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Yohimbine's Anxiogenic Action: Evidence for Noradrenergic and Dopaminergic Sites

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JOHNSTON, A. L. AND S. E. FILE. *Yohimbine's anxiogenic action: Evidence for noradrenergic and dopaminergic sites.* PHARMACOL BIOCHEM BEHAV 32(1) 151–156, 1989.—Yohimbine (2.5 or 4 mg/kg) reduced the percentage of open arm entries and the percentage of time spent on the open arms displayed by rats on an elevated plus-maze indicating anxiogenic activity. These effects were reversed by the α_2-adrenoceptor agonist clonidine (0.01 mg/kg) and by the dopamine receptor agonist apomorphine (0.57 mg/kg). The following failed to reverse the effects of yohimbine: the selective α_2-adrenoceptor agonists, guanfacine (0.25 and 1 mg/kg), B-HT920 (0.025 and 0.1 mg/kg), B-HT933 (1 and 10 mg/kg); the β-blocker propranolol (2.5 and 10 mg/kg); the α_1-adrenoceptor agonist phenylephrine; the D_1 agonist SK&F 38393 (5 and 10 mg/kg) and the D_2 agonist LY 171555 (0.5 and 1 mg/kg). Therefore, it is unlikely that activity at only the α_1, α_2, β, D_1 or D_2 sites can entirely account for the anxiogenic actions of yohimbine in the elevated plus-maze. Evidence that clonidine affects the dopaminergic system and that apomorphine affects the noradrenergic system suggests that yohimbine may produce its anxiogenic response by activity on both the noradrenergic and dopaminergic systems.

Yohimbine Apomorphine Clonidine Anxiety Rat Noradrenergic sites Dopaminergic sites

YOHIMBINE has been found to induce anxiety in man (3,9) and to produce anxiogenic-like effects in several animal models of anxiety (8, 17, 18). It is generally assumed that many of the behavioral actions of yohimbine arise from an increase in central noradrenergic activity (16) produced by yohimbine's antagonist activity at presynapitc α_2-adrenoceptors (2,7). However, the inactivity of the more selective α_2-adrenoceptor antagonist, idazoxan, in two animal tests of anxiety [see (5)] raises the possibility that yohimbine may have other sites of action which contribute to its anxiogenic effects.

In addition to α_2-adrenoreceptor effects, yohimbine affects the 5-hydroxytryptamine (5-HT) (13, 20, 21), dopamine (22,27) and benzodiazepine (12) systems. In the social interaction test of anxiety, the anxiogenic action of yohimbine was not reversed by either chlordiazepoxide or the benzodiazepine antagonist flumazenil (RO 15-1788) (17); it is therefore unlikely that the effects of yohimbine are due to activity at the benzodiazepine receptors. Neither have antagonism studies with serotonergic receptor ligands detected a major role for serotonin in mediating the anxiogenic effects of yohimbine (19). Given the wide variety of evidence which demonstrates interactions between yohimbine and the dopaminergic system, this would be an obvious alternative site of action. Yohimbine could affect dopaminergic transmission by two possible mechanisms: through an indirect action exerted by changes in noradrenaline neurotransmission (1); and through a direct action of dopaminergic receptors (27,28). Yohimbine has been reported to increase dopamine synthesis and turnover (20, 22, 27); to inhibit in vivo ^{3}H-spiperone binding in the hippocampus (spiperone labels dopamine receptors in this region) (29); to act as an antagonist at D_2 postsynaptic receptors [Scatton *et al.* (24)] and dopaminergic autoreceptors (20,27); and to antagonise amphetamine-induced stereotyped behavior (28).

To elucidate the roles played by the noradrenergic and dopaminergic systems in mediating the anxiogenic effects of yohimbine, we tried to antagonise these effects using a variety of ligands which have activity on either the noradrenergic or dopaminergic systems. The noradrenergic ligands chosen were: the α_2-adrenoceptor agonists, clonidine, guanfacine, B-HT920 (6-allyl-2-amino-5,6,7,8,-tetrahydro-4H-thiazolo[4,5]-azepine) and B-HT933 (2-amino-6-ethyl-4,5,7,8-tetrahydro-6H-oxazolo-[5,4-d]-azepine) (10, 15, 26); phenylephrine, an α_1-adrenoceptor agonist; and propranolol, a β-adrenoceptor antagonist. The dopaminergic ligands were: the dopaminergic agonist, apomorphine; the D_1 agonist, SK&F 38393 (2,3,4,5-tetrahydro-7,8-dihydroxy-1-phenyl-1H-3-benzazepine (24); and the D_2 agonist quinpirole (LY 171555) (26). The doses used were selected on the basis of previous

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behavioral studies (4, 6, 17, 18, 25) and on the basis of pilot studies carried out in this laboratory.

The investigation was carried out using the elevated plus-maze test of anxiety (18). This is a test based on the natural aversion that rats show for the two open, elevated arms of the maze compared with the two enclosed arms. The number of entries made onto the open arms expressed as a percentage of the total arm entries and the time spent on the open arms expressed as a percentage of the time spent on both the open and enclosed arms are taken as measures of anxiety. Benzodiazepines and novel putative anxiolytics elevate these measures; anxiogenic agents decreased them. The total number of arm entries can provide a measure of overall activity.

METHOD

Animals

Animals were male hooded Lister rats (Olac Ltd., Bicester) weighing 250–350 g, housed in groups of 6–7 in a room with a 12 hr light:12 hr dark cycle, and allowed free access to food and water.

Apparatus

The plus-maze consisted of two open arms (50×10 cm) and two enclosed arms of the same size with 40-cm high walls, arranged so that the arms of the same type were opposite each other. There was a central square of 10 cm. The apparatus was wooden and was elevated to a height of 50 cm. The measures indicated were taken by an observer sitting 1 m away from the centre of the apparatus. The wooden test arena in which the rats were placed before exposure to the maze was 60×60×35 cm.

Drugs

Yohimbine hydrochloride (Sigma), clonidine hydrochloride (Sigma), guanfacine hydrochloride (Sandoz), B-HT920 dihydroxychloride (Boerhinger), B-HT933 dihydrochloride (Boerhinger), phenylephrine hydrochloride (Sigma), propranolol hydrochloride (Sigma), apomorphine hydrochloride (Sigma), SK&F 38393 hydrochloride (Research Biochemicals Inc.) and quinpirole (Lilly) were dissolved in distilled water. Control-treated animals received distilled water. All injections were given intraperitoneally in an injection volume of 2 ml/kg except for apomorphine and quinpirole which were given subcutaneously into the flank of the leg in an injection volume of 1 ml/kg. This route was chosen for apomorphine and quinpirole because these compounds undergo extensive first pass metabolism and therefore higher and more reliable levels are normally obtained following subcutaneous administration (personal communication, M. S. Starr, Department of Pharmacology, The School of Pharmacy, University of London). The doses of all drugs refer to their salts. All drugs were administered 30 min before testing.

Procedure

The investigation was carried out in 6 test groupings (a–g). Rats were allocated to the following drug groups, which were tested alone and in combination with yohimbine (2.5 or 4 mg/kg): a) control or clonidine (0.01 mg/kg), b) control, guanfacine (0.25 and 1 mg/kg) or B-HT920 (0.025 and 0.1 mg/kg), c) control, B-HT933 (1 and 10 mg/kg) or propranolol (2.5 and 10 mg/kg), d) control or phenylephrine (0.25 and 10 mg/kg), e) control or apomorphine (0.057 and 0.57 mg/kg), f) control or quinpirole (0.5 and 1 mg/kg), g) control or SK&F 38393 (5 and 10 mg/kg); n=6–8 per group. In the groupings with phenylephrine and quinpirole, the rats were found to be relatively insensitive to the effects of a 2.5 mg/kg dose of yohimbine and therefore a higher dose of 4 mg/kg was used. All rats received two injections given 30 min before the test on the plus-maze. For 5 min before the start of the test, each rat was placed individually in a wooden arena (previous studies had found that this procedure resulted in an elevation of the total arm entries on the maze). The rat was then placed in the centre of the maze, facing one of the enclosed arms. During a 5-min test period, the following measures were taken by an observer: the number of entries onto, and the time spent on, (a) open and (b) enclosed arms. The maze was cleaned after each trial. Rats were tested between 0800 and 1300 hr, in an order randomised for drug treatment.

Statistics

Data were analysed by analyses of variance (ANOVA) with drug treatments as the independent factors. ANOVA was performed on the percentage of entries made onto the open arms and the percentage of time spent on the open arms. ANOVA was also performed on the total number of arm entries. Where a drug increased or decreased both total arm entries and the percentage of open arm entries, analysis of covariance (ANCOVA) was performed to determine to what extent the change in open arm entries was independent of any effect on closed arm entries. ANCOVA was carried out with open arm entries as the dependent variable and closed arm entries as the covariate. A significant effect is indicated if the reduction in open arm entries is independent of effects on closed arm entries. A nonsignificant effect indicates that the reduction in open arm entries reflects a nonspecific depressant effect of the drug. Post hoc comparisons between individual drug groups were made using Duncan's Multiple Range tests.

RESULTS

Yohimbine

In all the groupings, yohimbine reduced both the percentage of open arm entries and the percentage of time spent on the open arms (the yohimbine factors were $p<0.1$–0.0001 and $p<0.05$–0.0001, respectively). In the experiment with apomorphine, there was a large mean square error for both of the above measures (introduced because of large standard errors in the apomorphine groups), therefore, in this case, the results included above are from an ANOVA performed only on the control and yohimbine-treated groups. Except in the groupings with apomorphine and quinpirole, yohimbine reduced the total number of arms entries (the yohimbine factor was $p<0.05$–0.0005). In each case, ANCOVA was significant ($p<0.05$–0.0005) and therefore the reduction in open arm entries was independent of the reduction in enclosed arm entries.

Clonidine and Yohimbine

Clonidine (0.01 mg/kg) prevented the reductions in the percentage of arm entries made onto the open arms, the percentage of time spent on the open arms and the total number of arm entries displayed by yohimbine alone. For all three measures, post hoc analysis showed that the scores

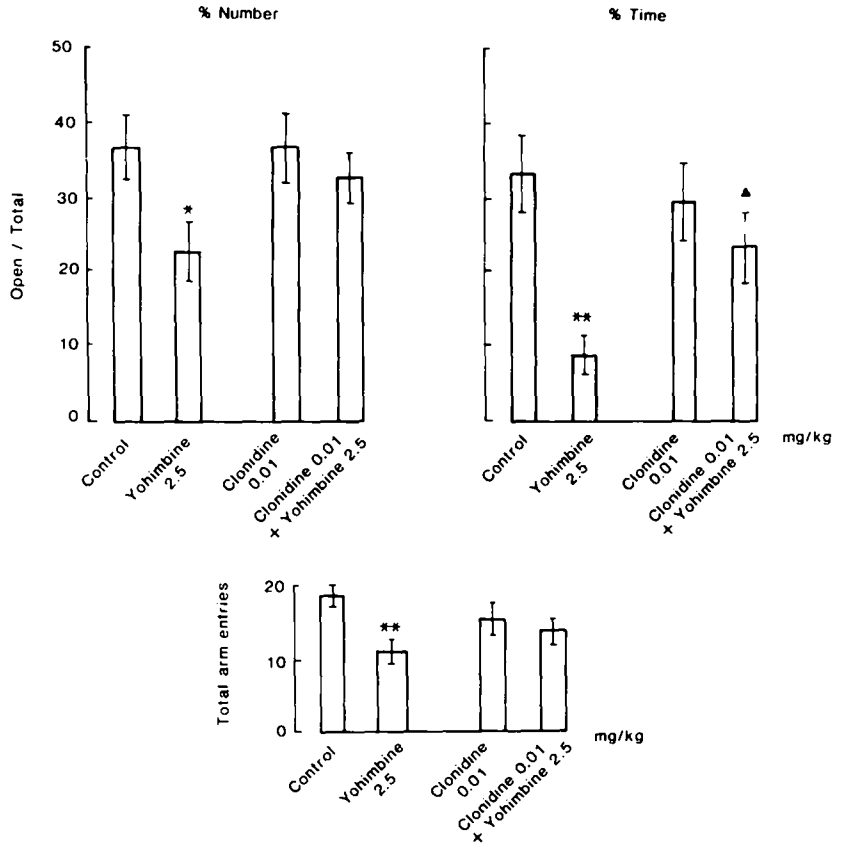

FIG. 1. Mean (±S.E.M.) percentage of arm entries made onto the open arms (% Number), percentage of time spent on the open arms (% Time) and total number of arm entries, in rats given a 5-min test on the elevated plus-maze, 30 min after IP injection with clonidine (0.01 mg/kg) alone and in combination with yohimbine (2.5 mg/kg). *$p<0.05$, **$p<0.01$, significantly different from controls and ▲$p<0.05$, significantly different from the group treated with yohimbine alone, Duncan's tests after ANOVA.

displayed by the group treated with both yohimbine and clonidine did not differ from the control-treated group (see Fig. 1); also, for the percentage of time spent on the open arms, the group treated with yohimbine and clonidine was significantly different from the group treated with yohimbine alone (post hoc analysis, $p<0.01$) (see Fig. 1).

Apomorphine and Yohimbine

Apomorphine (0.57 mg/kg) prevented the reductions in the percentage of arm entries made onto the open arms, the percentage of time spent on the open arms and the total number of arm entries displayed by yohimbine alone. For all three measures, post hoc analysis showed that the scores displayed by the group treated with both yohimbine and apomorphine (0.57 mg/kg) did not differ from the control-treated group (see Fig. 2); also, for the percentage of arm entries made onto the open arms and the percentage of time spent on the open arms, the group treated with yohimbine and clonidine was significantly different from the group treated with yohimbine alone (post hoc analysis, $p<0.01$) (see Fig. 2).

The addition of the lower dose of apomorphine (0.057 mg/kg) did not significantly change the effects displayed by yohimbine alone (see Fig. 2).

There was a tendency for the higher dose of apomorphine to increase the percentage of entries made onto the open arms and the percentage of time spent on the open arms, however, post hoc analysis showed that this group did not differ from controls on either of these measures.

No Significant Reversal of Yohimbine's Actions

The following compounds failed to reverse the effects of yohimbine on the elevated plus-maze: guanfacine, B-HT920, B-HT933, phenylephrine, propranolol, SK&F 38393 and quinpirole (see Tables 1 and 2).

DISCUSSION

In the elevated plus-maze, yohimbine reduced the percentage of open arm entries and the percentage of time spent on the open arms. These effects are consistent with previous studies on the actions of yohimbine in the elevated plus-

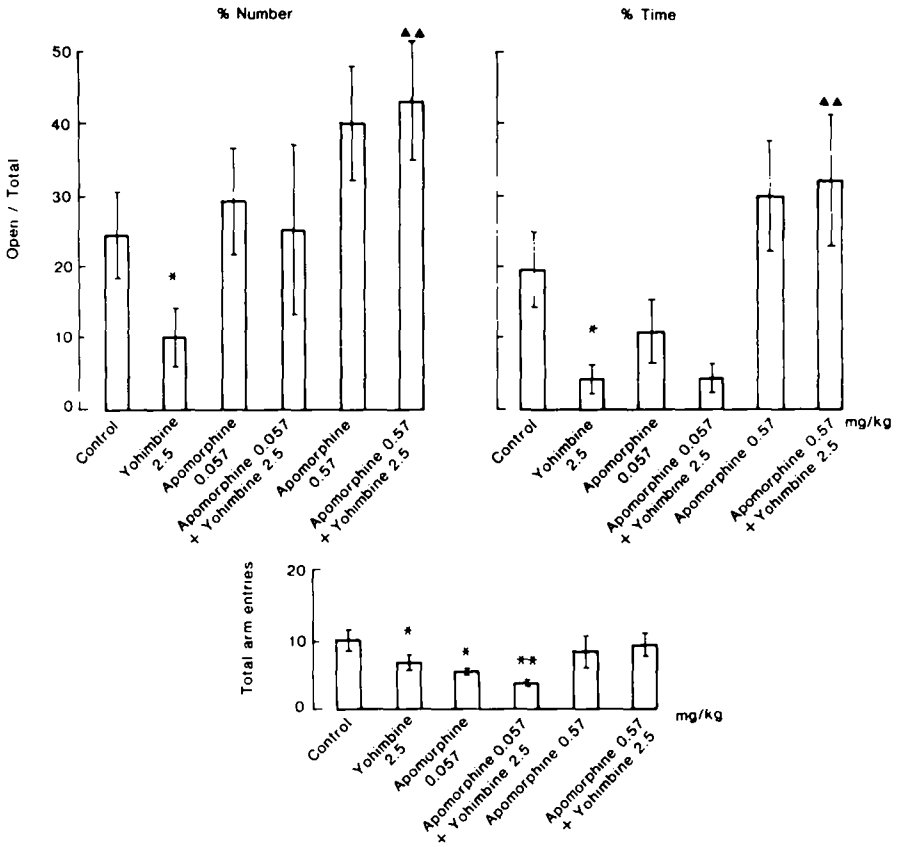

FIG. 2. Mean (±S.E.M.) percentage of arm entries made onto the open arms (% Number), percentage of time spent on the open arms (% Time) and total number of arm entries, in rats given a 5-min test on the elevated plus-maze, 30 min after SC injection with apomorphine (0.057 and 0.57 mg/kg) alone and in combination with yohimbine (2.5 mg/kg), given by IP injection. *$p<0.05$, **$p<0.01$, significantly different from controls and ▲▲$p<0.01$, significantly different from the group treated with yohimbine alone, Duncan's tests after ANOVA.

maze test (8, 18, 19) and are believed to reflect the compound's anxiogenic properties. In this study, these anxiogenic effects were reversed by the α_2-adrenoceptor agonist clonidine and by the higher dose (0.57 mg/kg), but not the lower dose (0.057 mg/kg), of the dopamine agonist apomorphine. The high and low doses of apomorphine are thought to act at post- and presynaptic sites, respectively [see (6)], and the differences observed may reflect these different sites of action. In contrast, guanfacine, B-HT920, B-HT933, phenylephrine, propranolol, SK&F 38393 and quinpirole were unable to antagonise the effects of yohimbine. Guanfacine, B-HT920 and B-HT933 have been suggested as more selective ligands for the α_2 site than clonidine (10, 11, 25); the inability of these compounds to reverse yohimbine's effects suggests that, in this test at least, the effects of yohimbine are not solely due to antagonistic activity at the α_2 site. Similarly, since neither phenylephrine, propranolol nor quinpirole antagonised the actions of yohimbine it is unlikely that the α_1, the β, the D_1, or the D_2 site is solely responsible for mediating the anxiogenic effects of yohimbine.

At first, the ability of clonidine and apomorphine to independently reverse the effects of yohimbine appeared conflicting: the reversal by clonidine suggested a role for α_2-adrenoreceptors, whilst the reversal by apomorphine suggested a role for postsynaptic dopaminergic receptors. However, there is evidence that clonidine may affect the dopaminergic system and that apomorphine may have affected the noradrenergic system. Clonidine has been shown to alter dopamine-dependent behavior in rodents (21), to reduce dopamine metabolism and to partly inhibit ^{3}H-spiperone binding in rat striatum (28); whilst apomorphine appears to influence noradrenaline release possibly through activity at the α_2-adrenoceptor (14). Since yohimbine affects both the dopaminergic and noradrenergic systems, and since the two compounds which are capable of reversing its anxiogenic effects also affect both these systems, it is possible that activity on both the noradrenergic and dopaminergic systems is necessary for the expression, and the reversal, of the anxiogenic effects of yohimbine. The results of the present study exclude the possibility of serial actions on these two pathways, since in this case yohimbine's effects in the plus-maze would have been reversed by antagonists at either site.

The proposal of action at two sites being involved in the anxiogenic effects of yohimbine could explain the inactivity

TABLE 1

MEAN (± S.E.M.) PERCENTAGE OF ARM ENTRIES MADE ONTO THE OPEN ARMS (% NUMBER), PERCENTAGE OF TIME SPENT ON THE OPEN ARMS (% TIME) AND TOTAL NUMBER OF ARM ENTRIES (TOTAL) FOR RATS GIVEN A 5-MIN TEST ON THE ELEVATED PLUS-MAZE, 30 MIN AFTER INJECTION WITH THE FOLLOWING DRUGS

mg/kg	% Number	% Time	Total
Control	19.6 (±3.6)	14.5 (±3.3)	13.3 (±1.5)
Phenylephrine 0.25	29.0 (±5.5)	25.8 (±6.1)	13.4 (±1.8)
0.5	21.9 (±6.0)	19.4 (±6.8)	16.4 (±1.7)
Yohimbine 4	5.5 (±2.3)	1.7 (±0.8)	9.3 (±0.9)
+ phenylephrine 0.25	3.0 (±1.9)	1.3 (±0.8)	7.9 (±1.1)
+ phenylephrine 0.5	5.7 (±3.6)	3.1 (±2.1)	9.3 (±1.9)
Control	22.2 (±4.5)	13.0 (±2.9)	11.4 (±1.4)
Quinpirole 0.5	22.1 (±6.4)	16.7 (±6.0)	8.4 (±1.4)
1.0	34.5 (±6.2)	25.8 (±5.3)	8.4 (±0.9)
Yohimbine 4	12.0 (±6.1)	8.7 (±5.1)	10.7 (±1.6)
+ Quinpirole 0.5	9.6 (±4.3)	6.8 (±4.1)	11.4 (±1.5)
+ Quinpirole 1.0	21.4 (±4.2)	15.7 (±3.8)	11.5 (±1.2)
Control	25.4 (±3.6)	25.9 (±4.2)	15.0 (±1.3)
SK&F 38393 5	4.9 (±2.8)	4.0 (±2.6)	11.0 (±2.0)
10	9.9 (±3.6)	7.5 (±2.9)	11.1 (±1.7)
Yohimbine 2.5	16.8 (±4.5)	9.9 (±3.3)	11.3 (±1.4)
+ SK&F 38393 5	1.0 (±1.0)	0.3 (±0.3)	8.5 (±1.4)
+ SK&F 38393 10	6.4 (±2.7)	1.8 (±0.7)	8.9 (±1.8)

TABLE 2

MEAN (± S.E.M.) PERCENTAGE OF ARM ENTRIES MADE ONTO THE OPEN ARMS (% NUMBER), PERCENTAGE OF TIME SPENT ON THE OPEN ARMS (% TIME) AND TOTAL NUMBER OF ARM ENTRIES (TOTAL) FOR RATS GIVEN A 5-MIN TEST ON THE ELEVATED PLUS-MAZE, 30 MIN AFTER INJECTION WITH THE FOLLOWING DRUGS

mg/kg	% Number	% Time	Total
Control	25.5 (±3.5)	17.5 (±3.1)	14.0 (±0.7)
Guanfacine 0.25	23.2 (±5.8)	20.8 (±6.8)	10.8 (±1.7)
1.0	35.3 (±3.7)	19.0 (±3.5)	11.7 (±1.8)
B-HT920 0.025	28.1 (±4.1)	19.5 (±4.2)	8.9 (±0.7)
0.1	31.3 (±2.7)	19.9 (±2.6)	9.1 (±0.7)
Yohimbine	17.7 (±3.7)	7.8 (±2.1)	11.1 (±1.2)
+ guanfacine 0.25	9.0 (±3.8)	2.8 (±1.4)	7.0 (±2.0)
+ guanfacine 1.0	20.7 (±4.7)	7.4 (±3.8)	9.1 (±2.4)
+ B-HT920 0.025	17.6 (±6.2)	12.2 (±6.5)	7.5 (±1.9)
+ B-HT920 0.1	10.4 (±5.2)	2.3 (±1.4)	5.0 (±1.1)
Control	28.9 (±3.0)	22.9 (±4.6)	13.4 (±1.3)
B-HT933 1.0	29.6 (±3.1)	15.7 (±5.3)	12.3 (±2.4)
10.0	35.0 (±7.0)	16.9 (±5.3)	6.9 (±1.8)
Propranolol 2.5	24.2 (±3.2)	13.7 (±3.8)	12.4 (±2.4)
10.0	26.1 (±6.9)	6.8 (±2.5)	9.4 (±2.5)
Yohimbine	14.3 (±3.7)	4.2 (±2.1)	6.9 (±1.6)
+ B-HT933 1.0	11.7 (±4.8)	4.9 (±2.4)	7.5 (±1.9)
+ B-HT933 10.0	10.6 (±5.5)	1.6 (±0.8)	2.8 (±0.6)
+ propranolol 2.5	18.6 (±4.6)	8.3 (±2.7)	9.9 (±1.5)
+ propranolol 10.0	8.9 (±4.8)	1.7 (±1.0)	5.5 (±1.7)

of the more selective α_2-antagonist idazoxan in animal tests of anxiety (5), which does not affect the dopamine system, as measured by changes in dopamine metabolism, binding to dopamine receptors and the ability to reverse amphetamine-induced stereotypy (28).

There is some evidence to suggest that B-HT920 can directly influence the dopamine system (23). In intact animals, it behaved as a presynaptic agonist to reduce dopaminergic function (23). But B-HT920 would not be expected to reverse any of yohimbine's direct dopaminergic effects, since yohimbine, by its postsynaptic antagonist actions, would also reduce dopaminergic function.

In summary, our investigation into the nature of yohimbine's anxiogenic action suggests that this response is mediated by both the noradrenergic and dopaminergic systems, and that a successful antagonist of this action may also need to possess activity on both these systems.

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