Pharmacology Biochemistry & Behavior, Vol. 30, pp. 471–477. © Pergamon Press plc, 1988. Printed in the U.S.A. 0091-3057/88 $3.00 + .00

Biphasic Effects of Clonidine on Conflict Behavior: Involvement of Different Alpha-Adrenoceptors

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Received 31 July 1987

SÖDERPALM, B. AND J. A. ENGEL. *Biphasic effects of clonidine on conflict behavior: Involvement of different alpha-adrenoceptors.* PHARMACOL BIOCHEM BEHAV 30(2) 471–477, 1988.—The effect of the alpha-2-adrenoceptor agonist clonidine on anxiety-related behavior was investigated using two different rat anxiety models: a modified Vogel's drinking conflict model and Montgomery's elevated plus-maze. In both models biphasic dose-response curves were obtained; in a narrow low-dose range (6.25–10.0 μg/kg) the drug produced anxiolytic-like effects, while anxiogenic-like properties were found after higher doses (12.5–80.0 μg/kg). Attempts to block the effects obtained were made in Montgomery's elevated plus-maze. The specific alpha-2-adrenoceptor antagonist idazoxan blocked the anxiolytic-like effect but did not influence the anxiogenic-like activity. Conversely, the specific alpha-1-adrenoceptor antagonist prazosin blocked the anxiogenic-like effect but did not alter the anxiolytic-like activity. These findings may suggest that alpha-1- and alpha-2-adrenergic receptor mechanisms are reciprocally involved in anxiety-related behavior.

Clonidine Anxiolytic-like Anxiogenic-like Alpha-adrenoceptors Vogel's conflict test Montgomery's conflict test Rat

BRAIN noradrenergic neurons have, mainly based on indirect evidence, frequently been claimed to be involved in the pathophysiology of anxiety syndromes (for review see, e.g., [19]). Already in 1961, Holmberg and Gershon reported that yohimbine, an antagonist of noradrenergic alpha-2-receptors, could provoke anxiety in various psychiatric patients [20]. Conversely, clonidine, an alpha-2-adrenoceptor agonist, has been shown effective not only in the treatment of panic disorder but also on opiate-, alcohol-, and nicotine-withdrawal states, all of which include components of anxiety [2, 12, 13, 18, 24, 37]. Furthermore, the tricyclic antidepressant imipramine and the benzodiazepine alprazolam lower baseline plasma levels of the noradrenaline metabolite 3-methoxy-4-hydroxy-phenylglycol (MHPG) in panic patients, indicative of decreased noradrenergic turnover as a result of anti-panic treatment with those drugs [5,6].

In primates, Redmond *et al.* [28] could induce a behavior resembling fear or anxiety when electrically stimulating the major brain noradrenergic nucleus, the locus ceruleus (LC). The same type of behavior was elicited after systemic administration of the alpha-2-adrenoceptor antagonist piperoxan [30]. Conversely, after lesioning of the LC, the animals no longer exhibited the normal signs of fear when subjected to fear-provoking situations [29].

Agonists and antagonists of the alpha-2-adrenoceptors, decrease and increase, respectively, firing in rat LC neurons after systemic, as well as after microiontophoretic administration [4,36]. In addition, numerous investigations have shown that most, but not all, potent anxiolytic drugs lower LC-firing (e.g., [32]).

Taken together, the above described data have provided the basis for a hypothesis on the pathophysiology of anxiety, focusing on LC neuronal activity; increased LC-firing is believed to promote anxiety, while decreased firing is thought to result in anxiolysis [31].

In the present study the effect of clonidine was investigated in two different animal "anxiety" models; Vogel's conflict test (VT) and Montgomery's conflict test (MT). The VT has earlier been shown specific and reliable for detecting substances with anxiolytic properties [40], while the MT specifically can detect both anxiolytic and anxiogenic compounds [26,27]. In the MT, antagonists of alpha-1- and alpha-2-adrenoceptors were used in order to determine the receptor systems involved in the effects obtained. The results are discussed in relation to the LC hypothesis of anxiety.

METHOD

Subjects

Male rats of the Sprague-Dawley strain (Anticimex; Sollentuna, Sweden) weighing 200–300 g were used. The

animals were kept under regular light-dark conditions (light on at 5:30 a.m. and off at 5:30 p.m.) and at a constant temperature (25°C) and humidity (65%). There was an acclimation period of at least 1 week in the animal maintenance facilities of the department prior to the start of the experiments. Food and tap-water were available ad lib when the animals were not participating in the VT or in the shock threshold test. Different groups of drug naive animals were used for each test.

Vogel's Conflict Test (VT)

A previously described [10] modification of Vogel's conflict model was used. On the first day of the experiment the animals were adapted for ten minutes to a Plexiglas box (inner dimension 30×24×20 cm) enclosed in a sound-proof cage and equipped with a grid-floor of stainless steel bars and a drinking bottle containing 5.5% (w/v) glucose solution. A 24-hour period of water deprivation followed after which the animals were adapted for another 5 minutes to the same test chamber. Also during this period the animals had free access to the glucose solution. Subsequently, they were allowed a 30-minute drinking session in their "home" cage. After another 24 hours of water deprivation the animals were again placed in the box. When finding the drinking-spout (usually within 20 sec) the subject was allowed to drink for 30 seconds after which the first electric shock (0.16 mA for 2 seconds) was administered between the spout of the drinking bottle and the grid-floor. Upon every further attempt to drink a new electric shock was administered. The number of shocks accepted during a 10 minute session was recorded.

Shock Threshold Test

In order to maintain conformity with the conflict test the animals were treated identically in the shock threshold test, including water deprivation for 48 hr. Ten minutes after drug injection, the rat was placed in the Plexiglas box described above. The shock regulator device was situated in another room. The shock threshold was determined step-wise by manually increasing the current delivered through the grid-floor (0.05, 0.06, 0.08, 0.10, 0.13, 0.16, 0.20, 0.25, 0.3, 0.4, 0.5, 0.6 mA) until the rat showed a reaction to the electrical stimulus (jump, jerk or similar) as judged by an assistant situated in the test room and blind to the treatment and the shock level applied. There was a 15 sec shock-free interval between each step. The current amplitude threshold was recorded.

Montgomery's Conflict Test (MT) (= the Elevated Plus-Maze)

The apparatus, which was placed in a semi-illuminated room, consisted of an elevated (1 m above ground) plus-formed maze with a mesh-wire floor. Every arm was 40 cm long and 10 cm wide. Two opposing arms were surrounded by black 10 cm high walls (closed arms), while the other arms were devoid of walls (open arms). The floor underneath the maze was covered with bright white paper.

Initially the animal was removed from its home cage and put in an unfamiliar environment for five minutes, immediately after which it was placed in the center of the maze facing a closed arm. The investigator was situated 2 m from the center equidistant from a closed and an open arm. Entry into an arm was defined as the animal placing all four paws into the arm. The cumulative time spent in, as well as the number of entries made into, open or closed arms was recorded during a five-minute test session. The time spent in, and the number of entries made into, the open arms were expressed as percent of the total time spent in, and of the total number of entries made into, both open and closed arms. In the present set of experiments control rats typically spent 20–30% of the total time in the open arms and made 20–30% of the total number of entries into open arms.

The plus-maze was carefully wiped with a wet towel after each tested animal. All experiments were carried out between 10 a.m. and 4 p.m. During this period of time control rats respond similarly (Söderpalm and Engel, unpublished data). Every animal was used only once. The placement of the animal in an unfamiliar environment prior to the test increases the total number of entries ([26]; unpublished data), thus reducing the risk of erroneous random distribution of the open:closed relationships.

Upon administering well-known anxiolytic drugs more time is spent in, and more entries are made into open arms [26,38]. Conversely, when administering anxiogenic compounds the time spent in, and the number of entries made into open arms decrease [27]. On the other hand, neuroleptics and antidepressants, drugs with pronounced psychotropic effects including sedation, are devoid of effects on the relationship open/closed arms [26]. The conflict moment in the MT is believed to be derived from the animal's inborn urge to explore the new environment and its simultaneous fear of the high open spaces [26]. This conflict behavior thus appears more physiological than that occurring in the commonly used punished procedures.

Drugs

Clonidine HCl (Boehringer-Ingelheim) was dissolved in 0.9% saline. Idazoxan (Reckitt and Colman) was dissolved in distilled H_2O, while prazosin HCl (Pfizer) was diluted in a few drops of glacial acetic acid, gently warmed and adjusted to acceptable pH with NaOH. The final volume was made up by 5.5% glucose. All drugs were administered IP in volumes of 2.0 ml/kg. Clonidine was given 30 minutes before the MT. Drugs used to block an effect (prazosin and idazoxan) were injected 50 minutes prior to the test (20 minutes before clonidine). In the VT clonidine was administered 10 minutes prior to the test situation.

Statistics

Differences between treatment groups were statistically evaluated by means of a one-way analysis of variance (ANOVA) followed by Student's *t*-test. Kruskal-Wallis' analysis of variance was used for evaluation of the shock threshold data. Probabilities of less than 5% were considered significant.

RESULTS

In the VT clonidine at 6.25 μg/kg increased the number of shocks accepted by approximately 50%, as compared to controls ($p<0.001$; Fig. 1). In the higher doses used (12.5 and 25.0 μg/kg) significant ($p<0.001$) decreases by approximately 50% were observed instead (Fig. 1). There were no changes in shock threshold amplitudes after 6.25 or 25.0 μg/kg (Table 1).

In the MT, significant increases, as compared to controls, of entries made into (139±14%, $p<0.01$), and of time spent in (221±40%, $p<0.001$), open arms were obtained at the lowest dose of clonidine used (10.0 μg/kg). On the contrary, de-

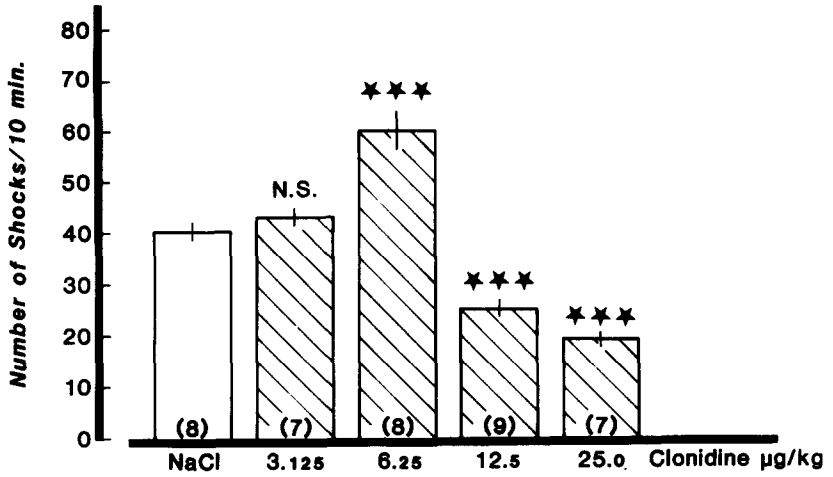

FIG. 1. Effect of clonidine in a modified Vogel's conflict test. The drug was injected IP 10 minutes prior to the test. The number of electric shocks accepted during a ten-minute test session was recorded. Shown are the means±S.E.M. Statistics: One-way ANOVA, $F(4,34)=41.35$, $p<0.001$, followed by t-test. ***$p<0.001$, n.s.=not significant ($p>0.05$) as compared to controls (NaCl). The number of animals in each group is indicated in brackets.

TABLE 1

EFFECT OF CLONIDINE ON SHOCK THRESHOLD

Dose µg/g	Shock Threshold mA	n
0 (vehicle)	0.16 ± 0.01	10
6.25	0.15 ± 0.01	10
25	0.17 ± 0.01	10

The drug was injected IP 10 minutes prior to the test. Shown are the means ± S.E.M. Statistics: Kruskal-Wallis' analysis of variance ($H=0.68$, no differences between treatment groups).

creases (entries: 62±16%, $p<0.01$; time: 48±15%, $p>0.05$; Fig. 2) were found at the highest dose (80.0 µg/kg). At a higher dose of clonidine (160.0 µg/kg) no entries were made into the open arms. Actually, at this dose, the animals made only one entry into the closed arms and remained there for the rest of the observation period (data not shown).

Clonidine thus exhibited biphasic inversely U-shaped dose-response relationships with regard to conflict behavior in the two different behavioral models used. In a narrow low dose-range anticonflict properties were observed, while proconflict effects (i.e., decreases, as compared to controls, of drinking attempts and percentage of entries made into open arms, respectively) were found after the higher doses.

In the MT, the anticonflict effect of clonidine was completely blocked (Entries: $p<0.01$; Time: $p<0.001$) after pretreatment with the specific alpha-2-adrenoceptor antagonist idazoxan [7] in a dose (10.0 µg/kg) not affecting the behavior per se (Fig. 3A). The alpha-1-adrenoceptor antagonist prazosin (250.0 µg/kg), however, had no statistically significant effect on the anticonflict effect of clonidine (Fig. 3A). The proconflict effect, on the other hand, was blocked by the same inert dose of prazosin, although this blockade reached statistical significance only with regard to the percentage of entries made into the open arms ($p<0.05$, Fig. 3B). Idazoxan (10.0 µg/kg), however, failed to block the proconflict effect. Also higher doses (30.0 µg/kg and 1.0 mg/kg) of idazoxan were tried without affecting this effect (data not shown).

Clonidine decreased the total number of entries at the highest dose (80.0 µg/kg) tried ($p<0.001$). This effect was not altered by pretreatment with prazosin (250.0 µg/kg) or idazoxan (10.0 µg/kg) (Table 2). There was no significant correlation between the percentage of entries made into open arms and the total number of entries made after clonidine 80.0 µg/kg ($k=0.37$, $p>0.05$).

DISCUSSION

Clonidine increased the number of shocks accepted in the VT at a dose not affecting the shock threshold amplitude. At approximately the same dose it increased the amount of time spent in, as well as the number of entries made into, the open arms in the MT. It is thus reasonable that clonidine exerts a true anticonflict effect in the VT, not due to unspecific drug effects such as increased drinking motivation or analgesia. Moreover, in the MT the total number of entries made (a measure of locomotor activity) was unaffected at the anticonflict dose, ruling out general sedative or stimulating effects being responsible for the anticonflict effects observed. Other investigators have also reported anxiolytic-like activity of clonidine in the MT at the dose used in the present study [15]. In punished conflict procedures, however, usually higher doses have been required to obtain anticonflict effects [23,33].

The efficacy in the VT was approximately 60 shocks, which about equals the efficacy of L-5-HTP and apomorphine with regard to anticonflict activity in this model [16,17]. Benzodiazepines, on the other hand, generally possess higher efficacies [38]. Thus, with regard to anticonflict activity in the VT, manipulations of the monoaminergic systems, as compared to that of the GABAergic, do not seem as efficient. This could implicate that GABA-benzodiazepine mechanisms are more directly involved in this type of conflict behavior.

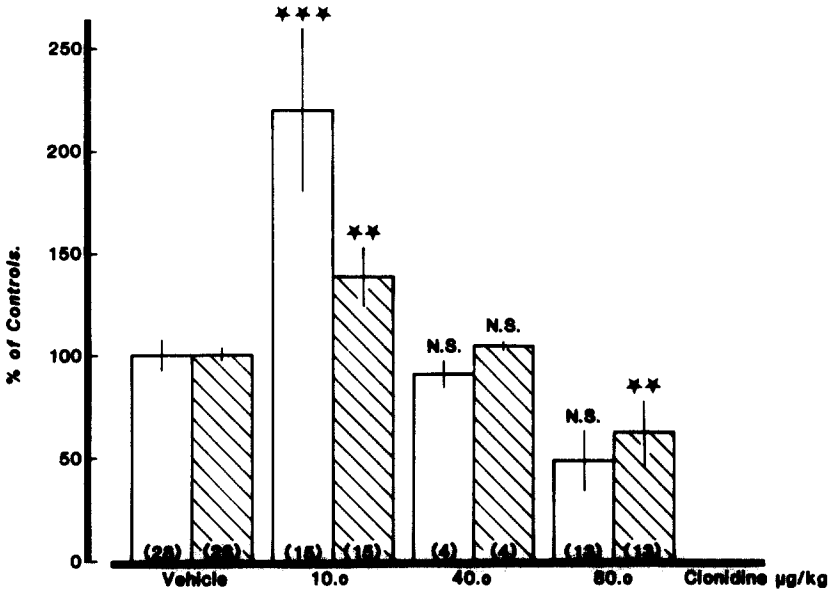

FIG. 2. Effect of clonidine in Montgomery's conflict test. The drug was injected IP 30 minutes prior to a five-minute test session. The recorded data were treated as outlined under the Method section and are presented as percent of controls. Shown are the means±S.E.M. Statistics: One-way ANOVA [Time: $F(3,56;=10.49$, $p<0.001$; Entries: $F(3,56)=8.50$, $p<0.001$] followed by t-test. $^{**}p<0.01$, $^{***}p<0.001$, n.s.=not significant ($p>0.05$) as compared to controls. For each group, n is indicated in brackets. Open bars: time in open arms; slashed bars: entries into open arms.

TABLE 2

DRUG EFFECTS ON THE TOTAL NUMBER OF ENTRIES MADE IN MONTGOMERY'S CONFLICT TEST DURING A FIVE MINUTE TEST SESSION

Treatment	µg/kg	Number of Entries	n	Level of Significance
Vehicle		15.2 ± 0.8	34	
Clonidine	10.0	15.4 ± 0.9	18	n.s.
	80.0	8.4 ± 1.2	13	$p<0.001$
Idazoxan	10.0	17.3 ± 1.2	12	n.s.
Prazosin	250.0	10.9 ± 0.8	8	$p<0.01$
Idazoxan + Clonidine	10.0 + 10.0	17.7 ± 1.3	10	n.s.
Prazosin + Clonidine	250.0 + 10.0	13.3 ± 0.7	6	n.s.
Idazoxan + Clonidine	10.0 + 80.0	8.6 ± 1.7	8	$p<0.001$
Prazosin + Clonidine	250.0 + 80.0	6.2 ± 2.0	6	$p<0.001$

Drugs were injected as outlined under Fig. 3. Shown are the means ± S.E.M. Statistics: One-way ANOVA, $F(8,106)=10.48$, $p<0.001$, followed by t-test (compared to vehicle).

In the higher dose-range clonidine exerted proconflict effects in both models. In the MT the total number of entries was lowered after clonidine 80.0 µg/kg, thus indicating sedative effects of the drug at this dose. It could be argued that decreased exploratory activity and putatively fewer drinking attempts due to sedation could be responsible for the anxiogenic-like effects observed in the two models in higher doses. An earlier evaluation of the MT by Pellow *et al.* [26] indicated, however, that other drugs causing sedation, such as haloperidol or mianserin, may lower the total sum of entries, without altering the ratio open/closed entries. Prazosin's inability in the present set of experiments to block the clonidine effect on overall activity (*vide infra*), while it reversed the effect on the percentage of open arm entries provides further evidence for these effects being mutually independent. In addition, the lack of a significant correlation between the percentage of entries made into open arms and the total number of entries made after clonidine 80.0 µg/kg is in line with the contention that the decreased ratio observed at this dose reflects a true proconflict effect. A similar anxiogenic-like effect of clonidine in the MT has earlier been reported at approximately the same dose [15].

Interestingly, in a clinical trial on panic disorder, some patients displayed increased anxiety when treated with clonidine [18]. Given the apparent narrow dose-range with respect to anxiolytic-like properties and the subsequent anxiogenic-like effect outlined above, it is not surprising that, at a given dose, some patients responded with increased anxiety.

In the MT, the anxiolytic-like effect of clonidine was completely blocked by the alpha-2-adrenoceptor antagonist idazoxan. This is in agreement with that the anticonflict effect of clonidine could be blocked with the alpha-2-adrenoceptor antagonist yohimbine in a punished conflict procedure [23]. The alpha-1-adrenoceptor antagonist prazosin, on the other hand, could not block the anticonflict effect. Thus,

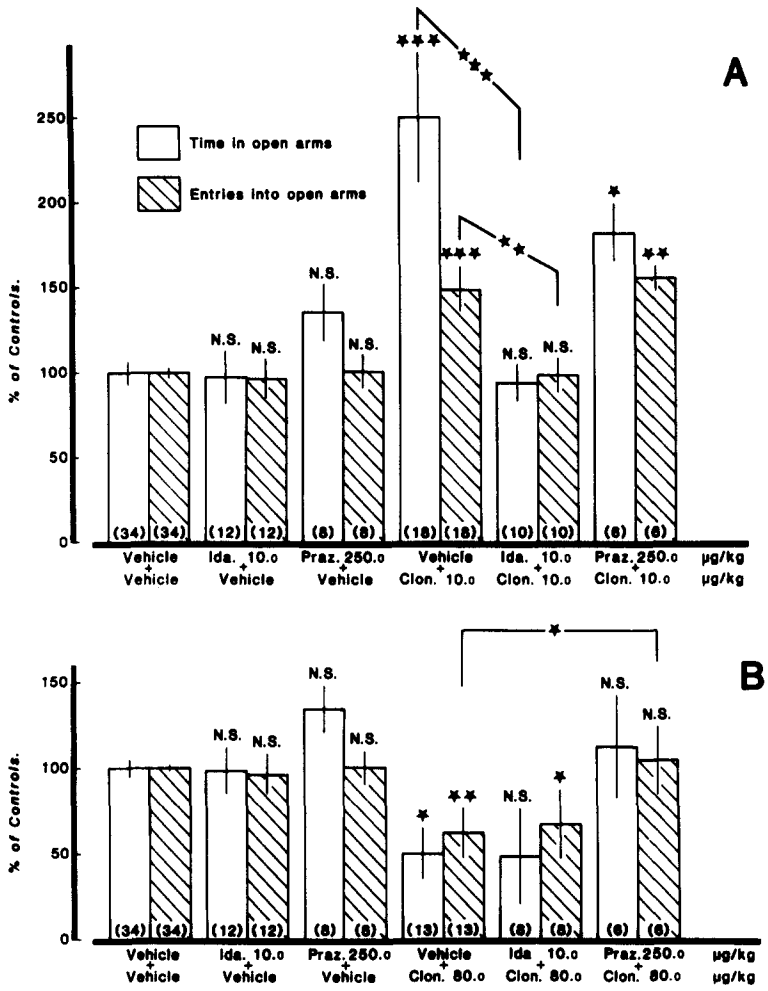

FIG. 3. The effects of idazoxan and prazosin on the anti-(A)- and pro-(B)-conflict effect of clonidine in Montgomery's conflict test. Idazoxan and prazosin were given IP 50 minutes and clonidine 30 minutes before the five-minute test session. The recorded data were treated as outlined under the Method section and are presented as percent of controls (vehicle). Shown are the means±S.E.M. Statistics: One-way ANOVA [Time: $F(8,106)=8.93$, $p<0.001$; Entries: $F(8,106)=6.37$, $p<0.001$] followed by t-test. $^{*}p<0.05$, $^{**}p<0.01$, $^{***}p<0.001$, n.s. =not significant ($p>0.05$). For each group, n is indicated in brackets.

these data provide further support for the assumption that the anxiolytic-like effect of clonidine is mediated through alpha-2-adrenoceptor mechanisms.

The anxiogenic-like effect, however, was not affected by idazoxan, whilst completely blocked by an inert dose of prazosin. It is known that clonidine can activate also central alpha-1-adrenoceptors [1,3]. Moreover, it has been shown that the alpha-1-adrenoceptor agonist ST 587 exerts proconflict effects in the MT [15]. Thus, the anxiogenic-like effect after higher doses of clonidine may be exerted through an alpha-1-agonistic action. Handley and Mithani earlier demonstrated a proconflict effect of clonidine in the MT in a dose similar to the one used in the present experiments [15]. These authors also blocked the effect with prazosin but used a dose with anticonflict action per se, thus making the interpretation difficult.

Surprisingly, neither idazoxan nor prazosin antagonized the decreased overall motor activity observed after the higher dose of clonidine. If the lowered motor activity reflected sedative properties, a reversal might have been expected after the alpha-2-adrenoceptor antagonist, since clonidine is known to induce sedation via alpha-2-adrenoceptors [8]. If instead the anxiogenic-like action of clonidine accounted for the effect, a prevention by the alpha-1-adrenoceptor antagonist would have been expected. It is possible, however, that the effect results from a combined action at alpha-1- and alpha-2-adrenoceptors at this high dose and thus pretreatment with both idazoxan and prazosin might reverse the effect. Alternatively other effects of clonidine, e.g., histaminergic [35], could be involved. Evidently this issue remains to be elucidated.

The results from the present study are compatible with the hypothesis that alpha-adrenergic receptor mechanisms may be involved in the regulation of different states of anx-

iety (see Introduction). Most investigators seem to believe that the anxiety-related effects of alpha-adrenergic agents are exerted through direct activation of receptors located in the CNS, although putative peripheral actions secondarily affecting brain functions have not been excluded (see, e.g., [9]).

If the anticonflict effect of clonidine observed in the present study is indeed primarily exerted in the CNS, it is by no means clear if it is mediated via pre- or postsynaptically located alpha-2-adrenoceptors. Even though anxiolytic-like effects of clonidine have been attributed to a presynaptic action (see Introduction), it has been shown that other central effects of clonidine, e.g., sedative, hypotensive and growth hormone releasing effects, appear to be mediated by postsynaptically located receptors [11, 22, 25, 34]. Moreover, after lesioning of the forebrain projections from rat LC, the ameliorating effect of clonidine on opiate-withdrawal remained unchanged [39], indicating that the effect is (1) exerted in brain areas different from the forebrain, (2) postsynaptically mediated or (3) primarily peripherally mediated. Furthermore, alpha-2-adrenoceptors are present presynaptically on serotonergic neurons (so-called heteroceptors), (14) and the activation of these attenuates serotonergic activity. Decreased serotonergic activity has earlier been shown to produce anticonflict effects in animals [10, 17, 21].

In conclusion, the present findings may suggest that alpha-1- and alpha-2-adrenergic receptor mechanisms are reciprocally involved in anxiety-related behaviors, while the locations of these receptors remain unknown.

ACKNOWLEDGEMENTS

This study was supported by grants from the Swedish Medical Research Council (Grant No. 4247), the Faculty of Medicine, University of Göteborg, Lundbecks fond för psykofarmakologisk forskning, the Tercentenary Fund of the Bank of Sweden, the Swedish Society of Medicine, Stiftelsen Söderström-Königska sjukhemmet and Gyllenstiernska Krapperups Stiftelsen. The expert technical assistance of Miss Margit Englund and Mr. Kenn Johannessen is gratefully acknowledged. Boehringer-Ingelheim, Reckitt and Colman and Pfizer are thanked for generously providing the drugs.

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