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Effects of alpha-adrenoceptor agonists and antagonists in a maze-exploration model of 'fear'-motivated behaviour

Sheila L. Handley and Siddika Mithani

Pharmacology Laboratories, Department of Pharmacy, University of Aston, Birmingham B4 7ET, Great Britain

Summary. An elevated X-maze with alternating open and enclosed arms was investigated as a model for the study of fear-induced behaviour. As predicted, the anxiolytics diazepam and amylobarbitone increased, and the putative anxiogenics ACTH and picrotoxin decreased the proportion of open arm entries. The α_1-adrenoceptor agonists phenylephrine and ST587, and the α_2-adrenoceptor antagonists idazoxan, piperoxane, RS-21361 and yohimbine decreased relative open-arm entries, thus resembling the putative anxiogenics. On the other hand, azepexole, clonidine and guanabenz, agonists at α_2-adrenoceptors, and the α_1-adrenoceptor antagonists prazosin and thymoxamine, enhanced the proportion of open arm entries at low doses, suggesting anxiolytic-like properties. A paradoxical fall in open arm entries occurred with these agents at higher doses. These results provide further evidence for the involvement of noradrenergic systems in 'fear'-motivated behaviour.

Key words: Anxiety – Central α-adrenoceptors – Clonidine – Exploratory activity – 'Fear'-motivated behaviour

Introduction

There is a considerable amount of pharmacological evidence that noradrenergic systems may be involved in fear and anxiety. Thus clonidine, an agonist at α_2-adrenoceptors, has been reported to reduce the signs of fear induced in monkeys by electrical stimulation of the Locus Coeruleus (Redmond and Huang 1979) and to reduce the potentiated startle response (Davies et al. 1977), as well as to increase lever pressing during the punished component of Geller-Seifter operant conflict (Kruse et al. 1981). It has also been proposed that clonidine may be clinically useful in certain types of anxiety (see Hoehn-Saric et al. 1981). Conversely, there have been several clinical reports that yohimbine and piperoxane can cause anxiety and panic attacks (Goldenberg et al. 1947; Soffer 1954; Holmberg and Gershon 1961; Margolis et al. 1971). These drugs are antagonists at α_2-adrenoceptors (Starke et al. 1975; Drew 1976). Yohimbine also accentuates signs of fear induced by threat in monkeys (Redmond and Huang 1979) and prevents the effects of clonidine on potentiated startle (Davies and Astrachan 1981) and punished responding (Kruse et al. 1981). The anxiogenic effects of yohimbine in human subjects have recently been found to be abolished by both clonidine and diazepam (Charney et al. 1983).

Although the drugs mentioned above have selective effects on α_2-rather than α_1-adrenoceptors, they are by no means the most selective available and are also known to have other effects. Clonidine, for instance can also act as a partial agonist at α_1-adrenoceptors (Bradshaw et al. 1982) and it's hypothermic action has been reported to involve histamine H_2 receptors (Bugajski et al. 1980). Yohimbine can affect -5-HT (Papeschi et al. 1971) and dopamine (Dedek et al. 1981) metabolism.

It was therefore desirable to examine the effects of other α_2-adrenoceptor agonists and antagonists. In addition the present study set out to examine the effects of a number of agents selective for α_1-adrenoceptors. Since several drugs were to be investigated in a range of doses, a simple and rapid test capable of yielding easily quantifiable data was required.

Montgomery (1955) examined the manner of exploration of open and enclosed arms in an elevated 'Y' maze. He attributed the rats' preference for the enclosed arm(s) to differences in the extent to which each elicited the fear and exploratory drives. He proposed that novel stimulation evokes 'both the fear drive and the exploratory drive, thus generating an approach-avoidance conflict.' He considered that both the open and enclosed arms evoke the exploratory drive but that the former evokes a greater strength of 'fear drive' than the latter, thus resulting in a greater relative exploration of the enclosed arm(s). If this explanation is correct, then it would be expected that anxiolytic drugs would increase the relative exploration of open arms while anxiety-inducing drugs would decrease it. A model based on these experiments was therefore devised, in which rats explored an X-shaped elevated maze with two open and two enclosed arms. This model was initially tested out using known anxiolytic and putative anxiogenic agents.

Methods

Animals and experimental conditions. Groups of 6 male hooded rats (Lister) (150–200 g) were caged together under a regulated light/dark cycle (lights on 08.00–20.00 h) and kept in a quiet room for at least 7 days prior to experiment.

Apparatus. The apparatus consisted of an X-shaped maze elevated 70 cm from the floor and comprising two (opposite) enclosed and two open arms. These arms were 45 cm long and 10 cm wide. The enclosed arms had sides and ends 10 cm high while the open arms had no sides or ends. The central

Send offprint requests to S. L. Handley at the above address

Table 1. Effects of anxiolytic and anxiogenic agents on maze exploration. Values are expressed as mean ± standard error. Significance of differences from corresponding vehicle control * 2 $P < 0.05$; ** 2 $P < 0.01$; [a] mean of (open/total) ratio for individual animals, see text

Drug/dose (mg/kg)		Mean number of entries in 10 min (vehicle control values in brackets)			
		Open	Total	Open/total[a]	Open/total ratio as % vehicle control
Amylobaritone	15.0	3.3 ± 0.6 (3.0 ± 0.6)	10.5 ± 1.8 (10.6 ± 1.7)	0.32 ± 0.02 (0.28 ± 0.01)	114.3
	30.0	4.2 ± 1.6 (3.0 ± 0.6)	9.3 ± 3.3 (10.6 ± 1.7)	0.41 ± 0.05 (0.28 ± 0.01)*	146.4
Diazepam	0.5	5.8 ± 1.9 (5.2 ± 1,3)	18.6 ± 5.7 (17.3 ± 4.3)	0.33 ± 0.04 (0.30 ± 0.01)	110.0
	1.0	4.8 ± 1.5 (4.4 ± 1.5)	9.8 ± 2.3 (12.4 ± 3.8)	0.49 ± 0.03 (0.35 ± 0.01)**	140.0
	2.0	9.0 ± 1.5 (3.6 ± 0.5)**	16.5 ± 1.7 (10.8 ± 0.7)**	0.54 ± 0.03 (0.34 ± 0.03)**	158.8
	5.0	4.2 ± 0.9 (3.8 ± 0.4)	9.2 ± 1.5 (12.4 ± 1.4)*	0.45 ± 0.03 (0.31 ± 0.31)**	145.2
	10.0	0.0 ± 0.0 (2.7 ± 0.5)	0.0 ± 0.0 (10.0 ± 1.4)**	0.0 ± 0.0 (0.27 ± 0.02)	–
ACTH	0.05	6.6 ± 2.9 (6.0 ± 1.6)	17.6 ± 6.6 (16.0 ± 3.7)	0.36 ± 0.02 (0.37 ± 0.02)	97.3
	0.075	1.8 ± 0.8 (6.0 ± 1.6)**	9.2 ± 3.9 (16.0 ± 3.7)	0.19 ± 0.02 (0.37 ± 0.02)	51.4
Picrotoxin	2.0	0.5 ± 0.2 (2.2 ± 0.2)**	5.7 ± 1.2 (7.6 ± 0.7)	0.06 ± 0.03 (0.32 ± 0.06)**	18.8
	4.0	0.5 ± 0.2 (2.2 ± 0.02)**	3.0 ± 0.4 (7.6 ± 0.7)**	0.08 ± 0.09 (0.32 ± 0.06)*	25.0

square formed by the arms was open. The floor of the maze was lined with wire mesh.

Experimental procedure. On the day before the experiment the cages were transferred to the experimental room and entry barred to all but the experimenter until completion of the experiment. Experiments were performed between 10.00 and 14.00 h. Animals were assigned randomly to test and vehicle control groups but remained in their home cages. Six rats received each treatment and a vehicle control group was included in every experiment. Drugs were injected i.p. 30 min before placement into the maze, except for ACTH which was injected 15 min beforehand since File and Vellucci (1978) obtained significant results in the social interaction test only between 3 and 30 min. Immediately before testing, rats were observed undisturbed in the home cage and the degree of gross sedation estimated as 0 (absent), 1 (minimal), 2 (moderate) or 3 (severe). Each rat was placed gently in the centre square of the maze, facing the same enclosed arm. The number of open and enclosed arm entries was recorded for a 10 min period by the observer sitting quietly at a distance of 1.5 m from the centre of the maze and equidistant between the nearest open and enclosed arms. On removal of the rat, the maze floor was thoroughly cleaned. Each rat was exposed to the maze once only.

During pilot experiments it was found to be most important that this procedure was adhered to strictly, particularly with regard to maintaining quiet conditions throughout the time the animals were in the experimental room. Any disturbance tended to reduce exploration.

Expression of the results. The number of open arm entries was determined as a proportion of the total number of entries (i.e. open/total) for each individual animal. Thus the group mean proportion 'P' was expressed as Σ (open/total)/n. For display in the tables, changes in this proportion were calculated relative to the vehicle control baseline for that experiment as:

$(P_{\text{test}}/P_{\text{control}}) \cdot 100.$

Statistical comparisons were carried out using the Mann-Whitney U-test (2-tailed).

Drugs used. The following drugs were used dissolved in 0.9% NaCl: ACTH (Sigma, St. Louis, MO, USA), amylobarbitone sodium (Lilly, Indianapolis, IN, USA), azepexole (Boehringer, Ingelheim, FRG), clonidine (Boehringer-Ingelheim), guanabenz (Wyeth, Maidenhead, England), idazoxan (Reckitt & Colman, Hull, England), phenylephrine HCl (Sigma), picrotoxin (Sigma), piperoxane (May & Baker, Dagenham, England), RS-21361 (Syntex, Edinburgh, Scotland), yohimbine (Sigma). Diazepam (Roche, Basel, Switzerland) was suspended in 2.5% gum acacia and prazosin (Pfizer, Croton, CT, USA) dissolved in 5% glycerol/5% glucose solution.

Results

Saline-treated animals

All control animals showed a preference for the enclosed arms. For 60 saline-pretreated animals the mean of the ratio of open/total entries was 0.28 ± 0.07 (sem), i.e. 28% of entries were into the open arms. The ratio of open to total entries was not dependent on the total number of entries ($r = 0.22$, slope 0.003).

Diazepam and amylobarbitone

Diazepam (0.5 – 5 mg/kg) caused a marked increase in relative open arm exploration (Table 1), however there was no consistent effect on total entries at these doses. Sedation was observed at 2.0 and 5.0 mg/kg and was so intense at 10 mg/kg that no exploration occurred. Amylobarbitone also increased relative open arm exploration at both 15 and 30 mg/kg while having no significant effect on total entries.

ACTH and picrotoxin

Picrotoxin significantly reduced the proportion of open arm entries (Table 1). At 2.0 mg/kg total entries were not affected while at 4.0 mg/kg these were reduced despite the complete absence of sedation. ACTH was inactive at 0.05 mg/kg but markedly reduced relative open arm exploration at

Table 2. Effects of α-adrenoceptor agonists on maze exploration. Values are expressed as mean ± standard error. Significance of differences from corresponding vehicle control * $2P < 0.05$; ** $2P < 0.01$; [a] mean of (open/total) ratio for individual animals, see text

Drug/dose (mg/kg)		Mean number of entries in 10 min (vehicle control values in brackets)			
		Open	Total	Open/total[a]	Open/total ratio as % vehicle control
Azepexole	1.0	5.7 ± 2.2 (6.5 ± 2.1)	14.7 ± 4.5 (19.0 ± 4.9)	0.40 ± 0.01 (0.34 ± 0.01)**	117.6
	2.0	6.7 ± 2.7 (4.8 ± 0.8)	17.3 ± 5.4 (17.1 ± 2.6)	0.38 ± 0.02 (0.29 ± 0.02)*	131.0
	4.0	1.2 ± 0.2 (3.8 ± 0.4)	3.8 ± 0.4 (12.4 ± 1.4)	0.31 ± 0.03 (0.31 ± 0.01)	100.0
Clonidine	0.005	3.8 ± 2.3 (4.8 ± 1.2)	13.8 ± 3.6 (17.0 ± 2.4)	0.27 ± 0.02 (0.28 ± 0.01)	96.4
	0.01	4.2 ± 1.0 (6.0 ± 1.3)*	11.3 ± 2.9 (18.6 ± 3.7)*	0.37 ± 0.02 (0.32 ± 0.01)*	115.6
	0.05	3.0 ± 1.7 (5.7 ± 1.8)*	9.2 ± 4.1 (16.0 ± 4.3)*	0.33 ± 0.01 (0.35 ± 0.01)	94.2
	0.075	1.0 ± 0.8 (5.7 ± 1.8)**	5.7 ± 1.8 (16.0 ± 4.3)**	0.19 ± 0.05 (0.35 ± 0.01)*	54.3
Guanabenz	0.1	6.8 ± 2.1 (4.7 ± 1.8)	17.3 ± 5.9 (14.8 ± 4.9)	0.40 ± 0.01 (0.31 ± 0.01)**	129.0
	0.25	4.2 ± 1.5 (6.0 ± 2.0)	11.2 ± 4.6 (17.8 ± 4.8)*	0.38 ± 0.02 (0.32 ± 0.04)*	118.8
	1.0	0.8 ± 0.4 (5.8 ± 1.0)**	4.0 ± 0.9 (16.8 ± 2.5)*	0.21 ± 0.05 (0.35 ± 0.01)**	60.0
Phenylephrine	0.25	0.5 ± 0.3 (3.0 ± 0.3)**	8.7 ± 1.6 (13.5 ± 1.0)	0.04 ± 0.03 (0.22 ± 0.02)**	18.2
	1.0	0.2 ± 0.2 (4.6 ± 0.5)**	5.0 ± 1.3 (15.8 ± 1.5)**	0.02 ± 0.02 (0.29 ± 0.01)**	6.9
	2.5	0.0 ± 0.0 (2.3 ± 0.5)**	1.2 ± 0.2 (9.3 ± 1.5)**	0.02 ± 0.0 (0.24 ± 0.01)**	0.0
ST 587	0.1	5.0 ± 0.9 (4.3 ± 0.9)	15.1 ± 1.4 (12.6 ± 0.2)	0.32 ± 0.04 (0.34 ± 0.04)	94.1
	0.5	3.3 ± 1.0 (4.6 ± 0.8)	11.3 ± 2.3 (14.3 ± 2.1)	0.29 ± 0.06 (0.30 ± 0.02)	96.7
	1.0	1.5 ± 0.9 (4.6 ± 0.8)**	8.1 ± 2.8 (14.3 ± 2.1)**	0.12 ± 0.06 (0.32 ± 0.02)**	37.5
	2.0	0.2 ± 0.2 (3.2 ± 0.8)**	3.2 ± 0.6 (10.1 ± 1.5)**	0.03 ± 0.04 (0.27 ± 0.05)**	11.1

Table 3. Effects of α-adrenoceptor antagonists on maze exploration. Values are expressed as mean ± standard error. Significance of differences from corresponding vehicle control * $2P < 0.05$; ** $2P < 0.01$; [a] mean of (open/total) ratio for individual animals, see text

Drug/dose (mg/kg)		Mean number of entries in 10 min (vehicle control values in brackets)			
		Open	Total	Open/total[a]	Open/total ratio as % vehicle control
Piperoxane	5.0	4.8 ± 1.5 (6.6 ± 1.3)	15.4 ± 2.6 (18.0 ± 2.9)	0.31 ± 0.03 (0.36 ± 0.02)	86.1
	10.0	2.4 ± 2.2 (4.4 ± 1.5)*	9.6 ± 4.8 (12.4 ± 3.8)	0.22 ± 0.06 (0.35 ± 0.01)**	62.9
RS21361	5.0	3.8 ± 2.9 (6.3 ± 2.1)	13.5 ± 2.2 (15.3 ± 2.2)	0.26 ± 0.05 (0.41 ± 0.05)*	63.4
	10.0	3.2 ± 3.4 (6.3 ± 2.7)	16.3 ± 7.5 (19.2 ± 6.9)	0.16 ± 0.04 (0.32 ± 0.02)*	50.0
Idazoxan	0.125	1.0 ± 0.6 (2.7 ± 0.4)	6.2 ± 0.9 (9.0 ± 1.0)	0.13 ± 0.07 (0.29 ± 0.01)*	44.8
	0.25	0.7 ± 0.4 (2.7 ± 0.4)*	4.7 ± 1.9 (9.0 ± 1.0)**	0.10 ± 0.05 (0.29 ± 0.01)**	34.5
Yohimbine	1.25	4.4 ± 0.9 (6.8 ± 0.5)**	15.8 ± 3.5 (19.6 ± 1.5)	0.28 ± 0.02 (0.35 ± 0.01)**	80.0
	2.5	2.0 ± 1.0 (6.8 ± 0.5)**	8.2 ± 4.9 (19.6 ± 1.5)**	0.26 ± 0.02 (0.35 ± 0.01)*	74.3
	5.0	0.2 ± 0.5 (6.8 ± 0.5)**	3.2 ± 1.1 (19.6 ± 1.5)**	0.04 ± 0.05 (0.35 ± 0.01)**	11.4
Prazosin	0.025	5.2 ± 1.0 (4.3 ± 0.9)	12.3 ± 1.9 (12.6 ± 2.3)	0.42 ± 0.04 (0.34 ± 0.03)	123.5
	0.05	3.8 ± 0.7 (2.7 ± 0.5)	9.0 ± 1.1 (10.0 ± 1.4)	0.42 ± 0.06 (0.27 ± 0.02)*	155.5
	0.1	1.2 ± 0.2 (1.4 ± 0.2)	10.6 ± 1.6 (12.5 ± 1.4)	0.11 ± 0.02 (0.10 ± 0.01)	110.0
	0.25	2.2 ± 0.2 (3.0 ± 0.3)	10.0 ± 0.3 (13.5 ± 1.0)	0.22 ± 0.03 (0.22 ± 0.02)	100.0
	0.5	2.2 ± 0.9 (4.6 ± 0.5)*	9.7 ± 1.9 (15.8 ± 1.5)**	0.18 ± 0.05 (0.29 ± 0.01)*	62.1
	1.0	1.0 ± 0.4 (2.3 ± 0.5)*	4.7 ± 1.1 (9.3 ± 1.5)**	0.17 ± 0.06 (0.24 ± 0.01)	70.8
Thymoxamine	0.1	3.2 ± 0.6 (3.2 ± 0.8)	13.3 ± 1.1 (10.1 ± 1.5)	0.24 ± 0.03 (0.27 ± 0.05)	88.9
	0.5	2.5 ± 0.5 (3.3 ± 0.5)	6.8 ± 0.8 (10.6 ± 1.3)*	0.37 ± 0.02 (0.31 ± 0.02)	119.4
	1.0	1.8 ± 0.3 (3.3 ± 0.5)	7.5 ± 1.0 (10.6 ± 1.3)*	0.24 ± 0.02 (0.31 ± 0.02)*	77.4

0.075 mg/kg despite a reduction in total entries. ACTH did not cause sedation.

Picrotoxin pretreated animals were hyperreactive, both in home cage and in the maze: startle responses occurred to slight sounds or movements such as made by another rat. Sometimes this would initiate a 'chain-reaction' in the home cage, with the startle response of one rat setting off similar responses in the other rats. This did not occur with ACTH.

α-Adrenoceptor agonists

The effects of these agents are shown in Table 2. The picture obtained depended on the dose. At low doses, all three agonists, azepexole, clonidine and guanabenz, significantly increased the proportion of open arm entries. As the dose was increased however, this effect became less and, in the case of clonidine and guanabenz, a significant reduction in

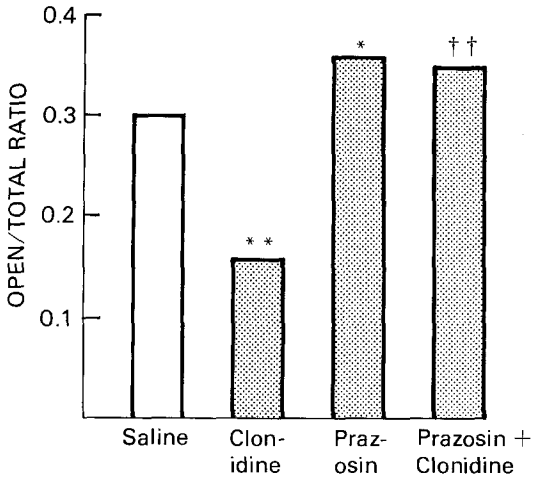

Fig. 1. Effect of prazosin on the reduction in the proportion of open arm/total entries induced by high dose clonidine. Prazosin 0.025 mg/kg injected i.p. 15 min before clonidine 0.075 mg/kg. Remaining groups received prazosin vehicle at this time. One way analysis of variance (Kruskal Wallis) $P < 0.001$. Significance of differences from saline: * $2P < 0.05$; ** $2P < 0.01$; significance of difference from clonidine: $^{++}$; $2P < 0.01$

the proportion of open arm entries ocurred. Total entries showed a dose-dependent decrease in line with increasing home-cage sedation. Phenylephrine and ST 587 produced dose-related decreases in relative open arm exploration. Total exploration decreased at higher doses although sedation was not marked. In fact hyperreactivity resembling that seen with picrotoxin was seen after both drugs at all doses except the highest dose of ST 587.

α-Adrenoceptor antagonists

The effects of these agents are shown in Table 3. Yohimbine produced a dose-dependent decrease in the proportion of open arm entries. Total entries decreased at higher doses despite the absence of sedation. The animals were hyperreactive at all doses. Both doses of RS-21361, idazoxan and piperoxane reduced the proportion of open arm entries, the higher dose in each case being more effective than the lower. Piperoxane and RS-21361 did not significantly affect total entries although idazoxan reduced these at both doses. In no case was sedation noted and hyperreactivity was present in all treatment groups.

Prazosin increased the proportion of open arm entries in doses below 0.1 mg/kg. As the dose was increased, this was reversed into a significant decrease, with a concomitant fall in overall exploration. At these doses (0.5 and 1.0 mg/kg), sedation was severe. Thymoxamine slightly increased relative open arm entries at 0.5 mg/kg although total entries were significantly reduced. When the dose was doubled however, there was a significant decrease in open arm exploration. Thymoxamine produced mild sedation only at the highest dose. Hyperreactivity was not seen with either agent.

Effect of clonidine in the presence of prazosin

In order to investigate further the reduction in the proportion of open arm entries caused by higher doses of α_2-adrenoceptor agonists, the effect of clonidine was investigated in the presence of prazosin, 0.025 mg/kg injected 15 min previously (Fig. 1). This dose of prazosin abolished the relative reduction in open arm entries induced by clonidine, 0.075 mg/kg.

Discussion

The results with control animals show that the X-maze used here behaved similarly to the Y-maze used by Montgomery (1955) in that the rats showed a clear and significant preference for the enclosed arms.

The effects of drugs on exploration in a novel environment could be exerted through mechanisms other than changes in the expression of the 'fear' drive. Changes in 'exploratory' drive (Montgomery 1955) or in general locomotor activity, the occurrence of sedation or drug induced debility could all be predicted to alter exploration. Montgomery (1955) suggested that 'fear' has a relatively greater effect on open than on enclosed arm exploration. In this case, expression of the results as the proportion of the total entries which are made into the open arms should provide a degree of compensation for extraneous effects on exploratory activity and thus give a rather more pure measure of changes in 'fear'-motivated behaviour.

The results obtained with known anxiolytic and putative anxiogenic drugs suggest that this indeed may be the case. Diazepam and amylobarbitone both significantly increased the proportion of open arm entries, even in the presence of severe sedation. Since total exploratory activity was not increased by any dose, it is unlikely that this shift in ratio was due to an enhancement of 'exploratory drive' or locomotor activity. The putative anxiogenic agents picrotoxin (File and Lister 1983) and ACTH (File and Vellucci 1978) reduced total exploration. In the absence of observed sedation or general debility, this could be attributed to a reduction in 'exploratory drive' or in locomotor activity as well as to an enhancement of the 'fear drive'. Open arm entries were, however, reduced to a greater extent than enclosed arms, thus resulting in a significant fall in open/total ratio as predicted by the initial hypothesis.

The alpha-adrenoceptor agonists phenylephrine and ST 587 whch have a high degree of selectivity for the -α_1-adrenoceptor (Drew 1976; de Jonge et al. 1981) consistently reduced the proportion of entries into open arms, thus resembling the putative anxiogenic agents. This occurred at doses not inducing sedation, indeed the animals were hyperreactive. Conversely, at least one dose could be found for each of the agonists with selectivity for the α_2-adrenoceptor which increased the relative exploration of open arms. Clonidine has been suggested to possess anxiolytic activity in the clinic (see Hoehn-Saric et al. 1981). In the present experiments, anxiolytic-like activity was seen over a very narrow dose-range: increasing the dose resulted in an 'anxiogenic-like' picture. This may reflect α_1-adrenoceptor activation since the decrease in relative open arm exploration induced by a high dose of clonidine was prevented by pretreatment with the α_1-adrenoceptor antagonist prazosin. The reversal of the effect of clonidine with increasing dose is consistent with reports that it may make anxiety worse in some patients (see Hoehn-Saric et al. 1981).

The four antagonists with selectivity for α_2-adrenoceptors, yohimbine, piperoxane (Starke et al. 1975; Drew 1976), idazoxan (Doxey et al. 1983) and RS-21361 (Michel et al. 1981) all produced a severe reduction in relative open arm

exploration. As mentioned in the introduction, both piperoxane and yohimbine have been reported to produce anxiety and panic attacks in man. From the present results it appears likely that this is due to an effect at α_2-adrenoceptors and not to idiosyncratic effects of the two drugs. Both the α_1-adrenoceptor agonists and the α_2-adrenoceptor antagonists resembled ACTH and picrotoxin in reducing total exploratory activity in the absence of sedation.

The effects of low doses of the highly selective α_1-adrenoceptor antagonist prazosin (Cavero et al. 1977) in inducing an anxiolytic-like increase in the proportion of open arm entries is consistent with the opposite effects of the corresponding agonists. Reversal of this effect into an 'anxiogenic-like' picture at higher doses is however more difficult to explain. Thymoxamine (Drew 1976) showed similar but less marked effects. Hyperreactivity was not seen with either agent. Prazosin significantly reduced total entries only at the highest dose used and thymoxamine did not have a significant effect on total exploration. Prazosin was very sedative at doses causing 'anxiogenic-like' effects but thymoxamine was not. It therefore appears unlikely that the differential reduction in open arm entries could be accounted for by sedation or by other variables capable of affecting total exploration.

In conclusion, the pattern of exploration of an elevated 'X' maze with alternate open and enclosed arms suggested that this model may provide a valid measure of drug effects on 'fear'-motivated behaviour. The results obtained with known anxiolytic and putative anxiogenic agents were consistent with this proposal. α_1-Adrenoceptor-selective agonists and α_2-adrenoceptor selective antagonists consistently resembled the putative anxiogenic agents ACTH and piperoxane in reducing the proportion of open arm entries. In the lower part of the dose ranges used, α_2-adrenoceptor selective agonists and α_1-adrenoceptor selective antagonists resembled the anxiolytic drugs in increasing relative open arm exploration. It should be noted however that the α-adrenoceptor ligands used have marked peripheral effects. The possibility that these may be at least partly responsible for the results obtained has not yet been completely excluded, especially since it has been demonstrated that elevation of blood pressure *per se* can have central effects such as an alerting effect on the EEG (Baust et al. 1963). The results do however reinforce suggestions that noradrenergic systems are involved in some way in 'fear'-motivated behaviour.

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