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BRIEF COMMUNICATION

The Effects of Atipamezole, an Alpha-2 Antagonist, on the Performance of Young and Aged Rats in the Delayed Nonmatching to Position Task

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SIRVIÖ, J., K. LUKKARINEN, P. RIEKKINEN, JR., E. KOIVISTO, R. VIRTANEN, A. PENNANEN, A. VALJAKKA AND P. J. RIEKKINEN. *The effects of atipamezole, an alpha-2 antagonist, on the performance of young and aged rats in the delayed nonmatching to position task.* PHARMACOL BIOCHEM BEHAV **39**(4) 1015–1019, 1991.—The present experiments were undertaken to study whether pharmacological activation of the noradrenergic system would improve age-related deficits in short-term memory. Thus, we investigated the effects the single dose administration (0.1, 0.3, 0.9 and 2.7 mg/kg, subcutaneously) or atipamezole, a specific alpha-2 adrenoceptor antagonist, had on the performance of young and aged rats in a delayed nonmatching to position task. After substantial training, aged rats made more errors at longer delays (4–30 seconds) than did young rats, although the percent correct responses at short delays (0–2 seconds) did not differ between young and aged rats. Atipamezole (0.1–0.9 mg/kg) did not improve the performance of young and aged rats in this task. Moreover, the highest dose (2.7 mg/kg) used increased the number of omissions and increased the latency to collect food pellets, indicating disruption of the performance of rats in this task. According to the present results, alpha-2 antagonist (administered peripherally at a single dose), which increases the release of noradrenaline, did not improve age-related deficit in short-term memory in rats.

Delayed nonmatching Aging Rat Noradrenergic system Alpha-2 adrenoceptors Atipamezole

AGED human subjects and nonhuman primates can show impairments in short-term memory (2,4). Recently, operant chamber tests analogous to those used for primates have been developed to test short-memory of rodents (8, 20, 25). A fimbria-fornix lesion disrupting innervation of the hippocampus produced a deficit in a delayed matching to position task in adult rats which resembled the short-term memory deficit found in aged rats (8,9). The prefrontal cortex, which has extensive connections with the parietal cortex, basal ganglia, thalamus and brain stem as well as with limbic structures, also contributes to short-term memory in primates (12) and rodents (10,13).

Both anatomical and electrophysiological findings suggest that noradrenergic systems play an important role in cognitive functions (3, 11, 14, 26). The results of clinical and experimental studies suggest the involvement of noradrenergic system in cortical arousal, attention, learning and memory storage, as well as retrieval of information (6, 7, 16, 23). Furthermore, clinical and experimental evidence suggest that noradrenergic dysfunction may contribute to an age-associated memory impairment (15,33).

The firing rate of the neurons in the locus coeruleus and the release of nonadrenaline, which may be decreased in brains of aged rats (17,19), are regulated by alpha-2 autoreceptors, and the antagonists of these adrenoceptors increase the firing rate of the locus coeruleus and turnover of noradrenaline in the brain (1,5). Alpha-2 adrenoceptors may also regulate the excitatory input to the locus coeruleus (28).

Atipamezole which is a selective and specific alpha-2 antagonist, increased the turnover of noradrenaline dose dependently (0.03–3.0 mg/kg) (26,32). The present experiments were undertaken to investigate whether the pharmacological stimulation of the noradrenergic system would improve short-term memory in rats. Thus we studied the effects of atipamezole on the performance of young and aged rats in the delayed nonmatching to position task. Our previous studies suggest that the single dose administration of atipamezole (1 and 3 mg/kg) may facilitate

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thalamo-cortical activation (21,22) and information transfer in the hippocampus (30,31) in rats.

METHOD

Animals

Male Wistar rats (National Animal Center, Kuopio, Finland) were used in the present experiments. At the beginning of the training, the rats were 4 (n = 14) and 22 months old (n = 10). The rats were housed singly in Makrolon cages in a temperature (20°C), humidity (50–60%) and light period (lights on 0700–2100) controlled room. During training and testing, the rats were food deprived 23 hours before behavioral training and experiment. After daily training, they received food pellets (Astra-Ewos, Sweden), 10–12.5 grams for young rats and 7.5–10 grams for aged rats. The rats had free access to water except when in the operant chamber. During the behavioral training, one young and one aged rat were excluded because of signs of illness.

Apparatus

Testing was conducted in two operant chambers equipped with two retractable levers and a food dispenser (Campden Instruments, London, UK). The operant chambers were under the online control of microprocessors (Paul Fray Ltd., Cambridge, UK) programmed using SPIDER (Paul Fray Ltd., Cambridge, UK). The food dispenser delivered 45 mg "dustless" precision pellets (Campden Instruments, UK).

Training Schedule

Rats were habituated to the chambers with two retractable levers retracted, and trained to collect food pellets and to associate the click of the dispenser plus illumination of the panel light with pellet delivery. During this training (phase one), a pellet was delivered every time a rat made a nose poke into an illuminated pellet magazine. If a rat did not respond within 45 seconds, the illumination of the magazine was turned off for 5 seconds. The rats were trained 20–30 minutes/day until they learned to obtain at least two pellets/minute. The aged rats learned to collect food pellets more slowly than young rats (data not shown). During phase one, three of nine aged rats collected no or only a few pellets during daily training. These rats were dropped from further testing after two weeks.

In the next phase (phase two), the rats learned to associate the pressing of a lever with delivery of a food pellet. Both levers were inserted and, every time a rat pressed a lever, a food pellet was delivered into the magazine, which was illuminated. If a rat did not react within 45 seconds, the levers were retracted for 5 seconds. Young and aged rats needed one or two training periods in phase two to learn the task (more than one response/minute), and no significant difference was found between young and aged rats (n = 6) (data not shown).

In phase three, rats learned to press a lever (either right or left) when it was inserted into the chamber in order to get a food pellet. The right or left lever was inserted randomly, and if a rat pressed the lever, a food pellet was delivered and the magazine was illuminated. Then, the lever was retracted, and after a 5-second period, one of the levers was inserted once again. If a rat did not press the lever within 45 seconds, the lever was retracted and the house light was turned off for 5 seconds. All the young and aged rats tested in phase three acquired the task in one session (more than one response/minute).

In the next phase, all the rats were trained for nonmatching to position task (0-delay). A right or left lever (cue), which was selected randomly, was inserted to an operant chamber. When a rat pressed the lever, it was retracted and a magazine was illuminated, but no food pellet was delivered. When a rat made a nose poke to a magazine, a magazine light was turned off and both levers were inserted. In this choice phase, the pressing of the noncue lever was reinforced with a delivery of a food pellet into the illuminated magazine. If the rat pressed the cue lever, the house light was turned off for 5 seconds. After a 5-second period, a new cue lever was inserted. If a rat did not press a cue lever (omission 1) or one of the choice levers (omission 2), the house light was turned off for 5 seconds and a new cue lever was inserted after a 5 second interval. During the nine days of testing, aged rats had a slightly lower percentage of correct responses, but nonsignificant interaction between age and training day was found (data not shown), which indicates that the rate of acquisition of nonmatching to position-task did not differ between young and aged rats.

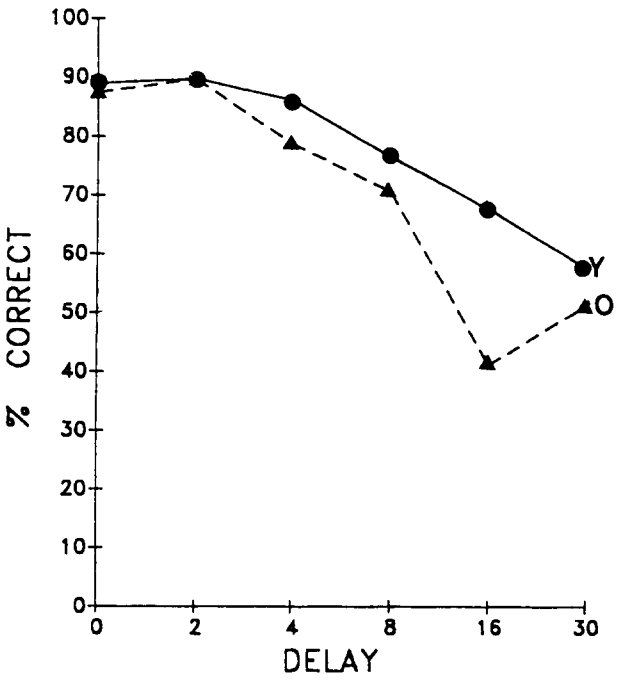

FIG. 1. The percent correct responses at each delay (0–30 seconds) of saline-treated (control treatment for atipamezole 0.1 mg/kg) young (n = 13; solid line) and aged (n = 6; broken line). The percent correct responses (% CORRECT) has been calculated as: correct responses/correct responses + incorrect responses × 100. Statistical analysis using ANOVA: data was analyzed using age and delay as variables. The effect of delay was significant, $F(5,102) = 14.4$, $p<0.01$. The age effect was significant, $F(1,102) = 6.6$, $p<0.02$. Note: The percent correct at short delays (0–2 s) did not differ between young and aged rats ($p>0.1$), but aged rats made more errors at longer (4–30 s) delays ($p<0.05$).

After the rats had been trained for 9 days in the task (>85% correct responses), delays (0, 2, 4, 8, 16 and 30 seconds after the nose poke) before inserting the choice levers were included in this nonmatching task (DNMTP). During each session of DNMTP-task, all delays, which were introduced randomly, were used (about 10 trials/delay). The training (20–30 minutes/day) continued for 38 days before the drug tests were performed. After this training, young rats showed better performance of the delayed task, because aged rats made more errors at long delays (4–30 seconds) than young rats did (Fig. 1).

Drug Tests

Following the training period, the effects of atipamezole [0.1, 0.3, 0.9 and 2.7 mg/kg, SC (0.5 ml/kg)] were tested. The drug

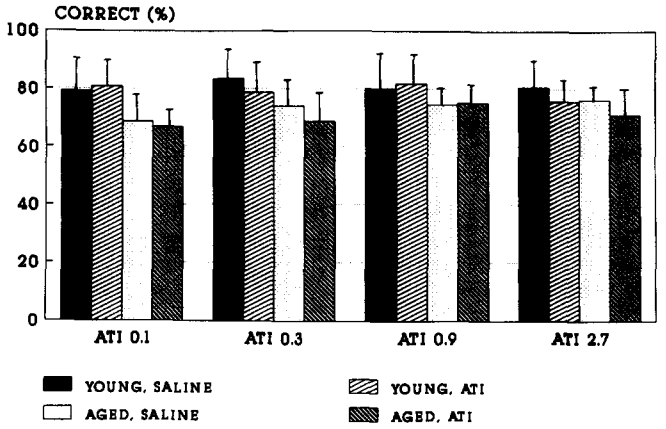

FIG. 2. The percent correct total responses including all delays (CORRECT) of saline and atipamezole (ATI 0.1–2.7 mg/kg)-treated young and aged rats in delayed nonmatching to position task (mean + SD). Statistical analysis using ANOVA: Data was analyzed using age, treatment and delay as variables. The effect of delay was highly significant in all four testings (data not shown). At the doses 0.1, 0.3, 0.9 and 2.7 mg/kg, the treatment and delay × treatment (data not shown) effects were not significant ($p>0.05$).

(one dose/week from the lowest dose to highest dose) was delivered 30 minutes before testing. After the injection of the drug, rats were moved to a laboratory where the operant chambers were situated. During testing, the following parameters were recorded and stored into the hard disk of the computer: the total number of correct and incorrect responses, the number of correct and incorrect responses at each delay, the number of omissions (1 and 2), the mean latencies for responding to cue (sample press), making a nose poke and collecting food. The effect of drug treatment was compared to saline treatment which was tested on the preceding day.

Statistical Analysis

Analysis of variance (ANOVA) was used to compare the effects of age, treatment and training on the parameters of the DNMTP-task measured.

RESULTS

For percentage correct responses, the age effect was significant (Figs. 1 and 2). At doses of 0.1, 0.3, 0.9 mg/kg and 2.7 mg/kg atipamezole did not increase the percentage of correct responses (no significant treatment effect was found in correct responses) (Fig. 2).

In the number of omissions (during cue), the age effect was significant (Table 1). At doses of 0.1, 0.3 and 0.9 mg/kg, no significant treatment effects were found in omissions during cue or choice (data not shown). At the dose of 2.7 mg/kg, atipamezole increased the number of omissions during cue and choice in young and aged rats (a significant treatment effect in the relative amount of omissions during cue and choice) (Table 1).

In the latency to collect food pellets, a significant age effect was found (Table 1). At doses of 0.1, 0.3 and 0.9 mg/kg, no significant treatment effects were found in the latency to collect food pellets (data not shown). At the dose of 2.7 mg/kg, atipamezole increased the latency to collect food pellets in young and aged rats (a significant treatment effect, Table 1).

In the latency of sample press and nose poke, the age effect was not significant (Table 1). At doses of 0.1, 0.3 and 0.9 mg/kg, no significant treatment effects were found in the latency of sample press and nose poke (data not shown). At the dose of 2.7 mg/kg, atipamezole increased the latency of sample press in young and aged rats (a significant treatment effect in the latency to sample press), but it did not affect the latency of nose poke (nonsignificant treatment effect) (Table 1).

TABLE 1

THE NUMBER OF OMISSIONS AT THE TIME TO RESPOND TO CUE (OMISSION 1) AND CHOICE (OMISSION 2), THE LATENCY OF SAMPLE PRESS, NOSE POKE AND FOOD COLLECTION OF YOUNG AND AGED RATS TREATED WITH SALINE (SAL) OR ATIPAMEZOLE (ATI) 2.7 mg/kg

	Young	Aged
Omission 1 (%)		
SAL	12.3 ± 10.4	1.3 ± 2.6
ATI 2.7	33.3 ± 24.9	29.3 ± 36.3
Omission 2 (%)		
SAL	0.1 ± 0.4	0.0
ATI 2.7	1.1 ± 1.2	0.9 ± 1.2
Food Collection (s)		
SAL	0.49 ± 0.11	0.60 ± 0.14
ATI 2.7	0.68 ± 0.28	0.75 ± 0.25
Sample Press (s)		
SAL	2.4 ± 0.7	2.2 ± 0.6
ATI 2.7	3.0 ± 1.1	3.1 ± 0.5
Nose Poke (s)		
SAL	1.1 ± 0.4	1.2 ± 0.6
ATI 2.7	3.1 ± 5.1	1.3 ± 0.7

The results are expressed as mean ± SD.

Omission 1: Age effect was significant, $F(1,34)=8.04$, $p<0.01$. At the dose of 2.7 mg/kg, treatment effect was significant, $F=14.2$, $p<0.01$.

Omission 2: Age effect was nonsignificant, $F(1,34)=0.0$, $p<0.1$. At the dose of 2.7 mg/kg, treatment effect was significant, $F=10.9$, $p<0.01$.

Food collection: Age effect was significant, $F(1,34)=11.1$, $p<0.01$. At the dose of 2.7 mg/kg, treatment effect was significant, $F=6.8$, $p<0.02$.

Sample press: Age effect was nonsignificant, $F(1,34)=1.8$, $p>0.1$. At the dose 2.7 mg/kg, treatment effect was significant, $F=5.0$, $p<0.05$.

Nose poke: Age, $F(1,34)=1.0$, and treatment effects ($F=2.5$) were nonsignificant ($p>0.1$).

DISCUSSION

In order to investigate whether pharmacological stimulation of noradrenergic system improves short-term spatial memory in rats, the effects of atipamezole, an alpha-2 adrenoceptor antagonist which increases the release of noradrenaline, on the performance of young and aged rats in delayed nonmatching to position task was studied.

Aged rats learned to collect food pellets more slowly than young rats. Indeed, three of the aged rats were in the front of the magazine, but they did not make a nose poke even if the magazine contained their normal food and the door of the magazine was open. This may be due to increased phobia or decreased motivation of aged rats. On the other hand, the rate of acquisition of nonmatching to position task (0-delay) did not differ between young rats and aged rats included to this training, because no interaction between age and training day was found between young and aged rats. This agrees with the original findings of Dunnett et al. (9). The forgetting curves of young and aged rats in DNMTP-task are also in line with the study of

Dunnett et al. (9), showing that aged rats had delay-dependent short-term memory deficit.

The main finding of the present study was that the single dose administration of atipamezole did not improve short-term memory of young and aged rats. Furthermore, we found no evidence that atipamezole improved the performance of those young and aged rats which had severely impaired performance (40–55% correct responses) at the longest delays (16 and 30 seconds) (data not shown). This suggests that noradrenergic dysfunction does not contribute to short-term memory impairment of aged rats, or atipamezole is not the optimal drug to restore noradrenergic dysfunction. In line with the first explanation, lesions of the dorsal noradrenergic bundle did not impair the performance of adult rats in delayed matching/nonmatching to position task (25). Furthermore, aged rats are also impaired in nonspatial delayed nonmatching task, but central noradrenaline depletion using DSP-4 or the administration of a β-adrenergic antagonist did not impair the performance of young rats (20). It is also important to note that the levels of cortical and hippocampal noradrenaline are slightly increased in aged Wistar rats (29), but it is not known whether the release of noradrenaline is affected in these rats.

At the highest dose of atipamezole, behavioural inactivity was observed, i.e., the rats made more omissions and had longer latency of sample press and food collection. It would be tempting to speculate that these changes reflect overarousal or anxiety which impair performance in memory task (24). The effects of atipamezole do not, however, seem to correlate well with the increased release of noradrenaline. Previously, it was found that the increase in the release of noradrenaline was almost equivalent at the doses 1 and 3 mg/kg (26), whereas the present behavioural changes showed marked difference between the doses 0.9 and 2.7 mg/kg. Thus the possibility remains that the effects of atipamezole 2.7 mg/kg are related to effects other than the blockade of alpha-2 autoreceptors. The dopaminergic system may play a role in the mechanisms of behavioural activation (7,23). However, atipamezole did not affect the amount of dopamine and metabolites of dopamine in brain tissue of rat or dopamine receptor binding (26,32). On the other hand, atipamezole increased the turnover of serotonin (26). The activation of the serotonergic system has been related to anxiety-like behaviour in animal models (18). At the dose of 2.7 mg/kg, the effects of alpha-1 adrenoceptor (agonism) cannot be excluded (32). Furthermore, the peripheral effects of atipamezole administered systematically can not be excluded.

In conclusion, aged rats had impaired retention on nonmatching to position task at long delays as compared to young rats. This deficit of short-term memory was not attenuated by the administration of atipamezole, which increases the activity of noradrenergic neurons in the central nervous system. The present results suggest that age-related spatial short-term memory impairment is not due to decreased activity of noradrenergic neurons. Further studies employing other noradrenergic drugs, noradrenergic grafts and the analysis of relationships between short-term memory and biochemical markers of noradrenergic system in aged rats are needed to test this hypothesis.

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