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ORIGINAL INVESTIGATION

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Blockade of the antidepressant-like effects of 8-OH-DPAT, buspirone and desipramine in the rat forced swim test by $5HT_{1A}$ receptor antagonists

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Abstract This study examined whether the antidepressant-like effect of serotonin $(5\text{-HT})_{1A}$ receptor agonists in the forced swim test (FST) is mediated by 5-HT_{1A} receptors. The 5-HT_{1A} receptor agonists 8-hydroxy-2-(di-*n*-propylamino) tetralin (8-OH-DPAT) and buspirone decreased immobility in the FST. The effect of 8-OH-DPAT was blocked by the 5-HT_{1A} receptor antagonists NAN 190, BMY 7378 and pindolol. The effect of buspirone was blocked by NAN 190 and pindolol. The antagonists produced no effects on their own. The norepinephrine (NE) uptake inhibitor desipramine (DMI) also reduced immobility, and this was also blocked by NAN 190, BMY 7378 and pindolol. The α_1, β_1 and β_2 adrenergic antagonists prazosin, betaxolol and ICI 118,551 did not block either 8-OH-DPAT or DMI, and produced no effects on their own. These results provide evidence that the antidepressant-like effects of 5-HT_{1A} receptor agonists in the FST are mediated through 5-HT_{1A} receptors, probably located postsynaptically. The finding that the 5-HT_{1A} receptor antagonists blocked the effect of DMI suggests that the NE and 5-HT systems interact in the FST.

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Introduction

The forced swim test (FST) is a behavioral test developed to predict the efficacy of antidepressant treatments (Porsolt et al. 1977, 1978; Porsolt 1981). The test consists of placing a rodent in a tank of water for a 15-min "pretest", and then returning the animal to the water 24 h later for a 5-min "test". Rats respond vigorously during the early part of the test, but then display little motor activity during later portions of the test period, which Porsolt termed immobility. If antidepressant drugs are administered between the pretest and test periods, the rats are more active, i.e. less "immobile", in the test. The FST is an attractive test for antidepressant drugs because it is sensitive and specific. All of the major classes of antidepressant reduce immobility time in the FST (see Borsini and Meli 1988, for review), including tricyclic antidepressants (e.g. imipramine and desipramine), monoamine oxidase inhibitors (e.g., tranylcypromine and clorgyline), and many atypical antidepressants (e.g. iprindole, mianserin and nomifensine). Although 5-HT uptake inhibitors have sometimes failed to produce positive effects in the FST (Porsolt and Lenegre 1992), several studies have demonstrated their effectiveness (Cervo et al. 1991; Detke et al. in press). Few other classes of psychoactive drugs elicit similar effects in the FST.

Several compounds with high affinity for 5-HT_{1A} receptors have been shown to decrease immobility in the FST. For example, the selective 5-HT_{1A} agonist 8-hydroxy-2-(di-*n*-propylamino) tetralin (8-OH-DPAT; Middlemiss and Fozard 1983) has been shown to reduce the immobility of rats in the FST (e.g. Cervo and Samanin 1987b; Cervo et al. 1988a; Tatarczynska

and Chojnacka-Wojcik 1989; Wieland and Lucki 1990; Kostowski et al. 1992). In addition, the azapirones (e.g. buspirone, gepirone, ipsapirone), another class of compounds which are 5-HT_{1A} receptor agonists (Peroutka 1985), have been shown to decrease immobility in the FST (Wieland and Lucki 1990; Chojnacka-Wojcik et al. 1991). The effects of 5-HT_{1A} receptor agonists in the FST are not caused by nonspecific increases in motor activity (Wieland and Lucki 1990). These, and other behavioral studies in animals (for review, see Lucki et al. 1994) agree with recent demonstrations of the clinical efficacy of the 5-HT_{1A} receptor agonists buspirone (Robinson et al. 1990; Rickels et al. 1991) and gepirone (Amsterdam et al. 1987) in treating depression in human patients.

It has been assumed that the 5-HT_{1A} receptor agonists which decrease immobility in the FST are doing so by acting at the 5-HT_{1A} receptor, but there has been little direct evidence that this is indeed the case. Recently, several compounds have been developed that appear to be antagonists at 5-HT_{1A} receptors, such as BMY 7378 (Yocca et al. 1987) or NAN 190 (Glennon et al. 1989). Chojnacka-Wojcik et al. (1991) showed that the reduction of immobility produced by gepirone was blocked by the 5-HT_{1A} receptor antagonists NAN 190 and pindolol. However, they did not examine the effects of antagonists given alone, to evaluate whether the apparent blockade might have been due to simple additive effects. In addition, some of these antagonists have not been examined in combination with other antidepressant drugs which decrease immobility, but are not thought to have an effect on serotonergic systems.

The present study was designed to determine whether the antidepressant-like effect of 5-HT_{1A} receptor agonists in the FST is mediated by 5-HT_{1A} receptors. Because specific 5-HT_{1A} receptor antagonists were not generally available, three compounds were chosen which share the ability to block 5-HT_{1A} receptors: NAN 190, BMY 7378, and pindolol. NAN 190 is an arylpiperazine derivative which has high affinity for the 5-HT_{1A} receptor and has been shown to act as a 5-HT_{1A} antagonist in vivo (Glennon et al. 1988, 1989; Hjorth and Sharp 1990; Chojnacka-Wojcik et al. 1991). However, it also has high affinity for the α_1-adrenergic receptor (Glennon et al. 1988). BMY 7378 is a buspirone analog with high affinity for the 5-HT_{1A} receptor that has been shown to antagonize biochemical, electrophysiological and behavioral responses to 8-OH-DPAT in vivo (Yocca et al. 1987; Chaput and de Montigny 1988; Lucki et al. 1988; Sharp et al. 1990). Pindolol, in addition to blockade of β-adrenergic receptors (Frishman 1983), binds to 5-HT_{1A} receptors (Hoyer 1988) and antagonizes the behavioral effects of 8-OH-DPAT (Tricklebank et al. 1987; Lucki 1989). Although NAN 190, BMY 7378 and pindolol all block responses mediated by postsynaptic 5-HT_{1A} receptors, NAN 190 and BMY 7378 are partial agonists at presynaptic 5-HT_{1A} receptors (Hyorth and Sharp 1990; Sharp et al. 1990), whereas pindolol is an antagonist at this site (Lucki 1992). The present study examined the ability of these antagonists to prevent the antidepressant-like behavioral effects of the selective 5-HT_{1A} receptor agonist 8-OH-DPAT and buspirone, which is a clinically effective antidepressant (Robinson et al. 1990; Rickels et al. 1991). The effect of the three 5-HT_{1A} receptor antagonists were also assessed when administered alone. Finally, these drugs were assessed for their ability to prevent the antidepressant-like behavioural effects of desipramine (DMI), another clinically effective antidepressant. Because DMI is a selective inhibitor of norepinephrine (NE) uptake (Richelson and Pfenning 1984), this study examined the potential interaction between 5-HT and NE systems in mediating antidepressant-like behavioral effects in the FST.

Materials and methods

Animals

Male Sprague-Dawley rats (Charles River, Wilmington, Mass.) weighing 126–150 g upon arrival, were housed in groups of two to five in polycarbonate cages. They were maintained on a 12:12-h light-dark schedule (lights on 0700–1900 hours) in a temperature controlled (22° C) colony room. Rats received free access to food and water, and were handled for 5 days prior to behavioral testing.

Forced swim test

The procedure used was very similar to that described by Porsolt et al. (1978) and Wieland and Lucki (1990). Swim sessions were conducted by placing rats in individual Plexiglas cylinders (46 cm tall × 20 cm in diameter) containing 24 cm water at 23–25° C. Two swim sessions were conducted: an initial 15-min pretest followed 24 h later by a 5-min test. Drug treatments were administered during the period between the two sessions. Following swim sessions, the rats were removed from the cylinders, dried with a towel, placed in heated cages for 15 min, and then returned to their home cages. Test sessions were videotaped from above the cylinder (Panasonic Color Video camera and recorder) for scoring later. A rat was judged to be immobile when it remained floating in the water without struggling and was making only those movements necessary to keep its head above water. Grooming behaviors (head shaking and face washing with paws) were not considered struggling. All scoring was done by a single rater, who was blind to treatment groups. Several sessions ($n = 40$ rats) were also scored by a second rater, who was again blind to treatment group. The Pearson product-moment correlation coefficient for inter-rater reliability for this study was very high ($r = 0.99$, $P < 0.001$).

Drug treatment

For subchronic treatment during the forced swim test, each drug was administered 23.5, 5, and 1 h prior to the start of the test. For subjects given two drugs, both were given consecutively at each time. DMI, betaxolol, ICI 118,551 and prazosin were administered subcutaneously in a volume equivalent to 4 ml/kg. All other drugs were administered subcutaneously in a volume equivalent to

1 ml/kg. All drugs were calculated as mg/kg base, and were dissolved in deionized water except as follows. NAN190 and ICI 118,551 were prepared as suspensions by adding 1–2 drops Tween 80 and then adding deionized water. Pindolol was dissolved in deionized water with 1 drop glacial acetic acid. All drugs were prepared freshly each morning. Most of the control subjects received 0.9% saline as the vehicle, but some groups received deionized water with either Tween 80 or glacial acetic acid in concentrations comparable to those used to prepare the NAN 190, ICI 118,551 and pindolol. There were no differences among these vehicle groups, and hereafter all of these controls will be referred to as saline groups.

Drugs

±8-Hydroxy-2-(di-*n*-propylamino)tetralin HBr (8-OH-DPAT), NAN 190, and prazosin HCl were purchased from Research Biochemicals Inc. (Natick, Mass). Desipramine HCl and pindolol were purchased from Sigma Chemical Co. (St Louis, Mo.). Buspirone HCl and BMY 7378 were obtained from Bristol-Myers (Wallingford, Conn.). ICI 118,551 was obtained from Stuart Pharmaceuticals (Wilmington, Del.). Betaxolol HCl was obtained from Alcon (Ft. Worth Tex.).

Statistical analysis

An experiment consisted of 30–50 subjects assigned randomly to groups of six to ten animals each. Each experiment included one vehicle-treated group. For each experiment in which a putative antidepressant was combined with an antagonist, the putative antidepressant was also administered alone. Thus, there were several separate experiments in which vehicle, 8-OH-DPAT, and DMI were administered. Statistical analyses using one-way ANOVAs showed that there were not significant differences among the vehicle-treated groups [$F(19,139) = 1.19$, $P = 0.27$] or among the 8-OH-DPAT groups at 0.25 mg/kg [$F(9,52) = 1.00$, $P = 0.45$] or 0.5 mg/kg [$F(1,19) = 0.02$, $P = 0.88$] , or among the DMI groups at 5 mg/kg, [$F(4,28) = 0.85$, $P = 0.51$] , or 15 mg/kg [$F(4,24) = 0.52$, $P = 0.72$]. Therefore, subjects in the same treatment conditions were combined in the appropriate analyses.

All statistical outliers (> 2 standard deviations from the mean) were eliminated from each treatment condition prior to analysis. The data presented in each table or figure were subjected to a one-way factorial analysis of variance and for those which are reliable ($P < 0.05$), post-hoc tests were conducted as follows. Duncan's multiple range test (two tailed; Bruning and Kintz 1987) with adjustments for unequal *n*s (Kramer 1956) was used for the following comparisons only: between a) saline and all other groups, and b) the putative antidepressant-like compound alone (8-OH-DPAT, buspirone or DMI) and its effects when combined with antagonists.

Results

The ability of three 5-HT_{1A} receptor antagonists to block the behavioral effects of the selective 5-HT_{1A} receptor agonist 8-OH-DPAT (0.25 mg/kg) is shown in Fig. 1. In the FST, 8-OH-DPAT reduced immobility on its own, and this effect was blocked by all three of the 5-HT_{1A} receptor antagonists. The overall ANOVA was reliable [$F(10,224) = 7.59$; $P < 0.0001$]. Subsequent analyses showed that 8-OH-DPAT reliably decreased immobility from the saline baseline [$k(7,224) = 8.36$; $P < 0.01$] and that the following antagonists when combined with 8-OH-DPAT reliably increased immobility over that of 8-OH-DPAT alone: NAN 190 (0.32 and 1.0 mg/kg), BMY 7378 (0.32 and 1.0 mg/kg) and pindolol (1.0 and 5.0 mg/kg).

Similar effects were obtained when the dose of 8-OH-DPAT was raised to 0.5 mg/kg, as shown in Fig. 2. Administration of 8-OH-DPAT alone reduced immobility, and this effect was blocked by each of the three 5-HT_{1A} receptor antagonists. The overall ANOVA was reliable [$F(4,55) = 16.11$; $P < 0.0001$]. Subsequent analyses showed that the 8-OH-DPAT group was reliably less immobile than the saline group [$k(3,55) = 4.77$, $P < 0.01$], and that all of the combinations of

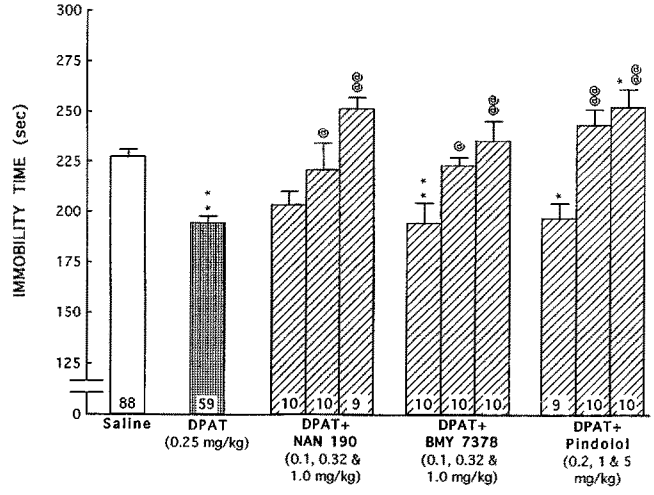

Fig. 1 Immobility time in the FST in response to saline, and to 8-OH-DPAT (0.25 mg/kg) both alone and when combined with NAN 190, BMY 7378, and pindolol. The number of animals in each group is designated at the base of each bar. Differences in comparison to saline: $^{*}P < 0.05$, $^{**}P < 0.01$. Differences in comparison to 8-OH-DPAT alone: $^{@}P < 0.05$, $^{@@}P < 0.01$

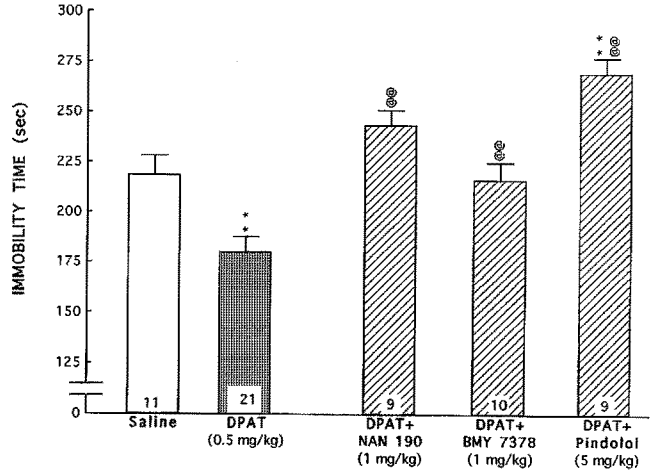

Fig. 2 Immobility time in the FST in response to saline, and to 8-OH-DPAT (0.5 mg/kg) both alone and when combined with NAN 190, BMY 7378, and pindolol. The number of animals in each group is designated at the base of each bar. Differences in comparison to saline: $^{*}P < 0.05$, $^{**}P < 0.01$. Differences in comparison to 8-OH-DPAT alone: $^{@}P < 0.05$, $^{@@}P < 0.01$

8-OH-DPAT and antagonists were reliably more immobile than 8-OH-DPAT alone. It should be noted, however, the 8-OH-DPAT + pindolol group was reliably more immobile than saline controls [$k(3,55) = 5.26$; $P < 0.01$].

Buspirone (20.0 mg/kg) reduced immobility in the FST, and this effect was blocked by the 5-HT_{1A} receptor antagonists NAN 190 and pindolol, as shown in Fig. 3. The overall ANOVA was reliable [$F(4,47) = 11.89$); $P < 0.0001$]. Subsequent analyses showed that the buspirone group was reliably less immobile than the saline group [$k(4,47) = 5.77$; $P < 0.01$], and that combining buspirone with NAN 190 and pindolol increased immobility above values for buspirone given alone. Combining buspirone with BMY 7378 increased the immobility, but this difference was not statistically reliable. However, the buspirone + pindolol group was also reliably more immobile than the saline baseline.

As shown in Fig. 4, DMI (5.0 mg/kg) also reduced immobility in the FST, and this effect was blocked by the 5-HT_{1A} receptor antagonists. The overall ANOVA was reliable [$F(10,148) = 6.33$, $P < 0.0001$]. Subsequent analyses showed that treatment with DMI produced reliably less immobility than saline [$k(10,148) = 9.73$; $P < 0.01$] and that NAN 190 (0.32–3.2 mg/kg), BMY 7378 (1.0 and 3.2 mg/kg) and pindolol (1.0–10.0 mg/kg), when combined with DMI, produced more immobility than did DMI given alone.

Similar effects were also obtained when the dose of DMI was raised to 15.0 mg/kg, as shown in Fig. 5. The overall ANOVA was reliable [$F(7,137) = 16.51$; $P < 0.0001$]. Subsequent analyses showed that the DMI group was reliably less immobile than the saline group [$k(7,137) = 14.19$; $P < 0.01$], and that NAN 190 (3.2 mg/kg), BMY 7378 (1.0 and 3.2 mg/kg) and pindolol (5.0–10.0 mg/kg), when combined with DMI, produced reliably more immobility than did DMI alone.

The 5-HT_{1A} receptor antagonists were administered alone, at all doses which were effective in blocking the antidepressant-like effects, to evaluate their independent effects on immobility time in the FST. These data are presented in Table 1. None of the 5-HT_{1A} receptor antagonists affected immobility time in the FST when given alone. For NAN 190, $F(3,50) = 1.77$, $P = 0.16$; for BMY 7378, $F(3,48) = 0.91$, $P = 0.44$; for pindolol, $F(3,49) = 1.64$, $P = 0.19$.

To determine whether α_1- or β-adrenergic blockade played any role in reversing the antidepressant-like

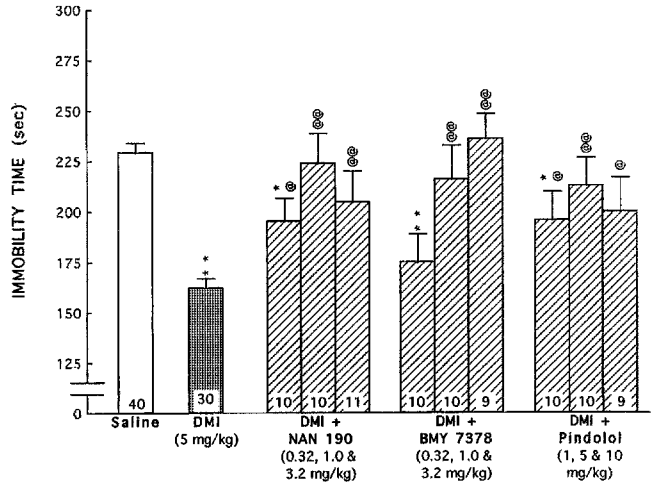

Fig. 4 Immobility time in the FST in response to saline, and to DMI (5.0 mg/kg) both alone and when combined with NAN 190, BMY 7378, and pindolol. The number of animals in each group is designated at the base of each bar. Differences in comparison to saline: $^{*}P < 0.05$, $^{**}P < 0.01$. Differences in comparison to DMI alone: $^{@}P < 0.05$, $^{@@}P < 0.01$

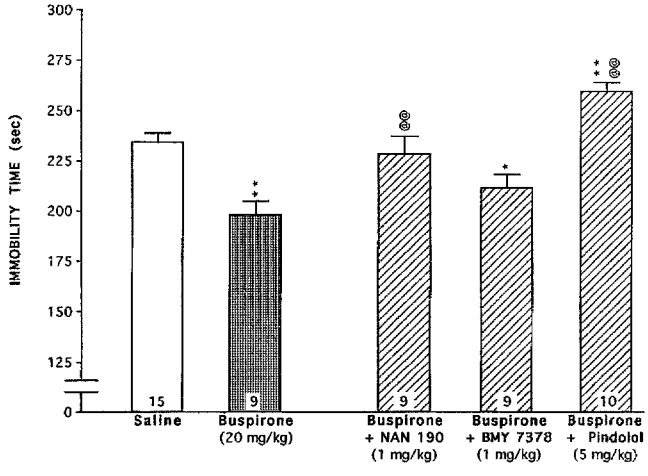

Fig. 3 Immobility time in the FST in response to saline, and to buspirone (20.0 mg/kg) both alone and when combined with NAN 190, BMY 7378, and pindolol. The number of animals in each group is designated at the base of each bar. Differences in comparison to saline: $^{*}P < 0.05$, $^{**}P < 0.01$. Differences in comparison to buspirone alone: $^{@}P < 0.05$, $^{@@}P < 0.01$

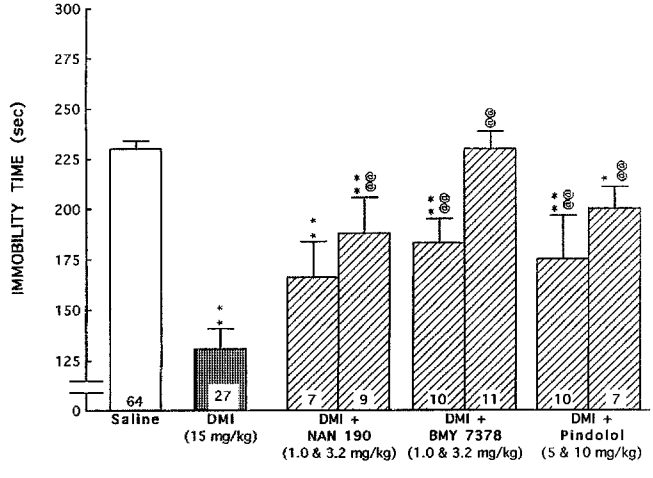

Fig. 5 Immobility time in the FST in response to saline, and to DMI (15.0 mg/kg) both alone and when combined with NAN 190, BMY 7378, and pindolol. The number of animals in each group is designated at the base of each bar. Differences in comparison to saline: $^{*}P < 0.05$, $^{**}P < 0.01$. Differences in comparison to DMI alone: $^{@}P < 0.05$, $^{@@}P < 0.01$

Table 1 Immobility times in the FST in response to treatment with several 5-HT_{1A} receptor antagonists. None of the differences was statistically reliable

	Dose (mg/kg)	*n*	Immobility time (s ± SEM)
Saline		24	246 ± 4
NAN 190	0.32	10	219 ± 10
	1.0	10	251 ± 5
	3.2	10	247 ± 7
Saline		24	220 ± 7
BMY 7378	0.32	10	236 ± 9
	1.0	9	224 ± 6
	3.2	9	233 ± 6
Saline		23	218 ± 8
Pindolol	1.0	10	239 ± 14
	5.0	10	248 ± 7
	10.0	10	238 ± 14

effects in the FST, the adrenergic receptor antagonists prazosin (1.0 mg/kg), betaxolol (10.0 mg/kg) and ICI 118,551 (10.0 mg/kg) were administered, in combination with 8-OH-DPAT, DMI, and on their own. The doses studied were selected from prior demonstrations of pharmacological activity for prazosin (Tricklebank et al. 1985), betaxolol (Callaway et al. 1992), and ICI 118,551 (Singh and Handley 1987).

As shown in Fig. 6, panel A, pretreatment with the three adrenergic receptor antagonists failed to alter the effects of 8-OH-DPAT (0.5 mg/kg) in the FST. The overall ANOVA was reliable [$F(4,34) = 5.13$; $P < 0.0025$]. Subsequent analyses showed that saline produced reliably more immobility than all four of the other groups. Each of the groups treated with 8-OH-DPAT and an antagonist did not differ reliably from that which received 8-OH-DPAT given alone.

In addition, the reduced immobility produced by DMI was not altered by any of the three adrenergic receptor antagonists (Fig. 6, panel B). The overall ANOVA was reliable [$F(4,37) = 7.10$; $P < 0.00025$]. Subsequent analyses showed that DMI produced reliably less immobility than the group treated with saline, as did the three groups which received DMI combined with prazosin, betaxolol or ICI 118,551. These last three groups did not differ reliably from that which received DMI alone.

The adrenergic receptor antagonists failed to reliably affect immobility time in the FST when given alone [$F(3,36) = 2.26$; $P = 0.10$] as shown in Table 2.

Discussion

The first major finding in the present study is that the reduction of immobility in the FST by the 5-HT_{1A} agonists 8-OH-DPAT and buspirone was blocked by pretreatment with the 5-HT_{1A} receptor antagonists NAN 190, BMY 7378 and pindolol. This provides strong support for the hypothesis that the antidepressant-like

Table 2 Immobility times in the FST in response to treatment with several NE antagonists. None of the differences was statistically reliable

	Dose (mg/kg)	*n*	Immobility time (s ± SEM)
Saline		10	231 ± 9
Prazosin	1	10	219 ± 8
Betaxolol	10	10	197 ± 14
ICI 118,551	10	10	199 ± 12

effect of 5-HT_{1A} agonists in the FST is mediated by the activation of 5-HT_{1A} receptors. These findings are in agreement with previous studies showing that NAN 190 and pindolol block the effects of gepirone (Chojnacka-Wojcik et al. 1991) and that NAN 190 blocks the effects of 8-OH-DPAT in the FST (Schreiber and De Vry 1993). In separate tests, doses of NAN 190, BMY 7378 and pindolol effective at blocking 5-HT_{1A} receptor agonists did not alter effects in the FST when given alone, indicating that the blockade was not due to a summation with sedative or behavioral effects opposite to those of 5-HT_{1A} receptor agonists. Since buspirone is a clinically effective antidepressant

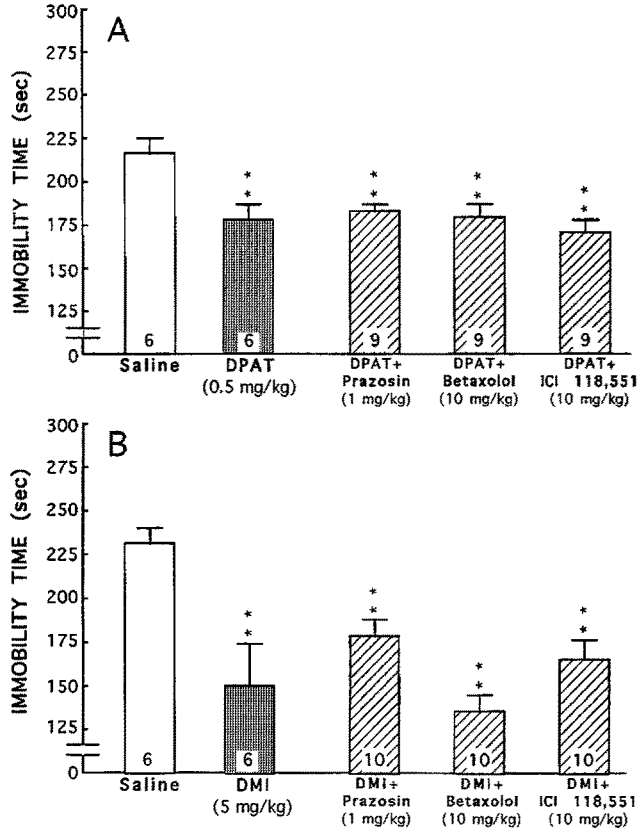

Fig. 6 Effects of pretreatment with betaxolol, ICI 118,551, and prazosin on immobility time in the FST produced either by 8-OH-DPAT (0.5 mg/kg) shown in **A**, or by DMI (5.0 mg/kg), shown in **B**. The number of animals in each group is designated at the base of each bar. Differences in comparison to saline: $^{*}P < 0.05$, $^{**}P < 0.01$. Differences in comparison to 8-OH-DPAT or DMI alone: $^{@}P<0.05$, $^{@@}P<0.01$

(Robinson et al. 1990; Rickels et al. 1991), the clinical antidepressant effects of buspirone may be mediated by stimulation of 5-HT_{1A} receptors.

In addition to 5-HT_{1A} receptors, each of the antagonists used in this study demonstrates substantial affinity for other receptors that potentially could account for its behavioral actions. NAN 190 shows affinity for the α_1-adrenergic receptor (Glennon et al. 1988), BMY 7378 for dopamine receptors (Yocca et al. 1987), and pindolol for β-adrenergic receptors (Frishman 1983). However, three types of evidence argue that the behavioral antagonism was mediated by effects at 5-HT_{1A} receptors. First, 8-OH-DPAT and buspirone are selective 5-HT_{1A} receptor agonists (Middlemiss and Fozard 1983; Peroutka 1985) and a variety of drugs that stimulate 5-HT_{1A} receptors produce antidepressant-like effects in the FST (Lucki et al. 1994). Secondly, all three antagonists used were effective at blocking 8-OH-DPAT's effects, despite their differing affinities for other receptors. Thirdly, it was shown that selective antagonists at α_1 (prazosin), β_1 (betaxolol) and β_2 (ICI 118,551) receptors do not block the effects of 8-OH-DPAT. Thus, there is strong evidence that blockade of the 5-HT_{1A} receptor was the essential component for preventing the behavioral effects of 8-OH-DPAT and buspirone. Newer, more selective antagonists at 5-HT_{1A} receptors have recently become available, such as WAY 100,135 (Fletcher et al. 1993), and may provide additional evidence for the involvement of 5-HT_{1A} receptors in the FST.

There is controversy over whether the antidepressant-like effects of 5-HT_{1A} receptor agonists in the FST are mediated by activation of 5-HT_{1A} receptors located at postsynaptic or presynaptic sites (for review see Lucki et al. 1994). A presynaptic site of action is supported by findings that local administration of 8-OH-DPAT or buspirone into the dorsal raphe decreased immobility in the FST (Cervo et al. 1988a, b; Schreiber and De Vry 1993), and the fact that destruction of 5-HT neurons with the neurotoxin 5,7-dihydroxytryptamine (5,7-DHT) blocked 8-OH-DPAT's immobility-reducing effect (Cervo and Samanin 1987b). However, several other findings suggest that the immobility-reducing effect is mediated via postsynaptic receptors. Pretreatment with the 5-HT synthesis inhibitor *p*-chlorophenylalanine did not affect immobility in the FST on its own (Porsolt et al. 1979; Wieland and Lucki 1990; Cervo and Samanin 1991; Schreiber and De Vry 1993), nor did it alter the immobility-reducing effects of 8-OH-DPAT, tandospirone, ipsapirone or gepirone (Wieland and Lucki 1990; Chojnacka-Wojcik et al. 1991; Schreiber and De Vry 1993). In addition, destruction of 5-HT neurons using 5,7-DHT did not reduce immobility time or block the effects of 8-OH-DPAT (Singh and Lucki 1992; Schreiber and De Vry 1993). And finally, local administration of 8-OH-DPAT or ipsapirone into the lateral septum reduced immobility time in the FST, which supports the possibility of at least one postsynaptic site of action (Schreiber and De Vry 1993).

The present data provide two pieces of evidence which support the hypothesis that the antidepressant-like effect of 5-HT_{1A} receptor agonists is mediated via postsynaptic receptors. NAN 190, BMY 7378 and pindolol all block responses mediated by postsynaptic 5-HT_{1A} receptors (Lucki et al. 1988; Hjorth and Sharp 1990; Sharp et al. 1990), but NAN 190 and BMY 7378 are partial agonists at presynaptic 5-HT_{1A} receptors (Hjorth and Sharp 1990; Sharp et al. 1990), whereas pindolol is an antagonist at this site (Lucki 1992). Because NAN 190 and BMY 7378 produced no effects on their own in the FST, it is unlikely that the antidepressant-like effect of 5-HT_{1A} receptor agonists is mediated presynaptically. Secondly, the finding that all three antagonists blocked the effect of 8-OH-DPAT in the FST supports a postsynaptic site for the antidepressant-like effect of 5-HT_{1A} receptor agonists in the FST.

In contrast to NAN 190 and pindolol, BMY 7378 did not reliably reverse the immobility produced by buspirone, although the effect was in that direction. This may be due to the fact that both BMY 7378 and buspirone are weak partial agonists. It is not surprising that BMY 7378 might effectively reverse the immobility induced by a full efficacy 5-HT_{1A} agonist, such as 8-OH-DPAT, but have a weaker effect on reversing the immobility induced by buspirone.

The second major finding of the present study is that 5-HT_{1A} receptor antagonists blocked the antidepressant-like effect of DMI. Because DMI reduced immobility more than did 8-OH-DPAT, direct comparison of the effects of the antagonists was complicated by different behavioral baselines. However, the effects on immobility of 8-OH-DPAT at 0.5 mg/kg and DMI at 5 mg/kg were not statistically different, and the overall patterns of antagonism of 8-OH-DPAT and DMI were nearly identical. Previously, α_2 adrenergic receptor antagonists (Kitada et al. 1983; Cervo et al. 1990a) and dopamine receptor antagonists (Cervo and Samanin, 1987a; Cervo et al. 1990b) were shown to block the anti-immobility effects of DMI. The present study demonstrates that 5-HT_{1A} receptor antagonists produce similar effects.

Drugs which enhance either 5-HT or NE neurotransmission are effective in treating clinical depression in humans. The ability of 5-HT_{1A} receptor antagonists to block the effects of DMI in the FST may indicate that both 5-HT and NE systems are involved in this behavioral test for antidepressant drug effects. Recent microdialysis studies have provided evidence that DMI can alter 5-HT neurotransmission, by showing that infusion of DMI into the ventral tegmental area increased extracellular levels of 5-HT to a greater extent than NE (Chen and Reith 1994) and that chronic administration of DMI for 14 days increased extracellular levels of 5-HT in the striatum (Kreiss and Lucki 1993). The application of stressors combined with DMI

treatment produced increases of 5-HT turnover in various forebrain regions (Naitoh and Nomura 1990). Furthermore, chronic administration of DMI to depressed patients and normal volunteers produces changes in the levels of 5-HT metabolites, indicating potential alterations of 5-HT neurotransmission (Potter et al. 1985; Cowen et al. 1986). DMI is a selective inhibitor of NE uptake according to in vitro studies (Richelson and Pfenning 1984) and is thought to produce its effects primarily by altering NE neurotransmission. However, evidence cited above makes it clear that DMI can produce changes in 5-HT neurotransmission as well. Changes in 5-HT neurotransmission may arise from the functional interaction between NE and 5-HT systems, or alternatively, DMI may alter 5-HT neurotransmission by some direct effect. Identification of the mechanism by which antagonists at different receptors, including 5-HT receptor antagonists, alter the effects of DMI in the FST is likely to provide important information concerning the role of different neurotransmitters in mediating the antidepressant effects of DMI.

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