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Involvement of 5-HT_{1A} Receptors in the Anxiolytic Action of S 14671 in the Pigeon Conflict Test

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SCHREIBER, R., M. BROCCO, B. LEFEBVRE DE LADONCHAMPS AND M. J. MILLAN. *Involvement of 5-HT_{1A} receptors in the anxiolytic action of S 14671 in the pigeon conflict test.* PHARMACOL BIOCHEM BEHAV **51**(2/3) 211-215, 1995. – In the pigeon conflict test of anxiety, the novel, high efficacy 5-HT_{1A} receptor ligand, S 14671, very potently [minimal effective dose (MED): 0.0025 mg/kg, IM] and markedly (maximal percentage increase relative to control: 17232%) increased punished responding. In analogy, its structural analogue, the 5-HT_{1A} receptor agonist, S 14506, equipotently, though less markedly, augmented punished responding (MED: 0.0025 mg/kg; maximal effect: 5557%). In contrast, the arylpiperazine 5-HT_{1A} receptor agonists, LY 165,163 and tandospirone, increased punished responding only at higher doses (MED: 0.16 and 0.63 mg/kg, respectively), and also with a lesser maximal effect (2065% and 3695%, respectively). Although S 14671 and S 14506 showed a 16-fold separation between doses, increasing punished and decreasing unpunished responding, respectively, this separation was only fourfold for LY 165,163 and tandospirone. The anticonflict activity of S 14671 (0.01 mg/kg) was significantly antagonised by the 5-HT_{1A} receptor antagonist, (−)-alprenolol (10 mg/kg), but not by combined treatment with the selective β_1 receptor antagonist, betaxolol, and the selective β_2 receptor antagonist, ICI 118,551. Further, a correlation analysis across each of the above agonists, as well as 8-OH-DPAT, buspirone, and (+)-flesinoxan, revealed a significant correlation for their relative potency in augmenting punished responding and their affinity for 5-HT_{1A} receptors in vitro ($r = +0.95$, $p < 0.001$). It is concluded that S 14671 is an exceptionally potent and efficacious ligand in the pigeon conflict test and that its anxiolytic action reflects the activation of 5-HT_{1A} receptors.

5-HT_{1A} receptor Anxiety Pigeon conflict S 14506 S 14671

IN COMPARISON to conflict procedures in rodents, the pigeon conflict test is particularly sensitive to the anxiolytic effects of "first-generation" 5-HT_{1A} receptor agonists such as buspirone, ipsapirone, and gepirone (2), as well as more recently described 5-HT_{1A} receptor ligands like (+)-flesinoxan and WY-50,324 (3,4). In view of the pronounced activity of the majority of 5-HT_{1A} receptor ligands at other 5-HT receptor types, as well as at dopaminergic and adrenergic receptors (26), it is important to evaluate whether 5-HT_{1A} receptors genuinely mediate the anxiolytic effects of 5-HT_{1A} receptor agonists.

One line of evidence that has been advanced to support an involvement of 5-HT_{1A} receptors is the ability of 5-HT_{1A} receptor agonists to reduce CSF levels of 5-HIAA in pigeons at doses corresponding to those increasing punished responding (15). However, although in certain rodent models of anxiety, an inhibition of serotoninergic neurotransmission may underlie the anxiolytic effects of 5-HT_{1A} receptor agonists (22,23), both pre- and postsynaptic 5-HT_{1A} receptors may be involved in the anticonflict effects of 5-HT_{1A} receptor agonists in the pigeon (2). A second argument in favour of a role for 5-HT_{1A} receptors is the observation that the 5-HT_{1A} receptor antagonist, NAN-190, reduced the anticonflict effects of the prototypical 5-HT_{1A} receptor agonist, 8-OH-DPAT (1). However, NAN-190 also possesses highly potent antagonist activity at α_1 adrenoceptors [e.g., (6)] and, in view of previous evidence for functional interactions amongst 5-HT_{1A} receptors and α_1 adrenoceptors (26), this property might be involved in its influence upon the action of 8-OH-DPAT. In addition,

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though a further 5-HT_{1A} receptor antagonist, BMY 7378, partially inhibited the anxiolytic action of 8-OH-DPAT (1), this action was not specific because it enhanced the rate-decreasing action of 8-OH-DPAT against nonpunished responding—probably owing to its marked antagonist activity at D_2 receptors. Nevertheless, additional evidence in support of a role of 5-HT_{1A} receptors comes from a recent study with the 5-HT_{1A} receptor antagonist possessing β-receptor antagonist properties, (−)-alprenolol, which inhibited the anxiolytic action of the high efficacy, methoxynaphtylpiperazine 5-HT_{1A} receptor agonist, S14506 (7).

We have recently described a structural analogue of S 14506, S 14671, which possesses very high affinity for 5-HT_{1A} receptors and which acts as a highly potent and high-efficacy agonist both at postsynaptic 5-HT_{1A} receptors and at 5-HT_{1A} autoreceptors in inducing, for example, spontaneous tail-flicks, hypothermia, and corticosterone secretion, and in reducing the firing rate of raphe neurones (19). In such models, the actions of S 14671 are antagonized by (−)-alprenolol (19). Thus, in the present study, we evaluated the potential anxiolytic properties of S 14671 in the pigeon and specifically examined the question as to the possible involvement of 5-HT_{1A} receptors in the mediation of its actions. Two complementary approaches were employed. First, the in vitro affinity of S 14671 and other 5-HT_{1A} receptor ligands at 5-HT_{1A} receptors was compared to their potency in modifying punished and unpunished responding. Second, the influence of (−)-alprenolol on the anticonflict activity of S 14671 was determined. In addition, it was verified whether the potent β-receptor antagonist properties of (−)-alprenolol contribute to its behavioural effects by testing the selective β_1-receptor antagonist, betaxolol, and the selective β_2-receptor antagonist, ICI 118,551.

METHOD

Animals

Carneaux pigeons of either sex (Grozek, Lewarde, France), weighing 500–600 g, were housed individually in a laminar flow unit (nominal conditions: 21 ± 1°C, relative humidity 60 ± 5%). The pigeons were maintained under a 12L : 12D cycle (light on at 0700 h), with restricted access to food.

Procedure

The procedure was essentially as described by Brocco et al. (3). Briefly, pigeons were trained in operant chambers to peck an illuminated (green or red) key for food. Every 30th reponse made during illumination of the green key produced access to food, whereas every 30th response made during illumination of the red key produced both food and electric shock to the groin. Sessions were terminated after five cycles of alternating components and lasted 30 min in all. After stabilization of performance (4–6 months), the pigeons were tested in a repeated-measures design employing an interval of minimally 48 h between two test sessions. Agonists were injected intramuscularly (IM, 1 ml/kg) 5 min prior to the session. In antagonism studies, agonists and antagonists were simultaneously injected 60 min before testing. For each pigeon, response rate during the unpunished (green) and punished (red) components of test sessions was expressed as a percentage of its own control rates during the previous saline session.

Binding

Brains of decapitated rats (male Wistar, 240–260 g) were dissected on ice to yield the hippocampus. The radioligand employed, [^{3}H]-8-OH-DPAT (1.0 nM), possesses a specific activity of 220 Ci/mmol. Specific binding was determined employing 10 M 5-HT [for further details concerning the binding assay, see (19)].

Drugs

Drugs were dissolved in sterile water, with the addition of a few drops of lactic acid, if necessary. For all solutions, pH was adjusted to 6.5. Doses are expressed in terms of the base. Drug salts were as follows: (−)-alprenolol *d*-tartate, LY 165,163 {1-[2-(4-aminophenyl)ethyl]-4-(3-trifluoromethylphenyl)-piperazine HCl}, S 14506 {1-[2-(4-fluorobenzoylamino)-ethyl]-4-(7-methoxynaphthyl)piperazine HCl}, and S 14671 {1-[2-(2-thenoylamino)ethyl]-4[1-(7-methoxynaphthyl]piperazine HCl}.

Statistics

For each treatment, the total number of responses obtained in the test session was compared to that recorded from the same animals on the preceding control session using the permutation test for paired replicates (24). A two-tailed test was used to analyse treatment effects on unpunished responding and punished responding. Probability levels of 5.0% were considered as statistically significant.

RESULTS

5-HT_{1A} Receptor Agonists

The 5-HT_{1A} receptor ligand, S 14671, potently and markedly increased punished responding (MED: 0.0025 mg/kg; maximal percentage increase relative to control: 17232%) (Fig. 1). Likewise, its structural analogue, the 5-HT_{1A} receptor agonist, S 14506, potently increased punished responding (MED: 0.0025 mg/kg; maximal effect: 5557%). Furthermore, significant anticonflict effects were obtained with the 5-HT_{1A} receptor agonists, LY 165,163 and tandospirone (MED: 0.16 and 0.63 mg/kg; maximal effect: 2065% and 3695%, respectively). Compared to S 14671 and S 14506, the anxiolytic effects induced by LY 165,163 and tandospirone were less marked, and were observed over a smaller dose range and at higher doses. Decreases of unpunished responding occurred at doses approximately fourfold higher than those that increased punished responding, except for S 14671 and S 14506, which reduced unpunished responding at 16-fold higher doses.

Correlation Studies

The relative potencies of the 5-HT_{1A} receptor ligands, S 14671, S 14506, 8-OH-DPAT, (+)-flesinoxan, LY 165,163, buspirone, and tandospirone for increasing punished responding correlated significantly with their affinity at rat hippocampal 5-HT_{1A} receptors ($r = +0.95$, $p < 0.001$) (Fig. 2). [We have previously published the behavioural data for 8-OH-DPAT, buspirone, and (+)-flesinoxan (7).] A similar correlation was found for their effects on unpunished responding ($r = +0.84$, $p < 0.05$; data not shown).

Antagonist Studies

The 5-HT_{1A} receptor antagonist, (−)-alprenolol (10 mg/kg), did not significantly modify punished responding when tested alone, whereas it significantly antagonised the anticonflict effect of S14671 (0.01 mg/kg) (Fig. 3). Further, unpunished responding was not modified by treatment with either S 14671 or (−)-alprenolol alone, nor by their combined injec-

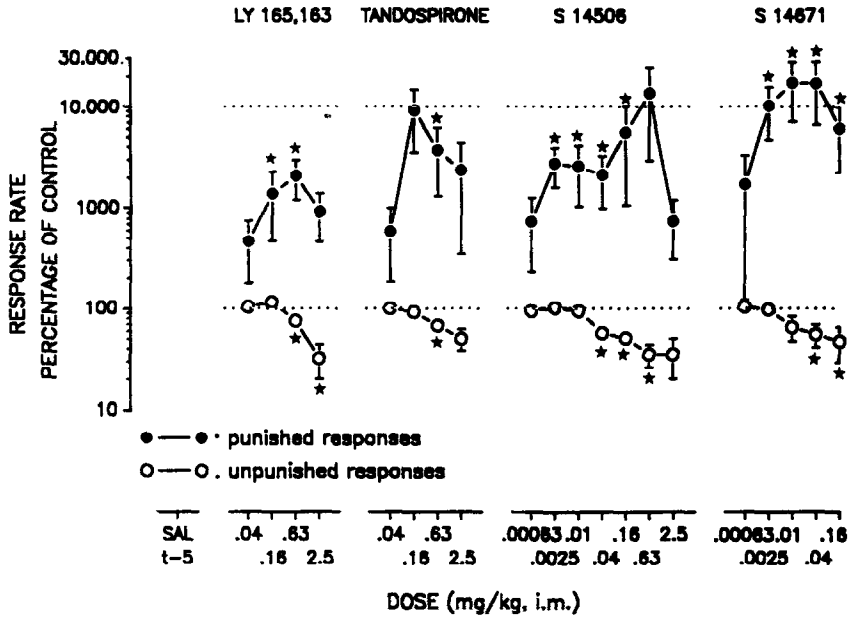

FIG. 1. Actions of 5-HT$_{1A}$ receptor ligands in the pigeon conflict test. Agonist actions were evaluated in seven to nine animals, 5 min following IM administration. Percentage responding as compared to the preceding control session of the same animals are shown. Asterisks indicate significance of differences ($p < 0.05$) to respective control values using the permutation test for paired replicates. The lower and upper values of the means ± SEM for unpunished and punished responding during the preceding control sessions are: 1711 ± 259/1950 ± 291 and 2 ± 1/4 ± 2, for LY 165,163; 1835 ± 134/2038 ± 209 and 6 ± 7/9 ± 9, for tandospirone; 1785 ± 278/2164 ± 94 and 5 ± 2/15 ± 8, for S 14506; and 1605 ± 207/1699 ± 203 and 9 ± 4/27 ± 10, for S 14671.

tion. Combined treatment with the selective β_1-receptor antagonist, betaxolol, and the selective β_2-receptor antagonist, ICI 118,551 (both at 2.5 mg/kg, IM), did not affect the activity of S 14671 (0.01 mg/kg, IM) [punished responding ± SEM (control values, significance vs. control values): 1180 ± 288 (1559 ± 203, $p > 0.05$), punished responding: 36 ± 14 (0 ± 0, $p < 0.05$, $n = 8$)].

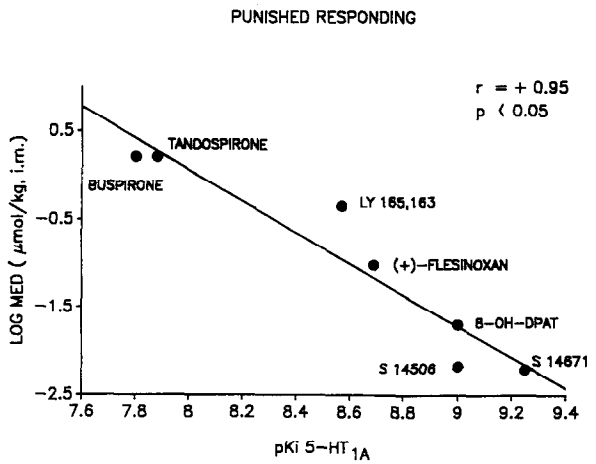

FIG. 2. Correlation analysis of the anticonflict activity of 5-HT$_{1A}$ receptor ligands and their affinity for 5-HT$_{1A}$ receptors. Drug doses are expressed in micromol per kilogram of the MED for increase of punished and unpunished responding. Drug affinities are in pKi.

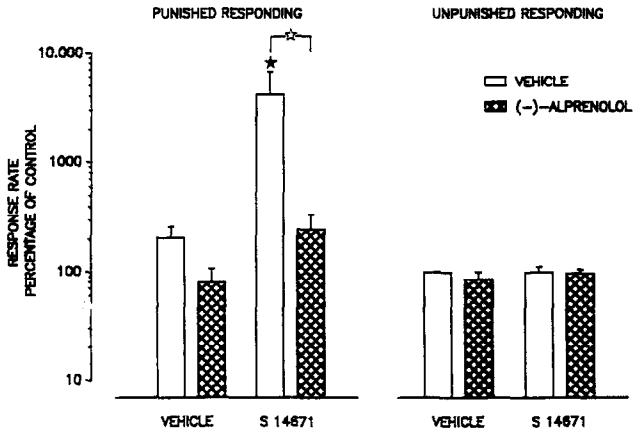

FIG. 3. Antagonism of the anti-conflict effects of S 14671 by (−)-alprenolol. (−)-Alprenolol (10 mg/kg) and S 14671 (0.01 mg/kg) were given simultaneously 60 min before test. Percentages responding as compared to the preceding control session of the same animals are shown. The black star indicates the significant difference ($p < 0.05$) between the vehicle × vehicle and the vehicle × S 14671 treated groups, whereas the white star indicates the significant difference between the vehicle × S 14671 and (−)-alprenolol × S 14671 treated groups employing the permutation test for paired replicates. Drugs were tested in eight to nine animals and the values ± SEM for punished and unpunished responding during the preceding control sessions were: 3.7 ± 1.9 and 1637 ± 215 (vehicle × vehicle); 11 ± 4.0 and 1689 ± 254 [vehicle × (−)-alprenolol]; 5 ± 4 and 1771 ± 246 (S 14671 × vehicle), and 3 ± 2 and 1727 ± 231 [S 14671 × (−)-alprenolol].

DISCUSSION

The present study demonstrates that the novel, methoxynaphtylpiperazine 5-HT_{1A} receptor agonist, S 14671, is a more potent and efficacious in the pigeon conflict test than the 5-HT_{1A} receptor agonists, LY 165,163 and tandospirone. The high separation found between the doses at which S 14671 increased punished responding and decreased unpunished responding may be of clinical pertinence and, interestingly, a comparable dissociation was found with the methoxynaphthylpiperazine derivative, S 14506. The effects of this agonist were, in contrast to a previous study involving an injection-test interval of 60 min (7), characterized 5 min after injection. The latter interval is the same as that employed for the other ligands, which allows for a more rigorous consideration of its relative activity. The remarkable potency and efficacy of S 14671 is consistent with previous in vivo studies in rodents in which the effects of S 14671 were compared to those of other 5-HT_{1A} receptor agonists (19) and, although the modest antagonist activity of S 14671 at 5-$HT_{2A/2C}$ receptors might contribute to its in vivo actions (see below), the precise reasons underlying its extraordinary potency and efficacy still remain to be explored.

The anxiolytic activity demonstrated herein for the 5-HT_{1A} receptor agonist, tandospirone, extends previous findings obtained in both pigeon and rat models of anxiety (10,14,21). The structurally related, halogenated arylpiperazine 5-HT_{1A} receptor agonist, LY 165,163 (11), also increased punished responding, thereby extending the group of arylpiperazine 5-HT_{1A} receptor agonists for which anxiolytic activity has been established (2,9). Although the present results suggest that, in analogy to the pyrimidinylpiperazines buspirone, ipsapirone, and gepirone (8), both tandospirone and LY 165,163 might display anxiolytic activity in man, their potential clinical efficacy remains to be evaluated.

Two major lines of evidence support the involvement of 5-HT_{1A} receptors in the anticonflict effects of S 14671. First, the potency of 5-HT_{1A} receptor agonists in increasing punished responding correlated strongly with their potency in displacing [^{3}H]-8-OH-DPAT from rat hippocampal 5-HT_{1A} sites, confirming and extending findings obtained with cerebral 5-HT_{1A} sites of the pigeon (2). A comparison of the affinity of 5-HT_{1A} receptor ligands in the rat and their behavioural effects in the pigeon is not likely to be confounded by species differences, because the characteristics of [^{3}H]-8-OH-DPAT binding in pigeon cerebrum and rat hippocampal membranes are very similar (28). Second, the 5-HT_{1A} receptor antagonist possessing potent β-receptor antagonist properties, (−)-alprenolol, antagonised the anticonflict effects of S 14671 (Fig. 3) and S 14506 (7). The finding that combined injection of the selective β_1-receptor antagonist, betaxolol, and the selective β_2-receptor antagonist, ICI 118,551, failed to block the S 14671-induced increase of punished responding suggests that the β-antagonist properties of (−)-alprenolol did not contribute to its pattern of action. Complete antagonism of the anticonflict activity of a 5-HT_{1A} receptor agonist was also obtained against 8-OH-DPAT with the 5-HT_{1A} receptor antagonist, NAN-190, which possesses marked α_1-adrenoceptor antagonist activity (1). Under similar conditions, the nonselective 5-HT_{1A} antagonist, BMY 7378, slightly increased punished responding and achieved only partial antagonism of the effect of 8-OH-DPAT (1), possibly owing to its D_2 antagonist and rate-decreasing properties. Nevertheless, the comparable effects of the 5-HT_{1A} receptor antagonists, (−)-alprenolol, NAN-190, and BMY 7378, collectively provide compelling evidence in favour of the involvement of 5-HT_{1A} receptors in the anxiolytic activity of 5-HT_{1A} agonists in the pigeon, because their common pharmacological property is antagonist activity at 5-HT_{1A} receptors.

Notwithstanding the evidence for a key role of 5-HT_{1A} receptors, several observations suggest that other receptors might also be involved in the anticonflict effects of 5-HT_{1A} receptor ligands. First, in addition to their high efficacy agonist activity at pre- and postsynaptic 5-HT_{1A} receptors, S 14506 and S 14671 display antagonist properties at 5-$HT_{2A/2C}$ receptors (7,19). As discussed elsewhere (17), 5-$HT_{2A/2C}$ receptors may act permissively in potentiating the 5-HT_{1A} agonist-mediated actions of S 14506 and S 14671. Indeed, this hypothesis is supported by the observation that the 5-$HT_{2A/2C}$ receptor antagonist, ritanserin, and the α_1/5-HT_{2A} receptor antagonist, ketanserin, slightly increase punished responding in the pigeon (5,13). In addition, the 5-HT_{1A}/5-$HT_{2A/2C}$ receptor ligand, WY-50,324, induced a more marked anticonflict effect in the pigeon than the 5-HT_{1A} receptor ligands, WY-47,846 and WY-48,723 (3). Second, it could be suggested that the dopaminergic activity of some 5-HT_{1A} receptor agonists might be involved in their anticonflict effects. However, in this case, it would not be predicted that 5-HT_{1A} receptor agonists with in vivo antagonist activity at dopaminergic receptors—such as buspirone (16) and LY 165,163(18)—and those with in vivo agonist activity at these receptors—such as 8-OH-DPAT (12)—would affect punished responding in the same direction. Moreover, dopamine antagonists and agonists such as haloperidol and apomorphine [(7) and unpublished results] fail to affect punished responding or to modify buspirone-induced anticonflict effects (27). Therefore, if dopaminergic receptors are involved in the effects of 5-HT_{1A} receptor agonists, it seems more likely that they act, in analogy to the putative role of 5-$HT_{2A/2C}$ receptors, *permissively* in potentating the actions expressed ultimately via 5-HT_{1A} receptors.

In conclusion, although an antagonism of 5-HT_{2A} and/or 5-HT_{2C} receptors may play a facilitatory role, it appears that the potent and marked anxiolytic action of S 14671 is predominantly mediated by 5-HT_{1A} receptors. This compound will therefore make a useful experimental tool, although clinical development is not currently envisaged. Finally, the present data suggest that 5-HT_{1A} receptors play a major role in the anxiolytic effects of 5-HT_{1A} receptor ligands in the pigeon conflict test.

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