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Modulation of Vigilance and Behavioral Activation by Alpha-1 Adrenoceptors in the Rat

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PUUMALA, T., P. RIEKKINEN, SR. AND J. SIRVIÖ. *Modulation of vigilance and behavioral activation by alpha-1 adrenoceptors in the rat.* PHARMACOL BIOCHEM BEHAV **56**(4) 705–712, 1997.—This study investigated the role of alpha-1 adrenergic receptors in the modulation of attention and behavioral activity by assessing the effects of alpha-1 adrenergic receptor stimulation or blockade on the performance of rats in tasks involving vigilance (sustained attention) and selective attention [five-choice serial reaction time (5-CSRT)]. Pretesting subcutaneous administration of St-587 (a putative alpha-1 agonist) at 100 μg/kg, but not at 300 or 1000 μg/kg, significantly improved the choice accuracy of rats in the 5-CSRT task (monitoring of visual stimuli), whereas prazosin (a prototype alpha-1 antagonist) at 300 μg/kg administered subcutaneously slightly impaired choice accuracy of the rats in this task. Prazosin at 100 μg/kg blocked the ability of St-587 at 100 μg/kg to improve choice accuracy. Furthermore, St-587 at 100 μg/kg significantly increased the number of trials completed and reduced the probability of premature responses, whereas prazosin at 300 μg/kg decreased the number of trials completed and the latency of animals to make correct responses in the task. Prazosin at 100 μg/kg blocked the effect of St-587 at 100 μg/kg in increasing the number of trials completed. However, prazosin at 100 μg/kg did not abolish the effect of St-587 in reducing the probability of premature responses. Because the effect of St-587 at 100 μg/kg in improving choice accuracy is rather modest, it is possible that when the 100- and 300-μg/kg doses of St-587 were administered in a counterbalanced order, this effect could have been overlooked due to day-to-day variation. Thus, the present results suggest that stimulation of alpha-1 adrenergic receptors can facilitate vigilance. © 1997 Elsevier Science Inc.

Arousal Attention Noradrenergic Alpha-1 adrenoceptors Vigilance Rat

ELECTROPHYSIOLOGICAL findings (5,18,40,43) and anatomical (1,18) and behavioural data (9–12,17,42) all point to an important role for the noradrenergic system in the regulation of neocortical arousal, vigilance, and responses to novel, salient stimuli. Noradrenaline enhances responses to sensory inputs in many brain areas and at the same time inhibits background activity. This enhancement of the signal-to-noise ratio has been suggested to be important in attention and memory (18–20). In addition, noradrenaline, with the other ascending systems, modulates signal transmission (21,29), synaptic and behavioral plasticity (4,13,18,20,23,24,26,31).

Noradrenaline exerts its functions through alpha and beta adrenoceptors, which are divided into subclasses [for review, see (33,50)]. Three main adrenoceptor families (alpha-1, alpha-2, and beta) each contain at least three distinct and closely related subtypes [see (33)].

The aim of our recent project has been to study whether alpha-1 adrenoceptors play a role in the modulation of cognitive functions. The experiments reported herein investigated the influence of alpha-1 agonism and antagonism on attention and behavioural activation. Therefore, the effects of St-587, which is a putative agonist of alpha-1 adrenoceptors (14,36,37), and prazosin, which is a prototype antagonist of alpha-1 adrenoceptors [see (25,35)], were studied on the performance of adult rats in a five-choice serial reaction time (5-CSRT) task. In this behavioral paradigm, rats are required to discriminate spatially a short visual stimulus occurring randomly in one of five locations. During the testing period, a rat is required to allocate its attention sufficiently that it is able to discriminate the brief stimulus and maintain a sufficient activity level so it can respond appropriately (8). The task resembles the Leonard's 5-CSRT task commonly used to assess different forms

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of arousal in humans (56), and it permits the investigator to separate attentional processes and motor activity from food-motivated behavior (12).

MATERIALS AND METHODS

Animals

Thirteen male Han:Wistar rats were used in the experiment. The rats were 2½ and 7 months old at the beginning of behavioral training and testing, respectively. The rats were housed singly in stainless steel shoebox cages (44 × 27 × 15 cm, length × width × height) with elevated coverings. The cages were placed in an environment with controlled temperature (20 ± 1°C), humidity (55 ± 10%), and light period (lights on 0700–1900). During training and testing, the rats were deprived of food for 16–17 h before the daily training or testing session. After daily behavioral training or testing, the rats received 15–18 g of food pellets (SDS, Special Diets Service Ltd., Witham, Essex, UK) so that they maintained approximately 80–85% of their free-feeding weight. Water was available ad lib except in the test apparatus. This study had the approval of the provincial government of Kuopio, Finland (approval number Zd 128, 1994).

Pharmacological Agents

The drugs used in the study were St-587 (Boehringer Ingelheim KG, Ingelheim am Rhein, Germany), an alpha-1 agonist (100, 300, and 1000 μg/kg), and prazosin (Research Biochemicals International, Natick, MA, USA), an alpha-1 antagonist (100 and 300 μg/kg). St-587 has been described as a selective alpha-1 adrenoceptor agonist (14), but it has also been shown to have alpha-2 antagonistic properties (37). Prazosin has been described as an antagonist of alpha-1 adrenoceptors [see (25, 35)], but recently it has been shown to bind with nanomolar affinity to alpha-2B and alpha-2C adrenoceptors (6) and to have a low affinity for alpha-2A adrenergic receptors (7). Prazosin was dissolved in deionized water (1 mg/ml) and injected subcutaneously. St-587 was dissolved in saline and injected subcutaneously (1 ml/kg). Prazosin and St-587 were administered 30 min and 45 min, respectively, before the training session.

Saline or vehicle and the different doses of drugs were tested in a counterbalanced order every third day. When the effects on performance of the attentional task of St-587 at 100 μg/kg and prazosin at 100 μg/kg alone and in combination were studied (see below, experiment VII), a Latin-square design was used. The wash-out period between drug administration in the different experiments was 15 days.

In the 5-CSRT task, the drug experiments were: I, St-587, 100 μg/kg (n = 13); II, St-587, 100 and 300 μg/kg (n = 13); III, repeat testing with St-587, 100 μg/kg (n = 13); IV, St-587, 300 and 1000 μg/kg (n = 13); V, prazosin, 100 and 300 μg/kg (n = 13); VI, prazosin, 300 μg/kg (n = 13); VII, St-587, 100 μg/kg + prazosin, 100 μg/kg (n = 12, because one trial was interrupted by a computer failure).

Five-Choice Serial Reaction Time Task

Testing was conducted in two testing apparatuses. The apparatuses (8), which were made in the Technical Center, University of Kuopio, each consisted of a 25 × 25-cm aluminium chamber with a curved rear wall. Nine 2.5-cm-square holes 4 cm deep were set 2.5 cm above floor level in the curved wall. Each hole had an infrared photocell beam crossing the entrance vertically and illuminating a photoelectric cell. A standard 3-W bulb at the rear of each hole provided illumination of the hole. The entrances to holes 2, 4, 6, and 8 were blocked with a metal cap. Food pellets (45 mg, dustless; Campden Instruments Ltd., Loughborough, UK) could be dispensed automatically into a magazine at the front of the chamber. Access to the magazine was gained through a Perspex door (= panel). The distances from the panel to the illuminated holes at the rear of the box were all 25 cm. The chambers were illuminated by a 3-W house light mounted in the roof. The animals were introduced to the chambers through a Perspex door in the upper half of the front wall. The apparatuses were housed in dark, soundproof compartments. On-line control of the apparatuses and data collection were performed by using microprocessors that had been programmed using Spider BASIC (Paul Fray Ltd., Cambridge, UK).

Rats were trained in the following manner to discriminate spatially a brief visual stimulus, presented randomly by the computer in one of the five holes (from left, holes 1, 3, 5, 7, and 9). On the first three days of behavioural training, all rats were magazine-trained by being placed in a chamber for 15 min with the house light on and the magazine containing 30–40 food pellets. In the next phase, during which the house light was on, the rats were placed in a chamber for 15 min and a food pellet was delivered into the magazine every 20 s. In the third phase, one of the holes was illuminated during the entire 15-min training period, and every time a rat made a response (nose-poke) in the illuminated hole it was reinforced by delivery of a food pellet into the magazine.

After this initial training, rats entered the next phase, which started with delivery of a single food pellet. The first trial was started when the rat opened the panel to collect the food pellet. After a fixed delay (intertrial interval, ITI), the light at the rear of one of the holes was illuminated for a short period (stimulus duration). The light stimulus was presented in each of the holes an equal number of times during each complete session, and the order of presentations was randomized by the computer. A response (nose-poke) by a rat in the illuminated hole and a response in that particular hole for a short time period after illumination (the limited hold) was rewarded with delivery of a food pellet, and a correct response was recorded. The next trial was initiated when the rat opened the panel to collect the food pellet. A response in any other hole (incorrect response) or a failure to respond at all during the limited hold (omission) resulted in a period of darkness (time-out). Therefore, if a rat was facing in the wrong direction when the visual stimulus was presented in a hole, it would not have detected it; such a trial resulted in an omission and a period of time-out. Responses made in the holes during the ITI period were recorded as premature (or anticipatory) responses, and these responses resulted in a period of time-out. Responses made into a magazine during the ITI were also recorded, but they did not result in a time-out. After a time-out, the next trial was initiated when the rat opened the panel (the magazine was empty). The latency between the onset of the stimulus and the response (whether correct or incorrect) was measured, as well as the latency to collect the earned food pellet after the completion of a correct response. Each daily training session (five sessions/week) consisted of 20–30 min training. During the first session of training, the stimulus duration and limited hold periods were set at 4.0 s and 0.5 s, respectively. These durations were then progressively altered to 0.5 s and 3.5 s, respectively during the training. The ITI and time-out were set at 5.0 s and 4.0 s, respectively. Each rat was trained on this schedule depending on its own perfor-

mance until a stable level of performance had been reached. The criteria for advancing in the training program were that the proportion of correct responses was over 50%, the proportion of errors of omission (i.e., failures to respond) was lower than 15%, and the number of trials was higher than 20 per 15-min training period. This required about 40–50 training sessions.

In order to avoid "ceiling effects" in the drug tests, during the period of drug testing the duration of light stimuli was shortened to half of the standard (0.25 s) and the limited hold was set at 3.75 s. The mean value of the percent correct parameter decreased from 78% to 60% due to shortening of the stimulus length. Chance level in the 5-CSRT task is 20%.

The following behavioural parameters were analyzed in each session: the total number of trials started (correct responses + incorrect responses + omissions + premature responses), the total number of trials completed (correct responses + incorrect responses), the percent omissions [number of omissions/(trials completed + omissions)], the percent correct responses (correct responses/trials completed), the percent premature responses (premature responses/trials started), and response latencies for correct responses as well as for food collection.

Statistical Analysis of Data

Behavioural data were assessed by analysis of variance (ANOVA), which was used to analyze the treatment effects (saline and different doses of drugs) and interactions between these effects on different parameters reflecting attention, memory, and behavioural activity. Before ANOVA, data were normalized using appropriate transformations. The percent correct, percent premature responses, and percent omissions data were transformed using arcsine transformation; the data for latencies were transformed using logarithmic transformation; and the data for the number of trials were transformed using square root transformation. Post hoc tests, e.g., two-tailed *t*-tests, were used to compare different doses of a drug with a vehicle treatment. The data from experiments in which two doses of the same drug were administered in a counterbalanced order were also analysed so that residual effects of the different treatments could be studied and the carryover effects could be evaluated. A 2×4 ANOVA was used when carryover effects in the experiment employing the combination of two drugs (St-587 at 100 μg/kg and prazosin at 100 μg/kg) were examined. When the residual effects were analysed, $p < 0.1$ was accepted as statistically significant.

RESULTS

St-587 at a dose of 100 μg/kg significantly improved the choice accuracy of rats in the 5-CSRT task [$F(1, 12) = 4.95$, $p < 0.05$ and $F(1, 12) = 10.96$, $p < 0.01$ for repeat testing] (Fig. 1). St-587 at 100 μg/kg significantly increased the number of trials completed and decreased the proportion of premature hole responses, as well as slightly decreasing the percent omissions (Table 1).

When administered in a counterbalanced order with 100 μg/kg of St-587, 300 μg/kg did not affect choice accuracy of rats in the attentional task (Fig. 1) [$F(2, 24) = 2.19$, $p > 0.1$]. St-587 at 300 μg/kg did not affect the number of trials completed, proportion of hole responses, percent omissions, or latencies for correct responses and food collection (Table 1). Statistical analysis of residual effects revealed a nonsignificant carryover effect of the doses on choice accuracy [$F(1, 11) = 0.07$, $p > 0.1$]. Furthermore, no significant time effect was observed in this analysis [$F(1, 11) = 0.96$, $p > 0.1$], and there was no significant interaction between time and administration order of the drug doses [$F(1, 11) = 0.58$, $p > 0.1$]. No significant residual effects of the drug doses were found on trials completed [$F(1, 11) = 0.52$, $p > 0.1$], percent premature hole responses [$F(1, 11) = 0.39$, $p > 0.1$], percent omissions made [$F(1, 11) = 2.49$, $p > 0.1$], and latencies for correct responses [$F(1, 11) = 0.00$, $p > 0.1$] and for food collection after correct responses [$F(1, 11) = 1.32$, $p > 0.1$]. Further analysis of the data revealed a significant time effect on percent premature hole responses [$F(1, 11) = 5.16$, $p < 0.05$], percent errors of omission [$F(1, 11) = 3.40$, $p < 0.1$], and latency for correct responses [$F(1, 11) = 4.52$, $p = 0.057$]. Furthermore, the interaction between time and the order of the drug administrations was found to be significant when the percent omission values were analysed [$F(1, 11) = 6.69$, $p < 0.05$]; this also approached the level of significance when values for percent premature responses were analysed [$F(1, 11) = 3.95$, $p = 0.072$].

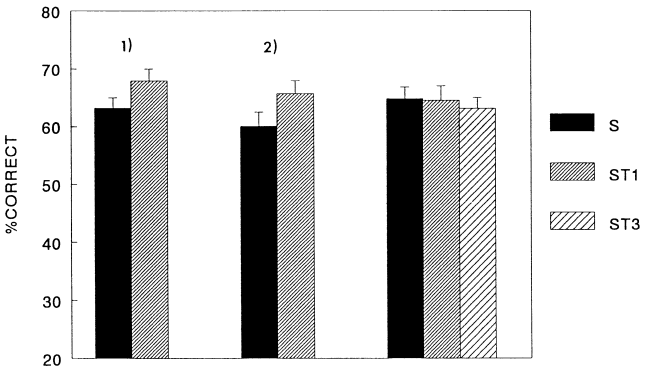

FIG. 1. Percent correct responses in the 5-CSRT task at the shortened stimulus duration (25 cs) for rats treated with saline (S) or 100 μg/kg of St-587 (ST1) ["1"] indicates the results of the first testing and "2"] indicates the results of the second testing with 100 μg/kg of St-587] and for rats treated with saline (S) or 100 or 300 μg/kg of St-587 (ST1 and ST3, respectively). Data are expressed as mean + SEM.

Seven of the 13 animals tested and treated with 1000 μg/kg of St-587 did not complete any trials, and the rest of the rats tested with this dose completed only a few trials, making a great number of omissions. Thus, the data from this experiment were excluded from further analysis (data not shown).

Prazosin at 300 μg/kg significantly reduced choice accuracy of rats in the attentional task [$F(1, 12) = 4.89$, $p < 0.05$] (Fig. 2). In addition, prazosin at 300 μg/kg markedly decreased the number of trials completed and lengthened the latency for correct responses. When prazosin doses of 100 and 300 μg/kg were administered in a counterbalanced order, the 300-μg/kg dose level no longer had any effect on choice accuracy (Fig. 2), number of trials completed, or latency to make correct responses (Table 2). No significant residual effect of the drug doses was found on choice accuracy [$F(1, 11) = 0.84$, $p > 0.1$], trials completed [$F(1, 11) = 0.47$, $p > 0.1$], percent premature hole responses [$F(1, 11) = 0.03$, $p > 0.1$], percent omissions [$F(1, 11) = 0.37$, $p > 0.1$], and latencies for correct responses [$F(1, 11) = 0.02$, $p > 0.1$] and for collection of food pellets from the magazine [$F(1, 11) = 0.94$, $p > 0.1$].

ANOVA revealed a significant overall treatment effect on choice accuracy [$F(2, 22) = 3.44$, $p = 0.050$] (vehicle, St-587 at 100 μg/kg, and the combination of St-587 at 100 μg/kg

TABLE 1

EFFECTS OF St-587 AT 100 (ST1) OR 300 μg/kg (ST3) ON TRIALS COMPLETED (Trials), PERCENT PREMATURE HOLE RESPONSES (% ITI Hole), PERCENT OMISSIONS (% Omissions), LATENCY TO MAKE CORRECT RESPONSES (Clate), AND LATENCY TO COLLECT EARNED FOOD PELLETS AFTER CORRECT RESPONSES (Mlate)

	Trials	% ITI Hole	% Omissions	Clate	Mlate
Saline	77.8 ± 5.3	30.3 ± 3.3	15.2 ± 2.9	0.76 ± 0.04	1.59 ± 0.20
ST1	95.1 ± 6.7***	22.7 ± 3.2*	12.2 ± 2.6	0.75 ± 0.04	1.82 ± 0.24
$F(1, 12), p$	25.70, <0.001	5.88, <0.05	4.54, = 0.055	0.23, >0.1	0.59, >0.1
Saline	86.5 ± 7.0	24.5 ± 2.9	13.1 ± 2.0	0.77 ± 0.04	2.00 ± 0.30
ST1	99.6 ± 10.2	24.7 ± 3.4	9.3 ± 2.6*	0.79 ± 0.06	2.02 ± 0.30
ST3	90.4 ± 10.0	18.4 ± 4.0	13.8 ± 3.9	0.79 ± 0.03	2.15 ± 0.40
$F(2, 24), p$	1.59, >0.1	2.18, >0.1	2.58, >0.05	0.21, >0.1	0.01, >0.1
Saline	98.6 ± 8.2	24.7 ± 3.0	8.7 ± 2.1	0.80 ± 0.08	2.09 ± 0.34
ST1	105.5 ± 10.0	18.9 ± 2.7***	10.2 ± 2.3	0.71 ± 0.03	1.92 ± 0.24
$F(1, 12), p$	1.03, >0.1	61.72, <0.001	2.17, >0.1	1.72, >0.1	0.10, >0.1

The upper results for St-587 at 100 μg/kg are data from the first testing, and the lower figures are data for repeat testing with this dose. Data are expressed as mean ± SEM. *$p < 0.05$, ***$p < 0.001$ vs. saline treatment (paired-samples t-test, two-tailed significance).

and prazosin at 100 μg/kg were taken into analysis) (Fig. 3). Prazosin at 100 μg/kg blocked the effect of St-587 at 100 μg/kg to improve choice accuracy ($t = -3.56$, df = 11, $p < 0.01$ for St-587 in comparison with vehicle and $t = -0.05$, df = 11, $p > 0.1$ for the combination of St-587 at 100 μg/kg and prazosin at 100 μg/kg compared with vehicle treatment, paired-samples t-test). ANOVA revealed a nonsignificant overall treatment effect on choice accuracy [$F(2, 22) = 1.08$, $p > 0.1$] (vehicle, prazosin at 100 μg/kg, and the combination of St-587 at 100 μg/kg and prazosin at 100 μg/kg were taken into analysis). Table 3 shows the effects of St-587 at 100 μg/kg, St-587 at 100 μg/kg plus prazosin at 100 μg/kg, and prazosin at 100 μg/kg alone on trials completed, percent premature hole responses, proportion of omissions, and latencies for correct responses and for food collection. Within-subject 2 × 4 ANOVA revealed a nonsignificant residual effect of the drug administrations on choice accuracy [$F(3, 8) = 0.39$, $p > 0.1$], trials completed [$F(3, 8) = 0.24$, $p > 0.1$], percent errors of omission made [$F(3, 8) = 1.38$, $p > 0.1$], percent premature hole responses [$F(3, 8) = 1.10$, $p > 0.1$], and latency for correct responses [$F(3, 8) = 0.85$, $p > 0.1$]. A significant residual effect was found on latency for food collection [$F(3, 8) = 3.6$, $p < 0.1$].

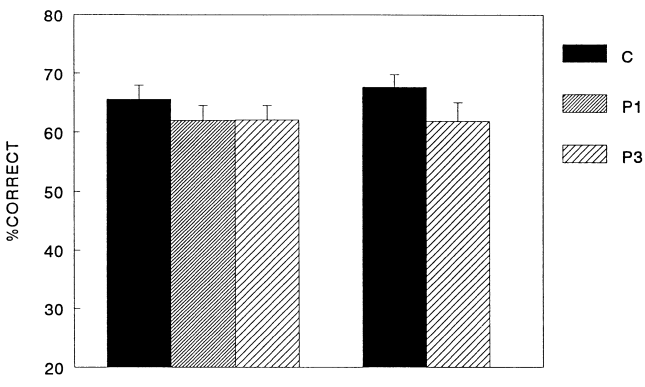

FIG. 2. Percent correct responses in the 5-CSRT task at the shortened stimulus duration (25 cs) for rats treated with vehicle (C) or 100 or 300 μg/kg of prazosin (P1 and P3, respectively) and for rats treated with vehicle or 300 μg/kg of prazosin. Data are expressed as mean + SEM.

DISCUSSION

The purpose of these experiments was to examine the role of alpha-1 adrenoceptors in the modulation of higher cerebral functions by investigating the effects of alpha-1 adrenergic receptor stimulation and blockade on the performance of rats in an attentional task.

Subcutaneous administration of the alpha-1 agonist St-587 at 100 μg/kg slightly improved choice accuracy of rats in the attentional task and decreased the proportion of premature hole responses, which is indicative of reduced impulsivity. Because the premature hole response interrupts an ongoing trial, St-587 at 100 μg/kg slightly increased the number of trials completed. Furthermore, the observation that St-587 at 100 μg/kg decreased the probability of omissions is interpreted as an increase in vigilance. Because St-587 at 100 μg/kg did not affect the latency to collect food pellets after correct responses or the latency to make correct responses, which are indicative of motivation for food reward and motoric output, respectively, it seems unlikely that this change reflects an alteration in motivation to perform the task or a change in motor function. In addition, prazosin at 100 μg/kg abolished the ability of St-587 to improve choice accuracy, suggesting that the effect was mediated through central alpha-1 adrenergic receptors. This is in accordance with recent findings that St-587 at 100 μg/kg slightly improved choice accuracy of rats in a delayed nonmatching to position task assessing working memory, but the effect was delay-independent, suggesting that it was probably due to increased vigilance of the animals (39). However, when St-587 at 100 μg/kg was administered with 300 μg/kg in a counterbalanced order, no significant effects on choice accuracy were found,which, according to statistical analysis of residual effects, does not indicate any carryover effect, i.e., the results with the lower dose of St-587 (100 μg/kg) were not dependent on the dosage regime. According to the significant

TABLE 2

EFFECTS OF PRAZOSIN AT 100 (P1) OR 300 μg/kg (P3) ON TRIALS COMPLETED (Trials), PERCENT PREMATURE HOLE RESPONSES (% ITI Hole), PERCENT OMISSIONS (% Omissions), LATENCY FOR CORRECT RESPONSES (Clate), AND LATENCY FOR FOOD COLLECTION (Mlate)

	Trials	% ITI Hole	% Omissions	Clate	Mlate
C	105.7 ± 9.4	22.5 ± 3.0	8.3 ± 2.3	0.73 ± 0.03	2.07 ± 0.53
P1	93.1 ± 9.8	24.0 ± 3.4	10.1 ± 2.5	0.73 ± 0.03	2.24 ± 0.48
P3	97.9 ± 9.3	20.7 ± 3.4	10.0 ± 2.6	0.75 ± 0.04	1.98 ± 0.23
$F(2, 24)$, p	2.75, >0.05	0.54, >0.1	1.01, >0.1	0.32, >0.1	0.48, >0.1
C	102.5 ± 8.7	24.5 ± 1.9	9.3 ± 2.4	0.71 ± 0.02	1.94 ± 0.29
P3	88.4 ± 10.0**	23.1 ± 3.4	10.7 ± 2.6	0.77 ± 0.03**	2.00 ± 0.34
$F(1, 12)$, p	9.25, = 0.01	0.41, >0.1	2.17, >0.1	9.21, = 0.01	0.00, = 1.000

C denotes vehicle treatment. Data are expressed as mean ± SEM. **p = 0.01 vs. vehicle (paired-samples t-test, two-tailed significance).

equal period effects that were found in the analysis of the values of other attentional task variables, there might have been some intra-experimental time effect that affected the results of this experiment; therefore, the slight improvement of choice accuracy seen with the lower dose of St-587 might have overlooked due to day-to-day variation. The baseline mean of trials completed seems to increase slightly from experiment to experiment, but learning to perform the task better from experiment to experiment does not seem to be the reason why St-587 at 100 μg/kg was unable to improve choice accuracy when administered in a counterbalanced order with St-587 at 300 μg/kg, because this experiment was done between two experiments in which the improvement of choice accuracy due to administration of 100 μg/kg was seen. Possibly, a dose–response experiment using a Latin-square design would be optimal for the study in future investigations. Further, the baseline response in the percent omissions decreases from experiment to experiment, and this is likely a reason why no decrease of probability of omissions due to administration of St-587 at 100 μg/kg was observed in later experiments. Additionally, peripheral side effects of St-587 possibly interfered with the performance of rats at higher doses (300 or 1000 μg/kg), because considerable piloerection was observed after St-587 injections at doses higher than or equal to 300 μg/kg, and rats that were given a dose of 1000 μg/kg usually did not even start the trials in the task. Furthermore, the alpha-1 antagonist prazosin, at 300 μg/kg, had an effect opposite the alpha-1 agonist on choice accuracy, and it decreased the number of trials completed.

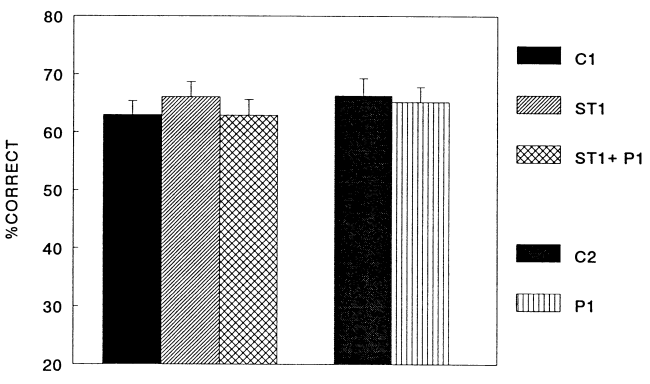

FIG. 3. Percent correct responses in the 5-CSRT task for rats treated with vehicle (C1) or 100 μg/kg of St-587 (ST1) or 100 μg/kg of St-587 plus 100 μg/kg of prazosin (ST1 + P1), or for rats treated with vehicle (C2) or 100 μg/kg of prazosin (P1). Data are expressed as mean + SEM.

Previously, the effects of modafinil, a putative alpha-1 adenoceptor agonist, on motor activity and arousal have been examined. Modafinil was found to increase motor output of mice and rats (16) and to induce an increase in nocturnal activity and behavioural arousal in monkeys (16,22). These effects were considered to be linked to stimulation of central alpha-1adrenoceptors, since they were prevented by prazosin treatment (16,22).

It is interesting that the alpha-1 antagonist prazosin, at 300 μg/kg, slightly impaired choice accuracy and decreased the number of trials completed in a 5-CSRT task. However, it has been shown that noradrenaline depletion caused by administration of a noradrenergic neurotoxin, such as 6-OHDA, which thus mimicks the situation of reduced activation of postsynaptic adrenergic receptors, has no significant effect on baseline performance of rats in a 5-CSRT task (8,11). Furthermore, systemic administration of the alpha-2 adrenoceptor agonist dexmedetomidine, which decreases the firing rate of locus coeruleus neurons, has been shown to have no significant effect on choice accuracy of normal rats in this task (48). However, a noradrenergic lesion was shown to produce a marked decrease in choice accuracy of rats when a burst of loud white noise was presented just prior to the onset of the visual stimuli or when the visual stimuli were presented at an unpredictable rate (11). Thus, one future aim would be to investigate the effects of alpha-1 adrenoceptor blockade on performance of rats with noradrenergic lesions when loud white noise is presented prior to the visual stimuli in this attentional task.

Prazosin at 300 μg/kg also lengthened the latency for correct responses but not the latency for food collection. This result suggests that inhibition of alpha-1 adrenergic receptors causes reduction of motor output and might not be due to reduced motivation for the food reward. However, it is possible that prazosin might have enhanced motivation, which should have been seen as shortened latencies for collection of food rewards, but could have been masked by the ability of the drug to reduce overall motor activity. On the other hand, it could be speculated that lengthening of the latency to respond correctly to the visual stimulus by prazosin 300

TABLE 3

EFFECTS OF PRAZOSIN AT 100 μg/kg (P1) ON TRIALS COMPLETED (Trials), PERCENT PREMATURE HOLE RESPONSES (% ITI Hole), PERCENT OMISSIONS (% Omissions), LATENCY FOR CORRECT RESPONSES (Clate), AND LATENCY FOR FOOD COLLECTION (Mlate) OF RATS TREATED WITH St-587 AT 100 μg/kg (ST1) OR VEHICLE

	Trials	% ITI Hole	% Omissions	Clate	Mlate
C1	97.8 ± 10.1	31.3 ± 2.8	7.7 ± 2.2	0.88 ± 0.14	1.51 ± 0.22
ST1	111.5 ± 7.7	20.1 ± 2.2**	7.1 ± 2.3	0.72 ± 0.03	1.63 ± 0.22
ST1 + P1	98.8 ± 7.8	18.8 ± 2.5**	9.2 ± 2.0	0.78 ± 0.05	1.90 ± 0.18*
C2	103.3 ± 8.6	25.2 ± 3.5	7.3 ± 2.1	0.92 ± 0.21	1.70 ± 0.26
P1	104.0 ± 8.4	22.3 ± 3.4	8.3 ± 2.4	0.73 ± 0.03	1.91 ± 0.27
ANOVA over C1, ST1, and ST1 + P1:					
$F(2, 22)$, p	1.08, >0.1	12.23, <0.001	1.28, >0.1	1.85, >0.1	3.71, <0.05
ANOVA over C2, P1, and ST1 + P1:					
$F(2, 22)$, p	0.38, >0.1	2.55, >0.1	0.47, >0.1	0.42, >0.1	0.85, >0.1

C1 denotes vehicle for St-587 at 100 μg/kg, and C2 denotes vehicle for prazosin at 100 μg/kg. Data are expressed as mean ± SEM. *$p < 0.05$, **$p < 0.01$ vs. C1 (paired-samples t-test, two-tailed significance).

μg/kg treated rats appears to represent a lengthening of the decisional process, which may occur as a result of a reduced ability of the rats to attend effectively to the relevant stimuli in the environment. Others (3) have suggested that the prazosin-induced reduction of the locomotor activity is linked to the regulatory role of prefrontocortical alpha-1 adrenoceptors on cortical dopaminergic transmission [see also (52)]. Interestingly, Trovero et al. (52) failed to demonstrate any [^{3}H]prazosin labelling in the striatum or nucleus accumbens, the subcortical projection areas of substantia nigra and tegmental dopaminergic nerves.

With respect to the ability of St-587 to improve the attentional performance of rats, it is possible to make some proposals about the site and mechanisms of action of the drug. Anatomical data suggest that noradrenergic fibers within the visual system preferentially innervate regions involved in spatial analysis and visuomotor responses (18). Trovero et al. (52) have found the highest amount of [^{3}H]prazosin labelling in the septum and layer III of the cerebral cortex. Slow excitatory (55) and inhibitory effects are evident on neuronal transmission in the neocortex (15,27). Other possibilities are that the effects of St-587 are mediated via alpha-1 adrenergic receptors on cortical cholinergic terminals by modulation of acetylcholine release or indirectly via modulation of GABA release (2,34).

The ascending systems are important in the gating of information at the thalamic level (29,49). A recent electrophysiological study demonstrated that prazosin increased in a dose-dependent manner the number of high-voltage spindles (spike-wave discharges) of adult (5,41) and aged control rats in the cortical electroencephalogram, which is an indication of increased thalamic oscillation (41). This kind of oscillation reduces the accuracy of signal transmission in the thalamic relay nuclei (49) and could lead to an inability to detect the signal. This would be reflected in an increased number of omissions or reduced choice accuracy in the attentional task. Additionally, it has been demonstrated a high density of cells synthesizing alpha-1 adrenoceptor mRNA of receptor type α_{1B} is present in virtually all neurons in the thalamus except the reticular and habenular nuclei, whereas type $\alpha_{1A/D}$ appears to be solely present in the reticular thalamic nucleus (38). Interestingly, St-587 has been shown to dose-dependently decrease neocortical spike-wave EEG discharge activity, a model of absence epilepsy (32), which suggests that stimulation of alpha-1 adrenergic receptors could improve signal transmission via the thalamus. Because the pulvinar nucleus of the thalamus is an important component in the neuronal network of attention (31), and the proper functioning of the lateral geniculate nuclei of the thalamus is essential in mediating visual sensory input to the primary visual cortical area, it is plausible that one site of action of alpha-1 adrenoceptor active agents could be on the thalamic cells, and stimulation or inhibition of these receptors can be reflected in an individual's attentional performance.

Because both St-587 and prazosin bind to alpha-2 adrenergic receptors and are weak antagonists of alpha-2 adrenoceptors, it is important to compare their effects to those of selective alpha-2 adrenergic agents. Atipamezole, a selective antagonist of alpha-2 adrenoceptors (45,53), increased the probability of premature hole responses (47,48), whereas a low dose of dexmedetomidine, a selective agonist of alpha-2 adrenergic receptors (28,44,54), reduced responses reflecting impulsivity of the animals and increased omissions and response latencies (48). Therefore, the alpha-2 antagonist facilitated behavioral activation, and the alpha-2 agonist sedated the rats. However, dexmedetomidine did not impair choice accuracy (48), whereas atipamezole facilitated choice accuracy, at least when the intensity of visual stimuli was reduced (47). Because the behavioral profiles of alpha-2 adrenergic agents differ from those of St-587 and prazosin, the effects of these putative alpha-1 adrenergic agents at alpha-2 adrenoceptors do not seem to account for the present behavioral observations.

Further, it must be noted that prazosin at 100 μg/kg could not abolish the effect of St-587 at 100 μg/kg in reducing the probability of premature responses. It is possible that the effects of St-587 on choice accuracy and premature response are mediated through different subtypes of alpha-1 adrenergic receptors and thus prazosin could not effectively block them completely, because different alpha-1 adrenoceptor subtypes may have different affinities for this prototype drug (33,50,52). Additionally, it could be that 100 μg/kg was not a sufficiently

high dose of prazosin to block this effect of St-587, since no other doses of prazosin were tested. The ability of higher doses of prazosin to block this effect was not investigated because prazosin at 300 μg/kg reduced choice accuracy and this effect would have confused the analysis of blockade on that parameter. The third possibility is that the impulsivity-reducing effect of St-587 is mediated via some unknown mechanism unrelated to alpha-1 adrenoceptors, e.g., through some other neurotransmitter system.

It is also important to consider the contributions of peripheral effects of adrenergic drugs and their interactions with the central mechanisms (30,51). With respect to peripherally mediated effects, St-587 has been shown to dose-dependently increase blood pressure in normotensive rats and cats, and this effect is thought to be mediated via peripheral postsynaptic alpha-1 adrenergic receptors on vascular smooth muscle cells (14), whereas central cardiovascular centres do not seem to be involved in this effect of St-587 treatment (14,36). It seems unlikely that the increased blood pressure per se would result in an improvement in choice accuracy in the attentional task, but it is possible that increased blood pressure could have affected arousal via feedback mechanisms (e.g., via enkephalin release and receptor stimulation on afferent parasympathetic nerves) [see (46)] and thus improved attentional performance.

In conclusion, the present results suggest that the systemic administration of a low dose of an alpha-1 adrenergic agonist facilitates vigilance and decreases impulsivity in rats.

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