by dose interaction ($p < 0.001$). Using the Bonferroni test for pair-wise comparisons, it may be shown that cyanopindolol, when given alone, increases significantly the number of escape attempts of isolated mice ($p < 0.01$) and does not antagonize TFMPP effect.

For tertatolol, the statistical analysis showed a significant drug effect ($p < 0.001$), and Dunnett test showed that only the S-tertatolol differed from the control ($p < 0.01$).

TABLE 2

EFFECT OF NONSPECIFIC BETA-BLOCKING DRUGS ALONE AND IN INTERACTION WITH TFMPP ON THE NUMBER OF ESCAPE ATTEMPTS OF ISOLATED MICE

Drugs mg/kg −45 m	TFMPP 2 mg/kg −30 m	*n*	Escape Attempts mean ± SEM
(±)Pindolol			
0	0	10	16.3 ± 2.5
1	0	10	16.4 ± 2.6
4	0	10	26.0 ± 2.5
8	0	10	25.1 ± 2.7
16	0	10	24.5 ± 1.8
0	2	10	31.0 ± 3.4
1	2	11	24.3 ± 3.7
4	2	11	26.0 ± 3.8
8	2	11	33.9 ± 4.3
16	2	10	27.2 ± 2.7
0	0	11	7.9 ± 1.2
(+)Pindolol 8	0	11	8.5 ± 1.4
(−)Pindolol 8	0	11	25.4 ± 1.9
SDZ 21009 4	0	10	10.7 ± 2.1
0	2	9	23.8 ± 3.7
(+)Pindolol 8	2	10	21.5 ± 3.9
(−)Pindolol 8	2	10	19.3 ± 4.0
SDZ 21009 4	2	10	23.1 ± 3.0
Cyanopindolol			
0	0	13	10.6 ± 1.5
16	0	13	27.5 ± 3.5
0	2	12	28.2 ± 3.2
16	2	13	25.7 ± 2.4
d-Penbutolol			
0	0	11	12.4 ± 2.8
16	0	12	13.6 ± 3.0
0	2	11	32.8 ± 2.9
16	2	9	30.7 ± 4.4
l-Penbutolol			
0	0	11	12.8 ± 1.2
16	0	10	9.9 ± 2.6
0	2	10	27.0 ± 3.2
16	2	10	6.2 ± 2.2
0	0	19	15.7 ± 1.7
R-Tertatolol 16	0	21	13.2 ± 1.4
S-Tertatolol 16	0	19	23.0 ± 2.2

TABLE 3

TOLERANCE TO THE EFFECT OF RU 24969 AND OF (±) PINDOLOL AFTER A SUBCHRONIC TREATMENT WITH RU 24969

Subchronic Treatment mg/kg (×3)	mg/kg −30 m	n	Escape Attempts mean ± SEM	p
0	0	13	15.8 ± 1.6	
0	(±) pindolol 8	11	33.4 ± 4.0	<0.001 (a)
0	RU 24969 2	20	28.5 ± 3.4	<0.01 (a)
RU 24969 5	0	11	15.5 ± 2.0	NS (a)
RU 24969 5	(±) pindolol 8	12	19.0 ± 3.5	NS (b)
RU 24969 5	RU 24969 2	20	14.7 ± 2.4	NS (b)

n = Number of values.

(a) Corresponding controls: water + water; (b) corresponding controls: RU 24969 + water.

Mechanism of Action of (±)Pindolol

Interaction between (±)pindolol and 1-penbutolol. An interaction has been studied between (±)pindolol and 1-penbutolol, the former drug being administered 30 min and the latter drug 45 min before the test. The results (Fig. 1) show that the increase in escape attempts induced by (±)pindolol was completely abolished after a pretreatment with 1-penbutolol.

Cross-tolerance to (±)pindolol (Table 3). Because 5-HT_{1B} receptors may be desensitized, the following experiment was performed to see whether (±)pindolol would increase the number of escape attempts after a desensitization of the 5-HT_{1B} receptors. RU 24969 (5 mg/kg) was given once a day, 3 days, and the test performed the fourth day. Control animals received water according to the same schedule. The results show that (±)pindolol increased, as RU 24969, the number of escape attempts and that the subchronic treatment with RU 24969 makes the effect of the test dose of RU 24969 or of (±)pindolol to disappear.

DISCUSSION

These results clearly show that all beta-blocking drugs are not equivalent regarding the stimulation or the blockade of the 5-HT_{1B} receptors.

The specific beta-1 blocking drugs, betaxolol and atenolol, and the specific beta-2 blocking drug, ICI 118 551, did not block the effect of TFMPP. This result confirms previous reports because it has been shown that some behavioral, physiological, and in vitro biochemical changes considered to be elicited via 5-HT receptor stimulation could be antagonized by the nonselective beta-adrenoceptor blocking agents—(−)propanolol, (−)alprenol, and (−)pindolol—but could not be antagonized by their dextro-isomer as well as by the selective beta-1 (betaxolol) and beta-2 (ICI 118551) beta-blocking drugs [for review, see (12)].

The nonspecific beta-blocking drug, penbutolol, has been reported to be a 5-HT_{1A} antagonist because it antagonized some behavioral effects of 8-OH-DPAT and a 5-HT_{1B} antagonist because it impaired RU 24969-induced increase in locomotor activity (1). In our model, the levo isomer, 1-penbutolol, behaved as an antagonist, whereas the dextro-isomer, *d*-penbutolol, was devoid of any activity.

Pindolol has been reported to act as an antagonist or as an agonist of 5-HT_1 receptors, depending on the models. (−)Pindolol acted as antagonist of 5-HT_{1A} receptors because it blocks 8-OH-DPAT-induced flat body posture and forepaw treading in rats (22). In the same way, (−)pindolol impaired, in rats, the 8-OH-DPAT-induced hypothermia (17). (−)Pindolol and (±)cyanopindolol antagonized the 5-HT-induced blockade of ^{3}(H) 5-HT release from superfused rat frontal cortex slices (16). Callaway and Geyer (2) and Callaway et al. (3) showed that the increase in locomotor activity induced by MDMA depends on stimulation of 5-HT_{1B} receptors because it disappears after chronic treatment with RU 24969 and also that this effect of MDMA was antagonized with pindolol. According to Moore et al. (18), pindolol may be an agonist-antagonist regarding 5-HT_{1A} receptors because it blocks the 8-OH-DPAT-induced lower lip retraction but induces, by itself, without 8-OH-DPAT, the same behavioral effect.

Similarly, Hjorth and Carlsson (12) reported that (−)pindolol decreased the rat brain 5-HT synthesis rate behaving as an agonist at 5-HT receptors. For Ybema et al. (23), pindolol acted as a serotonergic agonist because the rats did not discriminate between the serotonergic agonists TFMPP, RU 24969, 8-OH-DPAT, and pindolol. Cyanopindolol behaves as a serotonergic 5-HT_{1D} agonist, inhibiting the K^+-evoked release of ^{3}(H) 5-HT from guinea pig cortex slices (20). In binding experiments, Schoeffter and Hoyer (21) showed that (−)pindolol, cyanopindolol, and SDZ 21009 behaved as agonists of 5-HT_{1D} receptors and also as antagonists of 5-HT_{1B} receptors.

In our hands, pindolol acted as an agonist at the serotonergic receptors involved in the isolation-induced social behavioral deficit. We reasoned that if pindolol was acting through the stimulation of the same receptors as TFMPP did, so its effects might be impaired by the same treatment that are active to impair TFMPP effect. To verify this hypothesis, two experiments were conducted. In the first one, 1-penbutolol was able to antagonize (±)pindolol increase in escape attempts as it impairs the same TFMPP effect. In the second one, a subchronic treatment (3 days) with RU 24969 was used. This protocol has been previously reported to induce a tolerance to the effect of serotonergic 5-HT_{1B} agonists (19,10). This subchronic treatment with RU 24969 makes the effect of RU 24969, but also that of (±)pindolol, to disappear. So, the convergence of the three elements: a) (−) and (±)pindolol show the same effect as TFMPP, b) (±)pindolol and TFMPP effects are antagonized by the same beta-blocking drug (penbutolol), c) the same subchronic treatment with RU

24969 makes the effect of (±)pindolol, like that of RU 24969 to disappear, renders highly likely the fact that TFMPP and (−) or (±)pindolol increase the number of escape attempts through the stimulation of the same receptors. Two other beta-blocking drugs—S-tertatolol and cyanopindolol—behaved also as serotonergic agonists in our model. The lack of activity of SDZ 21009 was unexpected because this drug has the higher affinity for 5-HT_{1B} receptors (13). There are multiple possible explanations, such as a poor crossing through the blood-brain barrier, an inadequate dose range, or schedule of treatment or a rapid metabolization.

Most of the beta-blocking drugs studied behaved as agonists in our model; these results raise the question: which drugs apart from penbutolol, are really 5-HT_{1B} receptor-blocking drugs in the mouse? The opposite effects of pindolol, according to the models, may arise from it being an agonist-antagonist at central 5-HT receptors, as asked by Hjorth and Carlsson (12).

It is suggested that the different models responsive to 5-HT_{1B} agonists may be compared regarding their potentially different responsiveness to the beta-blocking drugs penbutolol and pindolol. Such a comparison would, perhaps, permit the discrimination of subtypes of the 5-HT_{1B} receptors.

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