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Medetomidine, Atipamezole, and Guanfacine in Delayed Response Performance of Aged Monkeys

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RÄMÄ, P., I. LINNANKOSKI, H. TANILA, A. PERTOVAARA AND S. CARLSON. *Medetomidine, atipamezole, and guanfacine in delayed response performance of aged monkeys.* PHARMACOL BIOCHEM BEHAV **55**(3) 415–422, 1996.— The effects of a highly selective alpha-2 adrenergic agonist medetomidine and its antagonist atipamezole were studied on the delayed response task performance of aged monkeys. Medetomidine, at the dose of 1.0 μg/kg, improved the memory task performance, whereas atipamezole had no effect on the performance at any dose. It has earlier been shown that alpha-2 adrenergic agonists clonidine and guanfacine improve age-associated memory impairment, but also contradictory effects of clonidine have been reported. There is evidence that the ability of alpha-2 agonists to improve DR task performance is due to its selective action on the alpha-2A receptor subtype. Clonidine and medetomidine are much less selective than guanfacine with respect to alpha-2A and alpha-2B receptor subtypes. Therefore, we also studied the effect of guanfacine on the memory task performance of the same aged monkeys in the same testing conditions to compare the effectiveness of these two alpha-2 adrenergic compounds. Guanfacine improved memory task performance at the dose of 0.0001 mg/kg. The results indicate that alpha-2 agonists, independent of their different selectivity with respect to alpha-2A/2B receptor subtypes, are beneficial drugs in improving the performance in the delayed response task. **Copyright © 1996 Elsevier Science Inc.**

Alpha-2 adrenergic drugs Delayed response task Monkeys

THE central catecholaminergic/noradrenergic function declines with aging in several species (12,16,20). This decline is shown to be related to age-associated memory impairment in rats and mice (20,25) and monkeys (32). There is evidence that alpha-2 adrenergic agonists, like clonidine and guanfacine, improve the performance of aged monkeys in the delayed response (DR) task (1,2), and also, but not as effectively, in the delayed matching-to-sample task (3). The ability of alpha-2 agonists to improve memory task performance is thought to result from drug actions at postsynaptic alpha-2 receptors in the prefrontal region (1). The improvement of performance induced by clonidine and guanfacine can be blocked by alpha-2 adrenergic antagonists yohimbine (1) and idazoxan (2) but not by alpha-1 antagonist prazosin (1). The administration of alpha-2 antagonist yohimbine alone has been demonstrated to increase cognitive deficits related to aging (1). However, recently it was shown that yohimbine at low doses improved memory performance in a subset of aged monkeys (6). The improvement was suggested to be due to increased noradrenaline (NA) release on to postsynaptic alpha-2 receptors and to depend on an intact NA system.

There are also contradictory reports on the effects of clonidine on DR performance in monkeys (7,11). Several explanations have been offered for the negative results. First, in the studies of Bartus and Dean (7) and Davis and co-workers (11) the monkeys were tested with an automatized procedure in which the trials were self-initiated, the experimenter was not present during the testing, and there was no need to raise or lower a screen at the beginning or end of the delay period. These factors may create a relatively nondistractive testing condition. Indeed, it has been suggested that the ability of alpha-2 agonists to improve memory is due to the protection of memory from distractive stimulation (5). Second, clonidine acts selectively on alpha-2B receptor subtypes (29) and there is evidence

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that the alpha-2 agents, like guanfacine, which act selectively on alpha-2A receptor subtypes (29) are more effective in improving cognitive functions in aged monkeys (2,4).

The aim of the present work was to study the effect of a highly selective alpha-2 adrenergic agonist medetomidine on the DR task performance of aged monkeys. Earlier we showed that medetomidine had a beneficial effect on the memory performance of aged rats, but not of young adult rats (10). Medetomidine is a selective and potent agonist at both pre- and postsynaptic alpha-2 adrenoceptors (30). The alpha-2/alpha-1 receptor binding selectivity ratio of medetomidine is 1620 compared with 220 of clonidine (30). Despite its high alpha-2/alpha-1 receptor binding ratio, medetomidine is much less selective than guanfacine with respect to alpha-2A and alpha-2B receptor subtypes (29). For this reason we also studied the effects of guanfacine on the memory task performance to compare the effects of these two compounds in the same testing conditions. In addition to medetomidine and guanfacine, we studied the effects of atipamezole, a highly selective alpha-2 antagonist, on the DR performance of the same aged monkeys. The alpha-2/alpha-1 receptor affinity of atipamezole is much higher than that of the reference compounds, idazoxan and yohimbine. The alpha-2/alpha-1 receptor binding selectivity ratio of atipamezole is 8526 compared with 27 of idazoxan and 40 of yohimbine (31).

METHOD

Subjects

Five stump-tailed macaques (*Macaca arctoides*), two females and three males, were used in this study. Their ages ranged from 15 to 26 years (mean 18.4 years). The oldest monkey is wild-born, and its age was estimated at the time of arrival at the department on the basis of the developmental status of its denture. This monkey had spent 20 years in our monkey colony by the time this study was conducted. Actual birth dates were available for the other four monkeys. The monkeys were housed individually in their standard home cages with the other monkeys of the colony during the training and testing. The animals had free access to water and the main proportion of the daily food was given after the testing session.

Training and Testing Procedure

The monkeys were trained to perform a spatial DR task with five varying delays. The testing apparatus which was attached to the cage had two horizontally located foodwells at the distance of 15 cm from each other. In the DR task the monkey watched through a transparent screen when a raisin was hidden in one of the two foodwells. The foodwells were covered with identical wooden lids and an opaque screen was lowered for the delay period. At the end of the delay both the opaque and transparent screens were raised, and through an opening in the cage the monkey reached the foodwells with its hand. If the monkey chose the correct well it found a raisin under the cover as a reward. The training was started with 0-s delays (pretraining), which means that the opaque screen was lowered and raised as quickly as possible. The daily training session consisted of 30 trials. Pretraining sessions were conducted until the monkeys had learned to respond correctly to 90% of the trials. Then the duration of the delay period was gradually lengthened but so that the same delay was used in all 30 daily trials (training period). At this stage of the training the delay was still the same in all of the 30 daily trials. After reaching a delay at which the performance was near chance level, the varying delays were introduced. The shortest delay was always 0 s and the longest was the one at which the performance was near chance level. The other three intermediate delays were adjusted individually for each monkeys so that the performance of the monkeys was about 65% correct choices of the 30 trials. All six delays and the positions of the rewarded foodwells were distributed evenly among the 30 trials.

Drug Administration

The effects of five doses of medetomidine (DOMITOR) (0.1, 0.3, 1.0, 3.0, and 10.0 μg/kg) and atipamezole (ANTISEDAN) (0.01, 0.03, 0.06, 0.1, and 0.3 mg/kg) and two doses of guanfacine (0.0001 and 0.001 mg/kg) on the DR performance were compared with the performance on saline. The doses of guanfacine were chosen on the basis of the results of Arnsten and co-workers (2,5). The testing was conducted in a double-blind manner. All drugs were studied in separate testing periods. Each dose of medetomidine or atipamezole was given once and the saline control twice during the testing of the drug. The testing of each drug was conducted twice, and the second time the drugs and saline controls were given in a reversed order. The injections were administered intramuscularly 15 min prior to testing.

The effect of guanfacine was studied once a week and the performance was compared with the saline performance of the same week. Guanfacine was administered intramuscularly 2 h prior to testing. At the end of the week, 0.1 mg/kg of idazoxan was given to wash out the long-lasting effects of guanfacine. Medetomidine and atipamezole were generously provided by Farmos Group, Ltd., Orion Pharmaceuticals Inc., Turku, Finland, and guanfacine by Wyeth-Ayerst.

Behavioral Assessment

Possible sedative effects of alpha-2 agonists were assessed by using a 5-point scale: 0 = normal, I = slower than usual, II = slightly drowsy (slowed and clumsy movements), III = intermittent sleeping, IV = too sedated to be tested.

Statistical Analysis

The task performance on each drug was compared with a matched saline control. Because the data are dichotomously categorical (correct vs. not correct) we preferred to analyze the results using methods designed for such data. The data were analyzed using a set of hierarchical log-linear models to fit responses in different experimental situations. Estimation of the relevant parameters (subject/the dose of the drug/the length of the delay) was carried out using the maximum likelihood method as implemented in the SAS procedure CATMOD (28).

RESULTS

Performance

The number of pretraining sessions (30 trials in each session) varied from 2 to 12 (mean 6.7, SD 3.8). During the training sessions the delay was gradually lengthened until chance level of performance was reached. The number of sessions needed to achieve this level varied from 7 to 21 (mean 12, SD 5.7). The monkeys were trained with individually adjusted varying delays in 5–22 sessions (mean 12.8, SD 6.1) before the drug testing was started. The means of the five delays used for testing the five monkeys were 0, 26, 47, 59,

TABLE 1

THE DELAYS AND AGES OF THE MONKEYS. THE MONKEYS ARE INDICATED AS #1–#5.

Monkey	Age	Delay*
#1	14.8	0, 52, 68, 84, 100
#2	15.3	0, 14, 33, 42, 51
#3	17.2	0, 10, 40, 47, 54
#4	26.3	0, 42, 52, 62, 72
#5	18.4	0, 10, 40, 60, 90

* The means of the delays used during the 2.5-year testing period.

and 73 s. Table 1 shows the lengths of the individual delays and the ages of each monkey.

The performance of one monkey (#5) did not drop near chance level with delays that were considerably longer (up to 7 min) than those used for the other monkeys. It was discovered that this monkey moved to or leaned towards that side of the cage where the raisin was placed or kept its hand on the left or right side of the cage during the delay period. To prevent this behavior, the foodwells for this monkey were located vertically (down and up). After this change the longest delay this monkey could master was 90 s, which is well within the range of the delays (51–100 s) of the other monkeys.

The Effect of the Drugs on the DR Task Performance

Medetomidine and Atipamezole Responses. Medetomidine significantly affected the performance of the five aged monkeys in the DR task [$\chi^2(5) = 11.23, p = 0.047$]. Inspection of the model parameters showed that the estimated probability of correct responses reached its maximum at the dose of 1.0 μg/kg of medetomidine ($\chi^2 = 4.65, p = 0.031$, Fig. 1). The dose of 1.0 μg/kg improved the task performance in four of the five monkeys, whereas the most beneficial dose of medetomidine for one monkey (#5) was 0.3 μg/kg (Fig. 2A–E). The mean number of errors was 6.8 on medetomidine (1.0 μg/kg) and 9.05 on saline. Slight sedative effects (I–II) were observed only at medetomidine dose of 10.0 μg/kg.

The number of errors on saline and medetomidine increased with increasing duration of the delay [$\chi^2(4) = 154.61$, $p < 0.0001$]. The beneficial effect of medetomidine (1.0 μg/kg for four monkeys and 0.3 μg/kg for monkey #5) was related to the length of the delay (Fig. 3A). There were significantly fewer errors on medetomidine than on saline at the two longest delays (IV and V) [paired t-test, $t(4) = 3.55, p = 0.024$]. The difference in the performance between medetomidine and saline at the medium–long delays (II and III) did not reach significance. The performance during the shortest delay (0 s) was not included in this statistical analysis because the performance was almost 100% correct on both saline and drug. Alpha-2 antagonist atipamezole had no significant effect at any dose on the task performance [$\chi^2(5) = 5.90, p = 0.32$, Fig. 4].

Atipamezole Reversal of the Medetomidine Response. The effective dose of medetomidine (1.0 μg/kg and 0.3 μg/kg for monkey #5) was also studied with coadministered atipamezole to find out whether the effect of medetomidine resulted from its binding to alpha-2 receptors. The dose of the coadministered atipamezole was 0.01 mg/kg. The effect of medetomidine with atipamezole and medetomidine alone were compared with that of saline control. The experimenter was unaware of the types of injections given to the monkey. The testing was conducted on three consecutive days and the order of the drug administration was saline, medetomidine, and atipamezole + medetomidine (atipamezole was coadministered only if medetomidine improved the performance).

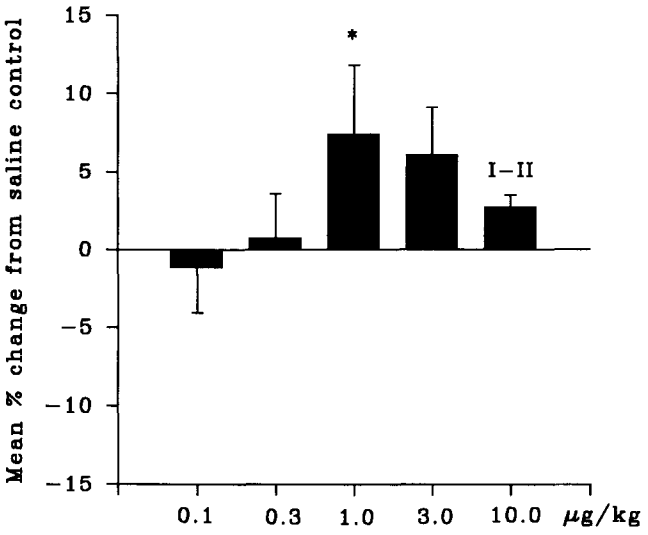

FIG. 1. The effects of five doses of medetomidine on the DR task performance of the monkeys ($n = 5$). The number of trials correct on drug was subtracted from the number of trials correct on saline. The difference score was multiplied by 3.3, as each trial constituted 3.3% of the total number of trials (30 trials/session). The bars show the mean change of medetomidine from saline over two testing sessions. The performance at different delays is pooled together for illustration. Medetomidine, at the dose of 1.0 μg/kg, improved the performance significantly (*$p < 0.05$). SEMs are indicated as vertical bars. I–II refer to a slightly sedative effect of medetomidine on the behavioral assessment scale.

Medetomidine 1.0 μg/kg again improved the DR task performance of the monkeys ($\chi^2 = 8.04, p = 0.0046, n = 5$). This time, however, neither 0.3 nor 1.0 μg/kg improved the performance of monkey #5 and, therefore, atipamezole was not coadministered with medetomidine for this monkey. Coadministered atipamezole reversed the beneficial effect of medetomidine of the other four monkeys, which means that their performance did not differ from that on saline ($\chi^2 = 2.01, p = 0.16$, Fig. 5).

Guanfacine Response. Guanfacine was studied to compare the effectiveness of the two alpha-2 agonists that have different selectivity to alpha-2 subtypes. Guanfacine had a significant effect on the memory task performance [$\chi^2(2) = 16.27, p = 0.0003$]. The lower dose of guanfacine (0.0001 mg/kg) improved the task performance in all five monkeys ($\chi^2 = 7.68$, $p = 0.006$, Fig. 6A), whereas the dose 0.001 mg/kg had no effect ($\chi^2 = 0.07, p = 0.79$, Fig. 6B). The mean number of errors was 6.25 on guanfacine (0.0001 mg/kg) and 11.0 on saline. Contrary to medetomidine, guanfacine improved the performance significantly at the medium–long delays (II and III) [paired t-test, $t(4) = 4.221, p = 0.014$], whereas the improvement at the longest delays was not significantly different from that of saline (Fig. 3B).

DISCUSSION

Alpha-2 adrenergic agonists medetomidine (1.0 μg/kg) and guanfacine (0.0001 mg/kg) improved spatial memory task per-

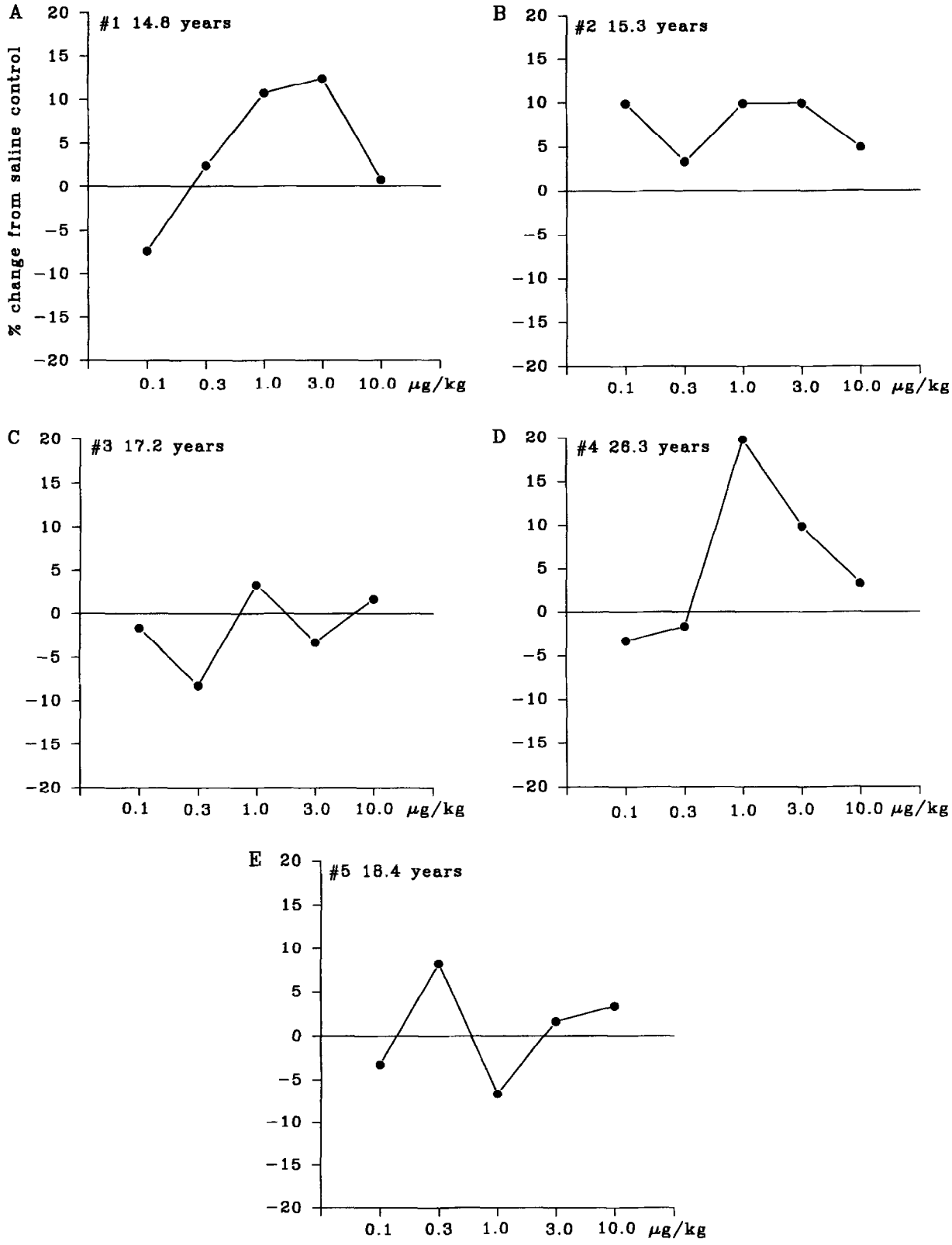

FIG. 2. (A–E) Individual dose–response curves of medetomidine. Each dot shows for the five concentrations the mean percentage change of medetomidine from saline over two testing sessions. The ages of the monkeys (No. 1–5) are shown in the insets of the figures. Other explanations as in Fig. 1.

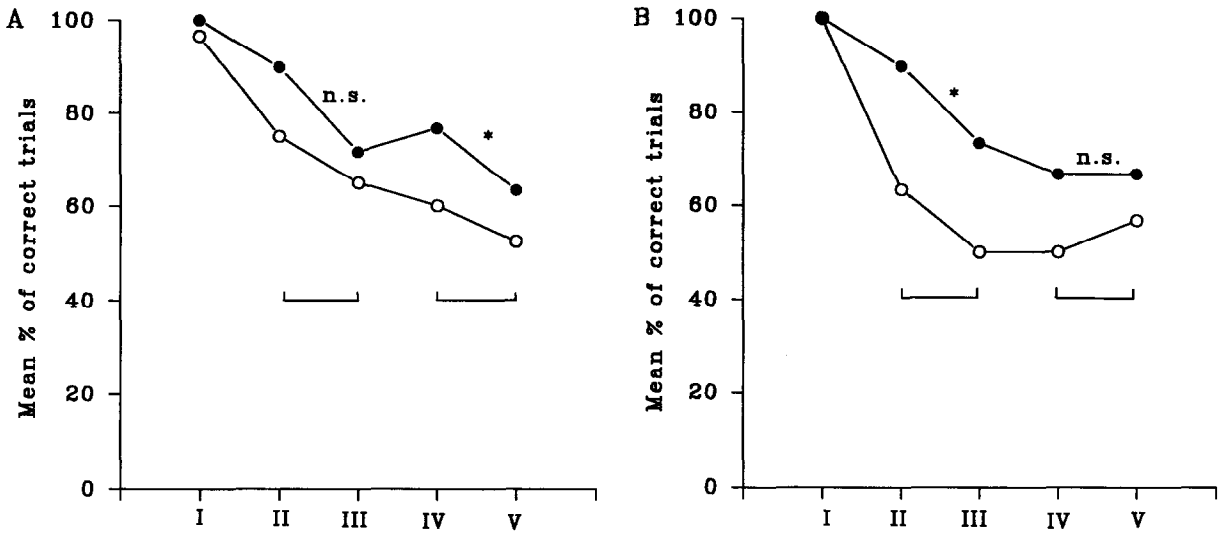

FIG. 3. (A–B) The mean percentage of correct trials at the most beneficial doses of medetomidine (1.0 μg/kg, n = 4; 0.3 μg/kg n = 1) and guanfacine (0.0001 mg/kg) are shown separately for each five delays for five monkeys. (A) The mean percentage of correct trials was significantly greater on medetomidine (filled circles) than on saline (open circles) at the two longest delays (IV and V). (B) The mean percentage of correct trials was significantly greater on guanfacine (filled circles) than on saline (open circles) at the two medium–long delays (II and III). The mean of the delays for the five monkeys were I = 0, II = 26, III = 47, IV = 59, and V = 73 s. *$p < 0.05$.

formance of aged monkeys, whereas alpha-2 antagonist atipamezole had no effect on the performance of the same monkeys. In the control experiment, atipamezole (0.01 mg/kg) reversed the effect of the beneficial dose of medetomidine indicating that the improved DR performance on medetomidine resulted from its selective action on alpha-2 receptors.

It has been well documented that the prefrontal cortex of monkeys is involved in spatial mnemonic functions [e.g. (14,17)]. The studies of single-unit activity in the prefrontal cortex of monkeys during the performance of DR tasks have demonstrated correlations between unit activity and the main events of the task [e.g. (9,13,15,18,24)]. There is also evidence that catecholaminergic innervation of the prefrontal cortex has an influence on spatial memory functions. Regional depletion of catecholamines by 6-hydroxydopamine (6-OHDA) in the prefrontal cortex of rhesus monkeys produces inability to perform the DR task (8,27), which can be reversed by alpha-2 agonist clonidine or dopamine agonists *l*-dopa and apomor-

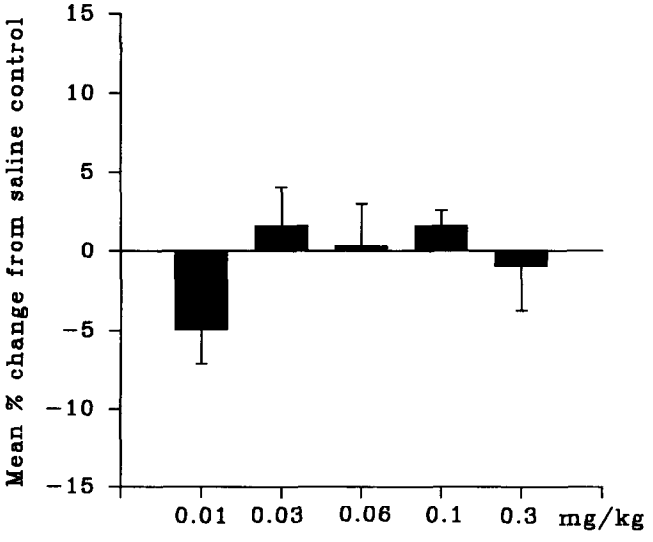

FIG. 4. The effects of the five doses of atipamezole on the DR task performance of the monkeys (n = 5). Other explanations as in Fig. 1.

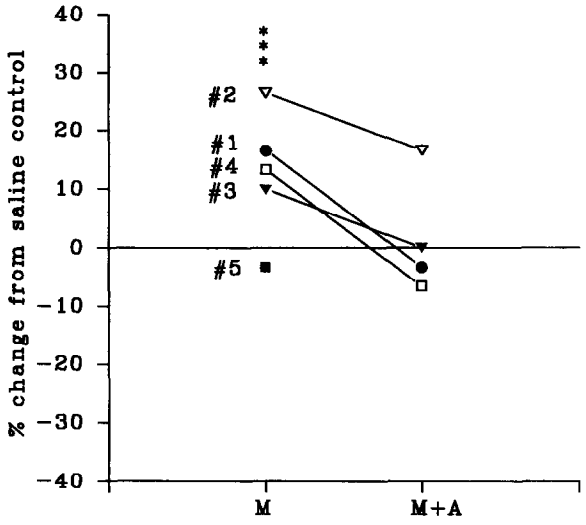

Fig. 5. In the atipamezole reversal experiment, medetomidine (M) again significantly improved the DR task performance of the monkeys (***$p < 0.005$, n = 5). Coadministered alpha-2 antagonist atipamezole reversed the beneficial effect of medetomidine (M+A). Because medetomidine did not improve the performance of monkey #5, atipamezole reversal was not performed in this monkey. The monkeys are indicated as #1–#5.

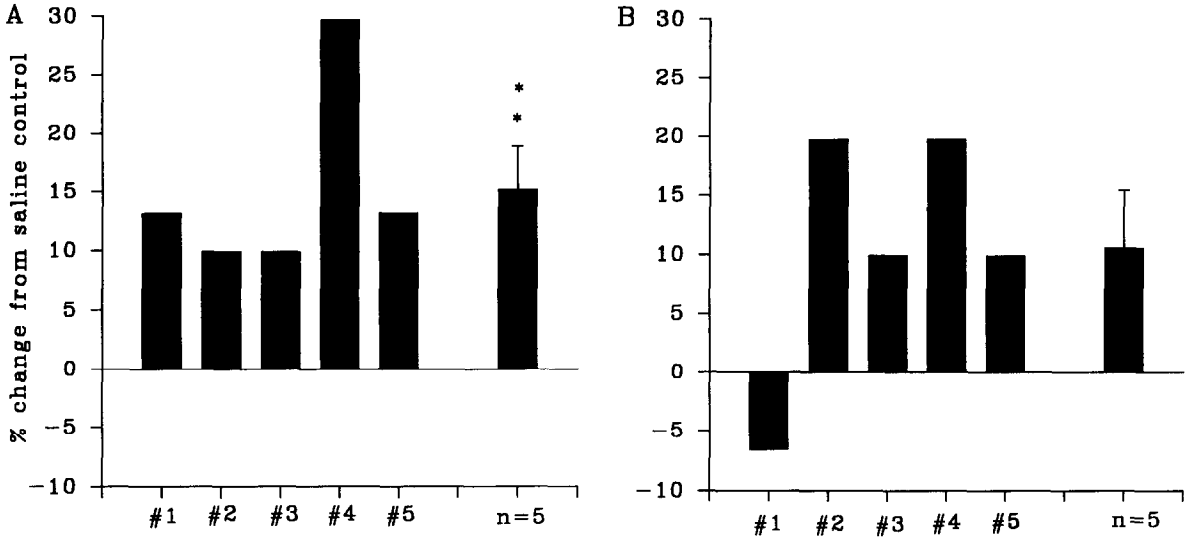

FIG. 6. (A) Individual and mean response bars for the dose of 0.0001 mg/kg of guanfacine for five monkeys. Guanfacine significantly improved the performance (**$p < 0.01$). (B) Individual and mean response bars for the dose of 0.001 mg/kg of guanfacine in all monkeys. SEMs are indicated as vertical bars. Other explanations as in Fig. 1.

phine (1,8). The ability of alpha-2 adrenergic agonists to improve the performance of aged monkeys in the delayed matching-to-sample (DMTS) task (3) is not as evident as in the DR task (1,2). The performance of the DR and DMTS tasks demands different types of memory: spatial and visual object memory, respectively. Rapp and Amaral (26) reported that the performance of aged monkeys was impaired in the DR task, whereas their performance in the DMTS task did not differ much from that of young adults. It has been suggested that separate areas in the prefrontal cortex are involved in the memory processes of spatial location ("where") and object identity ("what") (33).

Our earlier findings in rats showed that medetomidine had a beneficial effect on memory performance of aged animals, but not of young adults (10). This is in line with the present study in which both medetomidine and guanfacine had the most pronounced positive effect on the memory task performance of the oldest monkey. The beneficial effect of medetomidine may be related to the evidence that the levels of monoaminergic and cholinergic neurotransmitters decline with increasing age (21,22). In the present study, the age of the oldest monkey was about 26 years, whereas the other four monkeys were 15–18 years. The other laboratories studying age-related memory loss and alpha-2 adrenergic function have used monkeys with an age range of 17–30 years (1,6). Thus, the monkeys in the present study were slightly younger than those in the above studies but old enough to benefit from the alpha-2 agonists medetomidine and guanfacine in the DR task. It has been reported that the majority of macaques in captivity live to the age of 20–25 years and only occasionally longer (19).

There are also contradictory reports of the effects of clonidine on DR performance of monkeys (7,11) and of guanfacine on age-associated memory impairment (AAMI) in humans (23). Furthermore, there is evidence that alpha-2 adrenergic agonists improve DR task performance by protecting working memory from distractive stimulation (5). On the basis of this evidence it has been suggested that the negative results (11) or the not so evident improvement in the DMTS performance tested with unique stimuli for each trial (3) are due to testing conditions void of distraction (5). Davis and co-workers (11) used a DR task with nine different spatial locations. Such a testing paradigm might cause less interference from previous trials than the DR task with two spatial locations. There may be several reasons why the subjects with AAMI in the study by McEntee and co-workers (23) did not benefit from guanfacine treatment: the diagnosis of the memory impairment was based on self-reports, the age range of the subjects was quite large, and the manner of the guanfacine administration (a daily dose during four weeks) was different from that of the studies on monkeys.

Arnsten and Goldman-Rakic (1) showed that the effect of clonidine on memory task performance was related to the length of the delay; the improvement was most pronounced at longer delays. The delays in the present study were longer than those used in the other studies concerning DR task performance in monkeys [e.g. (6,26)]. The means of our delays were 0, 26, 47, 59, and 73 s. In a study by Rapp and Amaral (26), monkeys with ages between 22 and 26 years could not perform the DR task above chance level at delays longer than 5 s. In the study by Arnsten and Cai (6), the means of the delays were also shorter than in our study: 0, 5.7, 11.4, 17.1, and 22.8 s for aged (17–30 years) and 0, 9.7, 19.4, 29.1, and 38.8 s for younger (5–15 years) monkeys. The monkeys used in the other studies were rhesus macaques (*Macaca mulatta*) (2,6,26), whereas we studied the memory task performance of stump-tailed macaques. Thus, species-specific differences might explain the differences in the delays. In the present study, the beneficial effect of medetomidine was most pronounced at the longest delays, which supports the suggestion that the improvement of performance was due to improved working memory processing. Contrary to medetomidine, the beneficial effect of guanfacine was most pronounced at the medium–long delays. It must be remembered, however, that even our medium–long delays were longer than the longest delay in the study by Arnsten and Cai (6). Despite the relation between the drug effect and the length of the delay, it cannot

be excluded that the improvement of DR performance could also be related to more concentrated and attentive performance during the testing session.

The alpha-2/alpha-1 receptor binding selectivity ratios of medetomidine (30) and guanfacine are very high compared with that of clonidine. Medetomidine, however, is less selective than guanfacine with respect to alpha-2A and alpha-2B receptor subtypes (29). It has been suggested that the ability of alpha-2 agonists to improve the memory performance of aged monkeys is due to their selective actions on alpha-2A receptor subtype (2,4). It has earlier been shown that the dose range of guanfacine that improves DR task performance is wide compared with that of another alpha-2 adrenergic agonist compound, UK-14304 (4). Medetomidine and UK-14304 seem to be similar in some respects: they have similar alpha-2B/alpha-2A selectivity ratios (29) and they both seem to have a narrow effective dose range. The present results indicate that alpha-2 agonists, independent of their different selectivity with respect to alpha-2A/2B receptor subtypes, are beneficial drugs in improving the performance in the delayed response task.

It is noteworthy that there were no signs of sedation at the effective medetomidine dose 1.0 μg/kg. The first signs of sedation (evaluated as I–II) were observed only at the highest dose (10.0 μg/kg) used. Because a low dose of medetomidine, which caused no observable side effects, improved the memory task performance of monkeys, it would be worth while to study the effectiveness of medetomidine on cognitive performance also in humans.

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