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Dose- and Parameter-Dependent Effects of Atipamezole, an α_2-Antagonist, on the Performance of Rats in a Five-Choice Serial Reaction Time Task

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SIRVIÖ, J., P. JÄKÄLÄ, M. MAZURKIEWICZ, A. HAAPALINNA, P. RIEKKINEN, JR. AND P. J. RIEKKINEN. *Dose- and parameter-dependent effects of atipamezole, an α_2-antagonist, on the performance of rats in a five-choice serial reaction time task.* PHARMACOL BIOCHEM BEHAV **45**(1) 123–129, 1993.—The present study investigated whether atipamezole (ATI), a potent α_2-adrenoceptor antagonist that increases the release of noradrenaline in brain, improves attention in rats. Thus, the effects of ATI on the performance of adult male rats in the five-choice serial reaction time task were studied. Food-deprived rats were trained to detect and respond to brief flashes of light presented randomly in one of five spatially diverse locations. The effects of single-dose administration of ATI (0.03–3.0 mg/kg) on the performance of rats under different parametric manipulations of the task were tested: 1) the visual stimuli were presented at unpredictable intertrial intervals (ITIs) or b) the intensity (brightness) of visual stimuli was reduced, thus placing an additional load on attentional processing for animals. Presenting the stimuli earlier than normally or reducing its intensity markedly impaired the choice accuracy of rats. At doses of 0.03, 0.3, and 1.0 mg/kg, ATI improved the choice accuracy of rats when tested using reduced stimulus intensity. ATI 3.0 mg/kg did not affect accuracy performance when tested using reduced stimulus intensity but impaired it when tested using unpredictable ITIs. The other doses of ATI (0.03, 0.3, and 1.0 mg/kg) did not markedly affect choice accuracy of rats tested using unpredictable ITI. Our results could be explained by the assumption that an acute, systemic administration of ATI affects arousal mechanisms and facilitates the processing of visual stimuli related to reward.

α_2-Adrenoceptors Atipamezole Attention Noradrenergic system Rat

ANATOMIC findings have shown that the noradrenaline-containing neurons of the locus coeruleus (LC) are one of the ascending systems of the brain stem innervating the forebrain (16). Neurochemical findings suggest that noradrenaline can act, together with neuropeptides, as a neuromodulator in neuronal systems (5,26). Because the noradrenergic system is affected in disorders of dementia (30), electrophysiological and psychopharmacological studies have been undertaken to reveal the role of these neurons in brain functions.

Electrophysiological studies demonstrate that the noradrenergic system plays an important role in arousal, vigilance, and responses to novel, salient stimuli (3,16,20,23). Noradrenaline is thought to regulate cortical desychronization/synchronization (4,32) and increase the signal-to-noise ratio in the neocortex (26,48), regulate the responsivity of thalamocortical relay neurons (6,33), and facilitate excitatory and inhibitory responses in the limbic system (40,42). Altogether, these electrophysiological findings support a role for the noradrenergic system in maintaining accurate and efficient information processing in the brain.

Noradrenergic lesions disrupt event-related potentials, electrophysiological correlates of novelty detection and attention, both in nonhuman primates (29) and rodents [see the Discussion in (14)]. Psychopharmacological studies further suggest a role for the noradrenergic system in the mechanisms of attention and learning (9,11,15,18,35). Further, evidence for the relationship between reduced noradrenergic activity and impaired attention has been found in patients with Alzheimer's disease (17).

The pharmacological modulation of ascending systems that

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have state-dependent effects on the information networks of the forebrain offers an approach to alleviate age-associated cognitive dysfunctions (25). The firing rate of the neurons in the LC, the major source of the noradrenergic innervation of the forebrain, is regulated by α_2-adrenergic autoreceptors (1,2). The blockade of these receptors increases the firing rate of LC neurons and increases the release of noradrenaline in the brain (8,22). α_2-Receptor blockade can also increase the responsiveness of LC neurons to excitatory stimulation (43).

We are currently investigating whether α_2 antagonists can improve age-associated cognitive dysfunctions (31). The present experiments studied whether pharmacological activation of the noradrenergic system could improve attention. Therefore, the effects of atipamezole, a selective and potent α_2-antagonist (41,45), on the performance of adult rats in a five-choice serial reaction time task were studied. This task, considered to assess attention, requires an animal to detect and respond to brief flashes of light in spatially diverse locations (7). According to our previous findings, atipamezole (0.03–3.0 mg/kg) did not markedly improve the performance of rats when tested in a normal version of a five-choice serial reaction time task (21). In the present experiments, parametric manipulations of the task were used to place an additional load on attention processes for animals. First, the visual stimuli were made unpredictable through presenting the stimuli at varying rates (normal rate, faster or slower than normally). Second, the intensity of the visual stimuli was reduced (7).

METHOD

Animals

Male Kuo : Wistar rats (n = 30) were used. Rats were 4 and 8 months old at the beginning of behavioral training and testing, respectively. Rats were singly housed in Makrolon cages in a controlled environment (temperature 20°C, humidity 50–60%, lights on 0700–2100 h). During training and testing, rats were deprived of food for 22–23 h before daily training or testing. After daily behavioral training or testing, rats received 10–12 g of food pellets (Astra-Ewos, Sweden) so that they were maintained at approximately 85% of free-feeding weight. Water was available ad lib except in the test apparatus.

Behavioral Training and Testing

Apparatus. The test apparatus (7), which was made in the Technical Center (University of Kuopio, Finland), consisted of a 25 × 25-cm aluminium chamber with a curved rear wall. Set in the curved wall were nine 2.5 cm^2 holes, 4 cm deep and 2.5 cm above floor level. 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 the hole provided illumination for that hole. The entrances to holes 2, 4, 6, and 8 were blocked with a metal cap. Food pellets (45 mg, dustless, BioServ) could be dispensed automatically into a magazine at the front of the chamber. Access was gained to the magazine 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 chamber was illuminated by a 3-W houselamp mounted in the roof. Animals were introduced to the chamber through a Perspex door in the top half of the front wall. The apparatus was housed in a dark, soundproof compartment. On-line control of the apparatus and data collection was performed using microprocessors that were programmed using Spider (Paul Fray Ltd., Cambridge, UK).

Training

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 3 days of behavioral testing, all rats were magazine trained by being placed in the chambers for 20 min with the houselight on and the food tray containing 30–40 food pellets. On the next day, rats were placed in the chambers for 20 min and a food pellet was delivered every 15 s into the magazine. The houselight was on during this phase. In the third phase, one of the holes was illuminated all the time during the 20-min training period and every time the rat made a response (nose-poke) on the illuminated hole it was reinforced by a food pellet on the magazine.

After learning this, rats entered the next phase, which started by the free delivery of a single food pellet. The first trial started when the panel was opened 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 for an equal number of times during each complete session, and the order of presentations was randomized by the computer. Responses (nose-pokes) by the rat in the illuminated hole and responses in that particular hole for a short period after the illumination (the limited hold) were rewarded with the delivery of a food pellet and a correct response was recorded. The next trial was initiated when a rat opened the panel to collect a 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 punishment period of darkness (time-out). Therefore, if the rat was facing in the wrong direction when the visual stimulus was presented on a hole it would not detect it and this trial resulted in an omission and a period of time-out. Any response made during the time-out period restarted the time out. Responses made in the holes during the ITI period were recorded as premature (or anticipatory) responses and responses made in the panel during the ITI period were recorded as perseverative responses and they both resulted in a period of time-out. The next trial was initiated when a rat opened the panel after the completion of a time-out period. The latency between the onset of the stimulus and response, whether correct or incorrect, was measured, as well as the latency to collect the earned food pellet following the completion of a correct response. Each daily training session (three sessions a week) consisted of 15 min of training. During the first session of training, the stimulus duration and limited hold periods were set at 5.0 and 1.0 s, respectively. These durations were then progressively altered to 0.5 and 3.5 s, respectively, during the training. The ITI and time-out were both set at 2.0 s for the first training session and then increased to 5.0 and 4.0 s, respectively, during the training. About 70% of adult rats acquired the task within 25 trials.

Rats (n = 18) were trained on this schedule depending upon the rat's individual performance until a stable performance had been reached. It took about 40–50 training sessions to reach a stable level when no further improvement in the performance could be observed.

Behavioral variables. The following parameters are analyzed in each session: a) trials—the total number of trials (correct + incorrect) made during a 20-min testing session; b) ITI responses—the number of premature responses on the holes or perseverative responses in the panel made during the intertrial interval; c) omissions—the number of errors of omissions

TABLE 1

TOTAL NUMBER OF TRIALS COMPLETED (TRIALS), PERCENT CORRECT RESPONSES (%CORRECT), NUMBER OF OMISSIONS (OMISSIONS), NUMBER OF ITI PANEL RESPONSES (PANEL) AND HOLE RESPONSES (HOLES), LATENCY OF CORRECT RESPONSES (CORRECT), LATENCY OF INCORRECT RESPONSES (INCORRECT), AND LATENCY OF FOOD COLLECTION (MAGAZINE) IN A FIVE-CHOICE SERIAL REACTION TIME TASK WITH DIFFERENT INTERTRIAL INTERVALS IN RATS TREATED WITH SALINE OR ATIPAMEZOLE (ATI) (0.03-3.0 mg/kg)

ITI (s)	Saline	ATI 0.03	ATI 0.3	ATI 1.0	ATI 3.0
%CORRECT					
1.5	51.3 ± 7.3	56.2 ± 7.0	49.3 ± 5.8	54.5 ± 4.9	27.4 ± 7.8*
5.0	67.3 ± 3.5	68.9 ± 5.6	68.8 ± 4.1	67.3 ± 3.7	38.8 ± 9.1*
8.0	71.8 ± 3.3	58.8 ± 5.1	69.6 ± 2.3	65.3 ± 4.2	36.6 ± 8.3*
TRIALS					
1.5	7.6 ± 1.0	8.4 ± 1.6	7.6 ± 1.2	7.9 ± 0.9	3.6 ± 1.2*
5.0	16.8 ± 1.7	15.1 ± 2.0	15.4 ± 2.1	13.4 ± 1.9*	6.6 ± 1.8*
8.0	16.1 ± 1.6	12.3 ± 1.5	14.3 ± 1.7	11.6 ± 1.1*	7.8 ± 2.1*
OMISSIONS					
1.5	11.9 ± 1.8	8.7 ± 1.6†	8.6 ± 1.4†	10.5 ± 2.0	5.8 ± 1.3*
5.0	2.9 ± 0.4	2.5 ± 0.6	2.0 ± 0.5	2.3 ± 0.4	2.8 ± 0.6
8.0	2.5 ± 0.4	2.7 ± 0.6	2.7 ± 0.6	2.8 ± 0.6	2.9 ± 0.6
PANEL					
1.5	6.3 ± 1.5	5.1 ± 1.5	3.9 ± 1.2	4.2 ± 1.1	1.4 ± 0.4*
5.0	13.1 ± 3.7	16.2 ± 4.5	14.6 ± 3.1	10.6 ± 2.1	7.4 ± 3.5*
8.0	33.8 ± 10.2	30.8 ± 7.5	44.3 ± 12.4	58.8 ± 17.0	30.9 ± 17.2*
HOLES					
1.5	0	0.2 ± 0.2	0.1 ± 0.1	0.1 ± 0.1	0
5.0	5.1 ± 0.7	7.6 ± 1.6	8.7 ± 1.7*	7.4 ± 1.6	3.2 ± 1.1*
8.0	37.9 ± 5.2	38.0 ± 5.4	50.0 ± 7.0	47.8 ± 7.4	26.3 ± 8.0*
CORRECT					
1.5	1.15 ± 0.17	1.07 ± 0.10	1.18 ± 0.23	1.10 ± 0.19	0.90 ± 0.05
5.0	0.75 ± 0.05	0.72 ± 0.06	0.70 ± 0.06	0.79 ± 0.08	0.74 ± 0.03
8.0	0.68 ± 0.03	0.74 ± 0.04	0.69 ± 0.04	0.79 ± 0.08	0.83 ± 0.07
INCORRECT					
1.5	2.45 ± 0.14	2.30 ± 0.19	2.26 ± 0.15	2.41 ± 0.12	1.96 ± 0.20
5.0	1.49 ± 0.14	1.58 ± 0.10	1.39 ± 0.18	1.64 ± 0.16	1.64 ± 0.16
8.0	1.50 ± 0.16	1.38 ± 0.17	1.27 ± 0.15	1.40 ± 0.13	1.40 ± 0.16
MAGAZINE					
1.5	1.80 ± 0.37	1.33 ± 0.26	2.22 ± 0.58	2.59 ± 1.09	3.57 ± 1.61
5.0	2.48 ± 0.62	2.71 ± 0.57	1.83 ± 0.25	3.22 ± 0.72	5.41 ± 1.87
8.0	2.42 ± 0.54	2.23 ± 0.84	1.76 ± 0.41	2.12 ± 0.41	3.58 ± 1.42

%CORRECT: Treatment effect, $F(4) = 14.8$, $p < 0.001$; ITI effect, $F(3) = 5.2$, $p < 0.01$; Treatment × ITI, $F(8) = 0.7$, $p > 0.1$.

TRIALS: Treatment effect, $F(4) = 32.0$, $p < 0.001$; ITI effect, $F(2) = 6.8$, $p < 0.01$; Treatment × ITI, $F(8) = 0.9$, $p > 0.1$

OMISSIONS: Treatment effect, $F(4) = 2.7$, $p < 0.05$; ITI effect, $F(3) = 25.9$, $p < 0.001$; Treatment × ITI, $F(8) = 2.2$, $p < 0.05$

PANEL: Treatment effect, $F(4) = 6.2$, $p < 0.001$; ITI effect, $F(2) = 19.8$, $p < 0.001$; Treatment × ITI, $F(8) = 1.4$, $p < 0.1$

HOLES: Treatment effect, $F(4) = 10.1$, $p < 0.001$; ITI effect, $F(2) = 131.5$, $p < 0.001$; Treatment × ITI, $F(8) = 3.2$, $p < 0.01$.

CORRECT: Treatment effect, $F(4) = 2.2$, $p > 0.05$; ITI effect, $F(2) = 3.8$, $p < 0.05$; Treatment × ITI, $F(8) = 0.9$, $p < 0.1$

INCORRECT: Treatment effect, $F(4) = 1.5$, $p > 0.1$; ITI effect, $F(2) = 15.6$, $p < 0.001$; Treatment × ITI, $F(8) = 1.1$, $p > 0.1$.

MAGAZINE: Treatment effect, $F(4) = 1.5$, $p > 0.1$; ITI effect, $F(2) = 1.5$, $p > 0.1$; Treatment × ITI, $F(8) = 0.2$, $p > 0.1$.

Results are expressed as mean ± SEM. $n = 18$.

*$p < 0.01$, †$p < 0.05$ as compared to saline using the posthoc Wilcoxon test.

made, that is, the number of times rats failed to respond at all to the visual stimulus; d) response latencies—the latency to respond (the time between the onset of the stimulus and a nose-poke) was recorded separately for correct and incorrect responses; e) magazine latency—the latency to collect earned food pellets from the magazine after a correct response; f) discriminative accuracy—the proportion of correct responses (correct responses/correct + incorrect responses) made, expressed as a percentage.

Parametric manipulations. Varying the duration of the intertrial interval randomly places an additional load on attentional processing. Equal numbers of three different ITIs (1.5, 5.0, and 8.0 s) were randomly intermixed during a 20-min testing session. Reducing the intensity of the visual stimulus to one third of the standard makes it possible to detect possible visual sensory effects. The stimulus intensity was reduced by adding resistors in series with the stimulus bulbs.

Drug testings. Atipamezole HCl (Farmos, Finland) was dissolved in sterile saline. Drug solutions were injected SC (0.5 ml/kg) 30 min before testing sessions. On the first testing day of unpredictable ITIs, all rats (n = 18) were treated with saline. Then, rats were treated with saline and atipamezole (0.03, 0.3, and 1.0 mg/kg) in a counterbalanced order. Testing was performed every second or third day. Two days after this, all rats were treated with atipamezole 3.0 mg/kg before testing.

During the wash-out period of 10 days, all rats were tested three times using the normal version of the task (without any parametric manipulations) and did not receive any injections.

On the first testing day of reduced stimulus brightness, all rats were treated with saline before testing. Then, rats were treated with saline and atipamezole (0.03, 0.3, and 1.0 mg/kg, SC) in a counterbalanced order. Testing was performed every second or third day. After 2 days, all rats were treated with atipamezole 3.0 mg/kg before testing.

According to previous studies, atipamezole is a potent and selective α_2-adrenoceptor antagonist (45) and increases the release of noradrenaline in the brain in a dose-dependent manner (0.03–3.0 mg/kg) (41).

Statistical Analysis

Multivariate analysis of variance (MANOVA) was used to analyze the treatment effect (saline and different doses of a drug) and intertrial interval effect, as well as interactions between these effects in the percent correct responses, the number of trials and omissions, the latency of correct and incorrect responses, and food collection. Before MANOVA analysis, the percent correct data were transformed using arcsine transformation. The number of trials/omissions and latency data were transformed using square root and logarithmic transformations, respectively. If MANOVA revealed an overall treatment effect, the posthoc Wilcoxon signed-rank test was used to analyze differences between treatments (saline vs. different doses of a drug).

RESULTS

Baseline Performance

The baseline performance (mean ± SEM) of rats was as follows: the number of trials completed (50 ± 6), the percent correct responses (74 ± 4), the number of omissions (12 ± 2), the number of ITI panel responses (51 ± 10) and hole responses (17 ± 3), the latency of correct responses (0.87 ± 0.04), incorrect responses (1.53 ± 0.12), and food collection (3.76 ± 0.92).

Unpredictable ITI

MANOVA revealed an overall atipamezole treatment effect and ITI effect in the percent correct responses and a

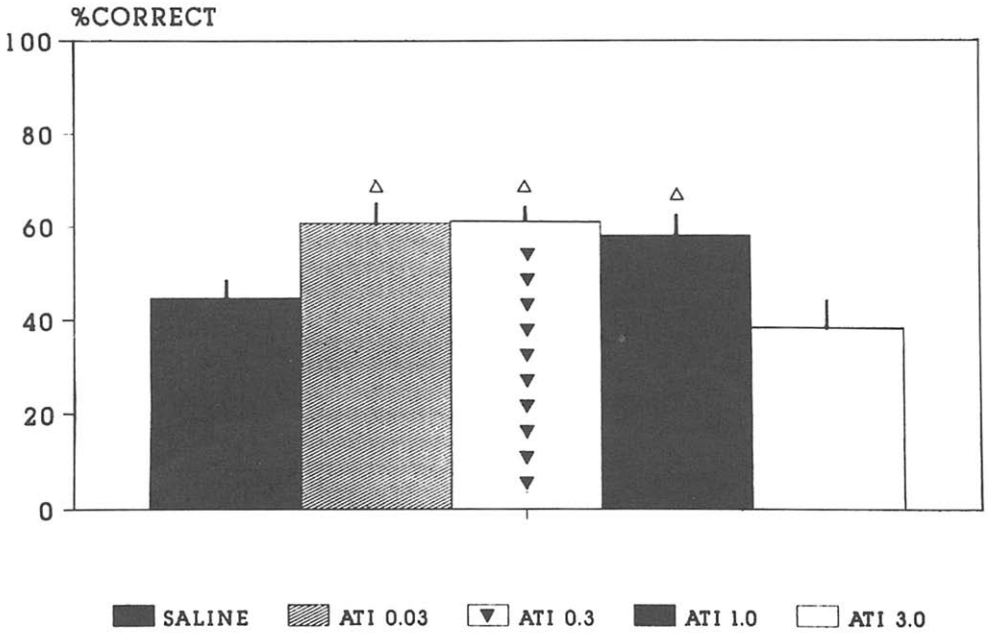

FIG. 1. Percent correct responses of rats treated with saline or atipamezole (ATI, 0.03–3.0 mg/kg, SC) tested in a five-choice serial reaction time task using reduced stimulus intensity. The results are expressed as mean ± SEM. Δ = $p < 0.01$ as compared to saline using the posthoc Wilcoxon test.

nonsignificant interaction between treatments and ITIs (Table 1). The choice accuracy of rats was poorest at the shortest ITI. At the 3.0-mg/kg dose, atipamezole impaired choice accuracy when compared to saline treatment at all intertrial intervals. Other doses of atipamezole (0.3 or 1.0 mg/kg) did not affect the percent correct responses (Table 1).

MANOVA revealed an overall atipamazole treatment and ITI effect in the number of trials completed (Table 1). The number of trials completed was lowest at the shortest ITI. Atipamezole 3.0 mg/kg decreased the number of trials completed at all intervals when compared to saline treatment. Atipamezole 0.03 and 1.0 mg/kg decreased them at the longest ITI (Table 1).

MANOVA revealed an overall atipamezole treatment effect and ITI effect in the number of omissions (Table 1). The number of omissions was highest at the shortest ITI. Atipamezole 0.03, 0.3, and 3.0 mg/kg decreased the number of omissions at the shortest interval. Atipamezole did not affect the number of omissions at the other intervals (Table 1).

MANOVA revealed an overall atipamezole treatment and ITI effect in the number of ITI panel and hole responses (Table 1). The number of responses was highest at the longest ITI. Atipamezole 3.0 mg/kg decreased the number of ITI panel and hole responses at all ITIs (Table 1).

MANOVA revealed a nonsignificant atipamezole treatment effect in the latency of correct and incorrect response, as well as food collection from the magazine after a correct response (Table 1).

Reduced Stimulus Intensity

MANOVA revealed an overall atipamezole treatment effect in the percent correct responses, $F(4) = 6.5$, $p < 0.001$. Atipamezole 0.03–1.0 mg/kg significantly improved choice accuracy of rats when compared to saline treatment (Fig. 1). Atipamezole 3.0 mg/kg did not significantly affect the percent correct responses when tested using reduced stimulus brightness (Fig. 1).

MANOVA revealed a nonsignificant overall atipamezole treatment effect in the number of trials completed, number of omissions, ITI panel and hole responses, as well as in the latency of correct and incorrect responses (Table 2).

MANOVA revealed an overall atipamezole treatment effect in the latency of food collection from the magazine after a correct response (Table 2). Atipamezole 1.0 mg/kg increased this latency (Table 2).

DISCUSSION

The present study investigated whether atipamezole, an α_2-adrenoceptor antagonist that increases the release of noradrenaline in the brain, improves attention assessed by a five-choice serial reaction time task in rats. This task is analogous to Leonard's five-choice serial reaction time task, which has been used in the analysis of different forms of arousal in humans (12).

The presentation of the stimulus at a shorter ITI than normal or the reduction of the intensity of the stimulus impaired the choice accuracy of rats, as has been found previously (7). According to the present findings, the highest dose (3.0 mg/kg) of atipamezole affected behavioral activity and impaired choice accuracy of rats at all intertrial intervals, whereas other doses of atipamezole did not markedly affect the choice accuracy when tested under unpredictable ITIs. According to our previous data, 0.03–3.0 mg/kg atipamezole did not have any effect on choice accuracy at the baseline conditions (21). On the other hand, the present findings showed that atipamezole (0.03–1.0 mg/kg) improved the choice accuracy of rats when tested using reduced stimulus intensity, whereas the highest dose did not affect the percent correct responses of rats tested using that version of the task. According to our preliminary data, 1.0 mg/kg atipamezole improved choice accuracy at the one third stimulus intensity but not at two thirds or normal stimulus intensity (unpublished findings).

It has become evident that interactions between peripheral mechanisms and the central noradrenergic system are important in some aspects of behavior (44). Because atipamezole did not affect choice accuracy at the baseline performance (our preliminary data) and unpredictable ITIs, the improvement in choice accuracy at the reduced stimulus intensity may not be due to altered motivation or homeostasis (e.g., glucose metabolism) of rats. In addition, atipamezole did not evidently improve attention processes per se because it did not increase the percent correct responses in all conditions of the task. However, it cannot be excluded that the ineffectiveness

TABLE 2

NUMBER OF TRIALS COMPLETED, NUMBER OF OMISSIONS, NUMBER OF PANEL AND HOLE RESPONSES DURING ITI, LATENCY FOR CORRECT AND INCORRECT RESPONSES, AND MAGAZINE LATENCY IN A FIVE-CHOICE SERIAL REACTION TIME TASK WITH THE REDUCED BRIGHTNESS OF A STIMULUS IN RATS TREATED WITH SALINE OR ATIPAMEZOLE (0.03–3.0 mg/kg)

	Saline	ATI 0.03	ATI 0.3	ATI 1.0	ATI 3.0
TRIALS	37.6 ± 3.8	44.3 ± 5.7	40.9 ± 5.3	36.8 ± 5.5	28.3 ± 5.1
OMISSIONS	10.5 ± 1.7	8.5 ± 1.9	10.9 ± 1.8	9.4 ± 1.4	9.1 ± 1.9
PANEL	57.1 ± 16.5	45.1 ± 15.0	55.3 ± 17.6	48.2 ± 14.5	48.8 ± 15.9
HOLES	24.3 ± 3.7	26.1 ± 4.3	20.9 ± 4.5	29.1 ± 5.7	21.6 ± 4.7
CORRECT	1.02 ± 0.07	0.95 ± 0.05	1.04 ± 0.12	1.06 ± 0.07	1.01 ± 0.06
INCORRECT	1.63 ± 0.07	1.61 ± 0.07	1.80 ± 0.13	1.73 ± 0.12	1.64 ± 0.13
MAGAZINE	2.43 ± 0.44	3.02 ± 0.88	5.29 ± 1.64	5.92 ± 1.47*	4.24 ± 1.35

Results are expressed as mean ± SEM. $n = 18$.

MANOVA (df = 4): TRIALS ($F = 2.5$, $p > 0.05$); OMISSIONS ($F = 1.4$, $p > 0.1$); PANEL ($F = 0.8$, $p > 0.1$); HOLE ($F = 1.3$, $p > 0.1$); CORRECT ($F = 0.3$, $p > 0.1$); INCORRECT ($F = 1.3$, $p > 0.1$); MAGAZINE ($F = 3.2$, $p < 0.05$).

*$p > 0.05$ as compared to saline using the posthoc Wilcoxon test

of atipamezole on choice accuracy at the baseline conditions could be due to a ceiling effect.

Although visual acuity of rats may not be affected by atipamezole, because this drug does not affect the pupil diameter, it is possible that atipamezole improved visual discrimination of rats. This interpretation of choice accuracy data is of interest in the context of the hypothesis about the role of noradrenaline in the tuning of signals in the brain (28) and the previous findings showing that the firing of the neurons in the LC was dependent upon the overall intensity of stimuli rather than upon some specific features of them (47). The effects of atipamezole on the processing of visual information could take place at the thalamic and/or cortical levels.

Atipamezole can affect the behavioral activity of rats. The present results showed a slightly reduced number of omissions at the shortest ITI and a slightly increased number of ITI hole responses at the longest ITI when tested using unpredictable ITIs. These findings suggest that the low to moderate doses of atipamezole facilitated behavioral activation in rats. A previous study showed behavioral stimulant effects of α_2- antagonists (idazoxan, yohimbine) in a fixed-interval schedule task in rats (38). Electrophysiological data support for the role of the noradrenergic system in activation (40).

One tentative explanation of the present results is increased arousal of rats. The present results indicate that there is an optimal dose range for atipamezole to improve accuracy performance at the reduced stimulus intensity, and the highest dose of atipamezole had disruptive effects on the performance of rats when tested under the conditions of mental stress induced by unpredictable ITIs (15). These findings and the ineffectiveness of atipamezole treatment at the baseline condition could be explained by the well-known inverted-U shaped relationship between arousal and performance, as well as the interaction of this relationship with task difficulty (34,37).

Previously, Carli et al. (7) found that a lesion of the dorsal noradrenergic bundle (DNAB), which markedly decreased the noradrenaline content of the forebrain, aggravated the impairment of short, unpredictable ITIs but did not affect baseline performance or the disruptive effects of reduced stimulus intensity. DNAB did not affect the behavioral activity of rats. Altogether, the results of Carli et al. and ours suggest that the depletion of noradrenaline in the forebrain by DNAB lesion or systemically administered low doses of α_2 adrenoceptor antagonist inducing a release of noradrenaline in brain do not produce an opposite pattern of effects on the performance of rats in a five-choice serial reaction time task. However, the duration of ITIs were different and only one stimulus intensity tested using shorter test sessions in our study when compared to the study design by Carli et al. (7). Further, it is not known how effectively atipamezole binds to the postjunctional α_2 adrenoceptors vs. α_2 autoreceptors, and atipamezole may have effects that are due to a blockade of α_2 adrenergic heteroreceptors. Atipamezole may stimulate dopaminergic and serotonergic neurons (41), and noradrenaline may also regulate the release of acetylcholine in the brain (36,46).

There is other psychopharmacological evidence that systemically administered α_2-adrenergic drugs can affect attention processes. Idazoxan, an α_2-antagonist, has been proposed to improve selective attention (improved conditioning to contextual cues in a maze learning task) (39) and facilitate attentional shift (tested using an acquisition of changed rule for a maze learning task) in rats (13). Equally, clonidine, an α_2- agonist known to decrease noradrenergic activity, impaired covert attention in humans (10). Further, clonidine slowed reaction time whereas yohimbine, a nonselective α_2-antagonist, tended to shorten reaction time in stimulus evaluation–response selection and spatial frequency tasks in humans (19). Halliday et al. (19) suggested that α_2-adrenergic drugs would act on visual information processes that occur relatively early during encoding of the stimulus. Recently, Mervaala et al. (24) suggested that atipamezole (0.1 mg/kg, IV) improved focused attention and impaired divided attention in humans.

In conclusion, our results suggest that a systemic, single-dose administration of atipamezole, an α_2-adrenoceptor antagonist, does not markedly improve choice accuracy of rats during baseline conditions (21) or when the visual stimuli are made unpredictable, but can improve choice accuracy of rats at the reduced stimulus intensity in the five-choice serial reaction time task. This suggests that atipamezole does not improve attentional processes per se but may facilitate the processing of visual information.

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