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Visual Recognition Memory in Squirrel Monkeys: Effects of Serotonin Antagonists on Baseline and Hypoxia-Induced Performance Deficits

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DENOBLE, V. J., L. M. SCHRACK, A. L. REIGEL AND K. F. DENOBLE. *Visual recognition memory in squirrel monkeys: Effects of serotonin antagonists on baseline and hypoxia-induced performance deficits.* PHARMACOL BIOCHEM BEHAV **39**(4) 991–996, 1991.—Cognitive deficits resulting from neuropathological brain changes such as Alzheimer's Disease or normal aging are most likely due to alterations in multiple neurotransmitter systems. While the majority of preclinical studies have focused on the effects of acetylcholine (ACh), it has been shown that activation of the serotonergic (5-HT) pathways in the central nervous system interferes with passive avoidance retention in rats. In contrast, decreased 5-HT activity has been shown to improve learning and memory in rats using similar procedures. In the present experiment, 5-HT antagonists were evaluated for their effects on performance in a delayed match to sample task (DMTS) in two groups of squirrel monkeys: one in which the baseline level of performance was low (<65% correct, N=5; group 1) and another in which DMTS performance was high (>80% correct, N=3; group 2) but impaired by exposure to hypoxia. Initial parametric tests exposing group 2 to various levels of oxygen deprivation were conducted to determine optimal conditions for performance deficits. Each monkey in both normoxia (group 1) and hypoxia (group 2) served as his own control and received an individualized range of doses for each test compound. For both groups, ketanserin and mianserin, the 5-HT_2-selective antagonists, produced dose-dependent increases in DMTS performance at 0.3–1.5 mg/kg PO and 0.05–1.5 mg/kg PO, respectively. Pirenperone, another 5-HT_2-selective antagonist, was active in improving performance in group 1 at 0.001 to 0.2 mg/kg PO but was not effective against hypoxia-induced performance deficits. Cyproheptadine, a nonselective antagonist, also produced increases in performance in both groups; however, the effects could not be replicated in the group (1) with a low performance baseline. The results of this study show that alterations of 5-HT are effective in preventing hypoxia-induced performance deficits and in improving normoxic performance levels, suggesting a major role for 5-HT in cognitive performance.

Serotonin Visual recognition task Alzheimer's Disease Primate Hypoxia

COGNITIVE deficits resulting from neuropathological brain changes or normal aging are most likely due to alterations in multiple neurotransmitter systems. Cholinergic, noradrenergic, dopaminergic, and peptidergic neurotransmitter systems have all been implicated in the mediation of learning and memory decline associated with aging (24,25). A majority of research has focused on the cholinergic nervous system with particular reference to cognitive deficits resulting from Alzheimer's Disease (AD). Numerous studies have clearly shown a marked cholinergic deficiency in AD (10,12) and, while it appears that hypocholinergic function results in dementia, dementia is not always due to a deficit in cholinergic transmission and can be mediated by other neurotransmitter systems. It is well established that there is a decrease in forebrain 5-hydroxytryptamine (5-HT-serotonin) in the AD brain. Specifically, concentrations of 5-HT and its metabolite, 5-hydroxyindole acetic acid, are reduced and the 5-HT_1- and 5-HT_2-receptor densities decreased in hippocampus, frontal, and temporal cortices (27). However, the loss of serotonin innervation does not parallel the loss of cholinergic or adrenergic innervation (1,12), and it may be hypothesized that the inhibitory tone that the serotonergic nervous system is suspected to have on other neurotransmitter systems would be maintained or even exaggerated (5). In that regard, 5-HT antagonists would be expected to improve performance by decreasing the inhibitory control maintained on the central nervous system.

A recent series of reports has shown that a number of 5-HT receptor antagonists, both nonselective (e.g., metergoline) and 5-HT_2 selective (e.g., pirenperone, ketanserin), can enhance memory of a previously learned inhibitory response in mice (3,4) and can reverse hypoxia-induced passive avoidance (PA) retention deficits in rats (31). These studies support the notion that 5-HT antagonists administered after avoidance training or after an experimentally induced memory deficit (exposure to hypoxia) can enhance retrieval in mice (3) and protect rats from experimentally induced amnesia (31). However, the effects of 5-HT antagonists on nonadversely motivated tasks and in species other than rodents have not been reported.

When animals are exposed to an environment containing a low level of oxygen, then trained in a learning test, the performance during retention testing is disrupted (15, 16, 30, 31). Catecholamines and ACh syntheses are impaired when oxygen supply is compromised, and compounds that restore neurotrans-

mitter function (16) or antagonize 5-HT (30) have been shown to ameliorate the consequences of hypoxia on a passive avoidance deficit in rats, suggesting that the performance deficit is most likely due to hypoxia-induced changes in neurotransmitter function (16). To extend the previously mentioned findings with drugs that alter 5-HT function on avoidance retention in rodents to another species, the effects of a number of 5-HT antagonists on performance in a DMTS task were evaluated in nonhuman primates, specifically in two groups of squirrel monkeys: one in which the baseline level of performance was low (<65% correct) and in a second group in which DMTS performance was high (>80% correct) but impaired by exposure to hypoxia.

METHOD

Animals

Eight male feral-born squirrel monkeys (*Saimiri sciureus*) with an approximate age of 12 years and weighing between 0.8–1.2 kg were housed individually in stainless steel cages (4.3 sq. ft.) in a colony room maintained on a 12-hour light/dark cycle (lights on from 0600 to 1800 h). Room temperature was maintained at 24±2°C with a relative humidity of 50±10%. Their diet consisted of Purina Monkey Chow which was supplemented with fruit and vitamins. Water was freely available in the home and test cages. Food was removed from home cages each test morning (6:00 a.m.), and the animals were fasted until the test session was completed in the afternoon (4:00 p.m.).

Apparatus

Four identical Coulbourn operant test cages (Model E10-10) enlarged to 29 cm L × 24 cm W × 40 cm H were maintained in sound-attenuated chambers. On one wall, there was a pellet receptable in the bottom center, a water bottle spout on the bottom right, and a houselight in the upper left corner. Three stimulus-response keys were located on the same wall with a target-stimulus key centered above two choice keys spaced equally apart and aligned horizontally. The chambers were equipped with two input and two output valves, to control gas flow, and an oxygen sensor (Sensitron Inc). Chambers were controlled by a PDP11/23 computer (Digital Equipment Corp.), SKED-11 software, and a State Systems interface (State Systems Inc.) using a Fortran program to compile data. Chambers were equipped with remote video recording apparatus such that each monkey was continuously monitored through each experimental session.

General Behavioral Training

The monkeys were shaped to key press for food during 60-min sessions under a fixed ratio 1 (FR1) schedule. Food delivery (45 mg banana pellet, Bio Serve, Inc.) was accompanied by illumination (2 s) of a light in the feeder trough and the sound of the feeder click. After the animals were shaped to key press, the contingency for reinforcement was gradually increased to FR 7.

After ten days of FR 7 training, the contingency for reinforcement was switched to an FR 1 on the target stimulus, which was illuminated by a yellow light. Responses on the target stimulus resulted in the illumination of a choice key, the position of which was randomly chosen. Food pellets were delivered after a correct choice key response. An incorrect response (pressing an unlit choice key) resulted in a five-s timeout (TO) during which the house light was turned off and responding had no consequence. When each monkey reached a criteria of 85% correct responding in three of five sessions with no increasing or decreasing trends in the percent correct, the yellow light was replaced by either a black dot or a vertical bar. These symbols would appear randomly on the target stimulus. When the monkey pressed the target stimulus, a matching symbol would appear on one of two choice keys. Pressing this key resulted in the delivery of food and initiated a new trial. After several days of training on this procedure, the monkeys were switched to a DMTS task. During this phase of testing, all monkeys reached a minimum of 80% correct responding.

Delayed Match-to-Sample Procedure

During a session, a target stimulus key displaying either a black dot or a black vertical bar was presented. The monkeys were required to press this key to initiate a 4-s delay followed by the random presentation of two choice keys displaying both target stimuli separately. A correct response was defined as pressing the choice key that matched the target stimulus key, resulting in the delivery of a reinforcer (45 mg banana pellet, Bio Serve, Inc.). An incorrect response resulted in a TO in which the houselight was extinguished for a period of 5 s and responses had no consequence. An incorrect response was followed by a presentation of the same stimuli. This procedure allows for performance measures to fall below 50% levels. All sessions lasted 60 min. The number of correct responses and total number of trials were recorded every six min for each choice symbol. After thirteen months of the testing (Mon–Fri), the monkeys were divided into two groups. The first group (group 1) consisted of monkeys whose baseline performance fell below 65% correct (monkey number, percent correct: M5, 50%; M6, 45%; M10, 60%; M16, 58%; M19, 62%). The second group (group 2) of monkeys consisted of three animals whose baseline level of performance was greater than 80% correct (e.g., M300, 96%; M14, 82%, and M15, 80%). In these animals, performance was disrupted by exposure to hypoxia.

Hypoxia-Induced Performance Deficits

In group 2, performance deficits were induced by exposing the monkeys to a gas mixture containing a gradually decreasing concentration of oxygen supplemented with nitrogen. During all baseline conditions, the concentration of oxygen was 21% (normal air). Prior to drug treatment, the oxygen concentration used to produce performance decrements for each monkey was determined in several test sessions and defined as the highest oxygen concentration that produced a statistically significant decrease in the number of correct responses. Oxygen concentrations of 11%, 12% or 13% were selected to produce maximal test performance deficits without overt signs of physical impairment in individual monkeys. Monkey 15 was exposed to 11% oxygen, while monkey 300 received 12% and 14 received 13% oxygen. The appropriate level of oxygen was attained gradually over a thirty-minute period from the beginning of the session and maintained for the duration of the test. The oxygen concentrations were continuously monitored in the chamber with an oxygen sensor (Sensitron, Inc., Reading, PA).

Drug Preparation and Administration

Ketanserin (Janssen, Belgium), mianserin HCl (Organon, Holland), cyproheptadine HCl (Merck Sharp and Dohme, West Point, PA) pirenperone (Janssen, Belgium) and d-amphetamine (Sigma Chemical Co.) were suspended in banana-flavored Nutrament®. In a nontraumatic dosing procedure, the monkeys voluntarily consumed a volume a 0.1 ml/100 g body weight of drug

camouflaged in Nutrament 15 min prior to testing. Monkeys were given a maximum of two drug sessions per week, each separated by a minimum of one test session in which the monkeys in group 1 were dosed with vehicle. For the hypoxia tests (group 2), sessions were separated by a minimum of one test session in which the oxygen concentration was 21% and dosed with vehicle. During these sessions, if test performance was not within the previously established baseline limits, the following days drug treatment was postponed. Drug treatments were randomly assigned, and not all monkeys received the same drug treatments.

Data Analysis

The number and percent of correct responses were recorded for six-min periods during the 60-min session. For group 1, data were accumulated over the last five weeks of baseline and averaged for the 60-min session to establish baseline conditions (see above). Student *t*-test analysis was performed comparing mean percent correct responding, drug versus nondrug data, for the 60-min session, with each monkey serving as his own control. For group 2, the data were accumulated over the last five weeks of testing and averaged for both normoxia and hypoxia vehicle control sessions separately to establish baseline conditions (see above). Each monkey served as his own control. Student *t*-test analysis was performed comparing mean percent correct responding for normoxia vehicle control and hypoxia vehicle control for the first and last 30 min of the test session (hypoxia-induced performance deficit). To evaluate the ability of test compound (under hypoxic conditions) to improve performance beyond established baseline levels of hypoxia control, mean percent correct responding for each dose was compared to hypoxia control using the Student *t*-test. Drug versus nondrug data were compared for the last 30 min of the session during which the oxygen levels were stable.

RESULTS

Under the general training procedure, all monkeys initiated key press responding for food and successfully completed the matching of target stimuli with choice stimuli. After several months of training in the DMTS procedure, the individual monkeys' performances were distributed into two accuracy levels. Five of the monkeys reliably performed below 65% correct (group 1, Fig. 1), whereas three monkeys had baseline performances that reliably exceeded 80% correct (group 2, Fig. 1). An analysis of variance performed within each group comparing individual monkeys' performances showed that there were no differences within groups for overall performance [Group 1, $F(4,45)=1.9$, $p>0.01$; Group 2, $F(2,27)=0.28$, $p>0.1$]; however, a between-group comparison revealed a significant difference between group 1 and group 2, $F(1,6)=41.9$, $p<0.01$, in the percent correct. These group differences were maintained throughout the experiment.

By maintaining the monkeys on the DMTS task under nondrug (group 2) and nonhypoxia conditions (group 2) prior to treatment and during treatment, it was possible to determine individual ranges of performance. For group 1, performance during vehicle versus drug conditions for individual monkeys was determined as percent of control (nondrug). Ketanserin, mianserin, and pirenperone produced significant increases in the percent correct responding in individual monkeys. With ketanserin, the active dose range included 0.3 to 1.5 mg/kg PO, with individual monkeys showing different sensitivities to the drug effect (Fig. 2). The range of drug-induced increases in performance is exemplified by monkey 10, who only responded to the 0.3-mg/kg PO dose of ketanserin compared to monkey 6, in which the effective dose range was 0.3 to 1.5 mg/kg PO, with a magnitude of effect much larger than either monkey 10 or 19. Similar patterns of drug effects were found with mianserin and pirenperone (Figs. 3 and 4, respectively). Despite the different sensitivities found between monkeys, replication of selected doses demonstrated the reliability of the effect within individual monkeys, irrespective of the width of the effective dose range or the magnitude of the response. In contrast, cyproheptadine was effective in only one monkey, and the effect could not be replicated.

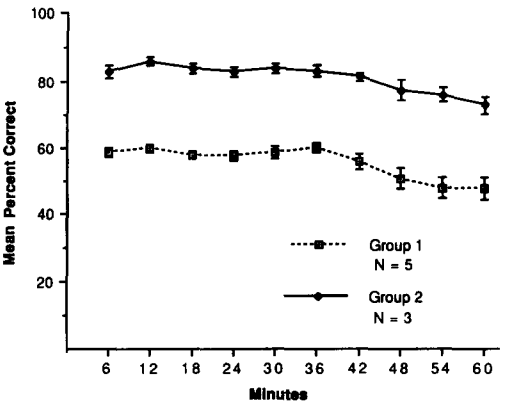

FIG. 1. Mean percent correct responding as a function of the 60-min session divided into six-min blocks is shown for ten days of baseline testing. Each point is a mean of ten days of combined data within a group (group 1, N=5; group 2, N=3), and vertical lines show the standard error of the mean. An analysis of variance revealed a significant difference between groups ($p<0.01$), but failed to show a difference between monkeys within the groups ($p>0.1$).

Performance levels in group 2 were significantly better than those of group 1 (Fig. 1). Under normoxia vehicle control sessions, the percent correct responding ranged from 79.7% to 84.9% across all baseline test sessions (Fig. 5, control). When exposed to hypoxia, performance during the first 24 min of the

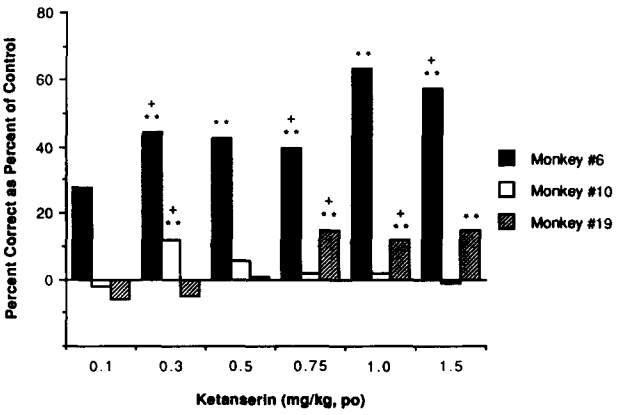

FIG. 2. Percent correct responding during 60-min sessions in which ketanserin was administered is shown as the percent of vehicle control sessions. Each bar represents an individual monkey, and crosses (+) indicate doses that were replicated. Asterisks show drug sessions that were significantly different from vehicle control sessions, $*p<0.05$; $**p<0.025$ (Student's *t*-test).

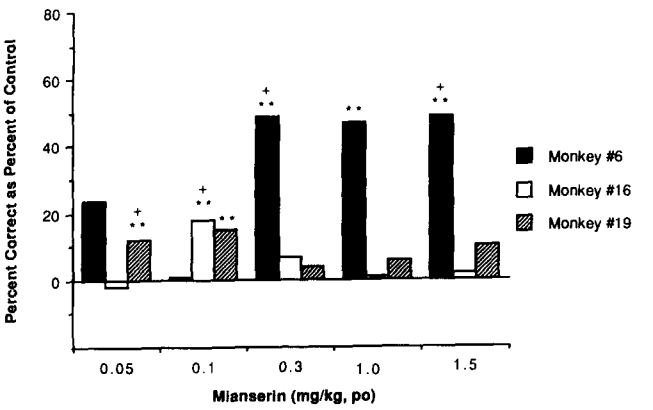

FIG. 3. Percent correct responding during 60-min sessions in which mianserin was administered is shown as the percent of vehicle control sessions. Each bar represents an individual monkey, and crosses (+) indicate doses that were replicated. Asterisks show drug sessions that were significantly different from vehicle control sessions, $*p<0.05$; $**p<0.025$ (Student's t-test).

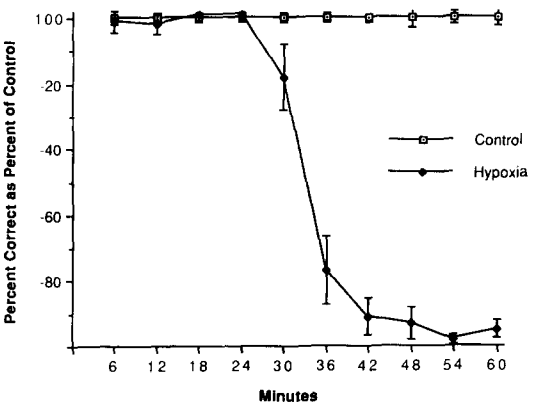

FIG. 5. Mean percent correct responding as a function of the 60-min sessions divided into six-min blocks is shown for control (nonhypoxia) and hypoxia sessions for three monkeys. Each point is the mean of 12 sessions (3 monkeys × 4 sessions) and the vertical lines show the standard error of the mean. During the control session, the oxygen level was maintained at 21%, and during the hypoxia session, the level of oxygen was gradually reduced to 11, 12 or 13% (see the Method section for details) over the first 30 min, then held constant for the remainder of the session.

session was equivalent to normoxia levels; however, the percent correct rapidly decreased during the next 18 min and remained low for the remainder of the session (Fig. 5, hypoxia). Throughout the entire experiment for all monkeys in group 2, each session's performance on the day after exposure to hypoxia was not different than the session preceding hypoxia, indicating that the effects of hypoxia were restricted to individual sessions without carryover to the next day.

Ketanserin, mianserin and cyproheptadine at doses ranging from 0.1 to 1.5 mg/kg PO administered 15 min before hypoxia sessions attenuated the effects of hypoxia on performance (Table 1). Ketanserin and cyproheptadine were active in two of three monkeys, and selected doses were replicated (Table 1). Mianserin was tested in one monkey and was active at two doses

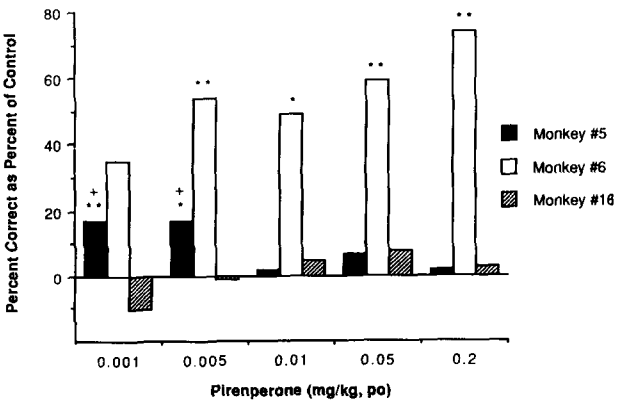

FIG. 4. Percent correct responding during 60-min sessions in which pirenperone was administered is shown as the percent of vehicle control sessions. Each bar represents an individual monkey, and crosses (+) indicate doses that were replicated. Asterisks show drug sessions that were significantly different from vehicle control sessions, $*p<0.05$; $**p<0.025$ (Student's t-test).

(Table 1). The mean number of trials per six-min period during the last 30 min of a normoxia control session was 33 ± 0.2 SEM. During the hypoxia session, this was reduced to a mean of 7 trials ± 0.8 SEM. During sessions in which serotonin antagonists reduced the effects of hypoxia on performance, the mean number of trials was increased above hypoxia-control levels (mean = 14.0 ± 2.0 SEM vs. mean = 7.0 ± 0.8 SEM, respectively). To determine if the drug-induced increase in the percent correct was an effect of increasing the number of trials without increasing accuracy, the monkeys were given a psychomotor stimulant and tested in hypoxia. Amphetamine at 0.1 and 0.3 mg/kg PO increased the number of responses in all monkeys to levels comparable to that of the serotonin antagonists (mean = 7.8 and 19.0 trials, respectively), however, the accuracy of responding during the hypoxia-amphetamine sessions was not different from hypoxia-control sessions, suggesting that the effects of the serotonin antagonists on the percent correct responding was not secondary to increases in the number of responses.

DISCUSSION

The behavioral procedure used in this experiment permitted an analysis of several 5-HT antagonists on experimentally induced performance deficits and on baseline performance that was low (e.g., <65% correct). It is interesting to note that, even after extended training on the DMTS task (13 months) at a relatively short delay interval (4 s), only three of eight monkeys had baseline performance above 80% correct. By comparison, numerous studies using similar delay response procedures with Macaque monkeys (6–8), *Papio ecyncephalus* (baboon) (18) or Capuchin monkeys (11) have shown that the accuracy of responding by these strains can be maintained at high levels across response delays that are four to 20 times longer than the one used in the present study. The nondrug performance of the five monkeys whose accuracy was below 65% did not change throughout the entire training or drug-testing phase, allowing for an evaluation of drug effects on low baseline performance over several weeks.

TABLE 1

EFFECT OF THREE SEROTONIN ANTAGONISTS ON PERCENT CORRECT RESPONDING IN MONKEYS EXPOSED TO HYPOXIA

Animal	Ketanserin		Mianserin		Cyproheptadine	
Number	mg/kg PO	%*	mg/kg PO	%*	mg/kg PO	%*
14	IA	—	—	—	0.75†, 1.0†, 1.5†	789, 778, 775
15	0.1	677	0.1, 0.3†	520, 695	IA	—
300	0.1†, 0.3†	447, 950	—	—	1.0†	645

*The percent increase in correct responding was calculated by dividing the percent correct obtained in the hypoxia-drug session by the percent correct obtained in the hypoxia-vehicle session and multiplying by 100 to = %.

†Dose replicated.

IA = Inactive.

In all monkeys, doses above and below those listed in the table did not produce significant changes in performance (Student's t-test $p>0.05$).

In recent years, the effects of 5-HT antagonists on processes underlying learning and memory in rodents have been well established. Specifically, acute administration of 5-HT antagonists after acquisition or before retention increased retention latencies of a PA response in mice, whereas before training, administration disrupted retention (3). To the best of our knowledge, this is the first report of the effects of 5-HT antagonists on performance of a visual recognition task in nonhuman primates. Previous research has shown that visual recognition memory in Rhesus monkeys can be enhanced by cholinergic drugs in a dose-related manner in the absence of a pharmacological challenge such as pretreatment with anticholinergic agents (2, 6, 29). In the present study, a similar enhancement in performance was found with three 5-HT antagonists (ketanserin, mianserin, and pirenperone). It has been shown that the ability to identify objects correctly using a visual recognition task is reduced in patients with probable AD (22,25). Since probable AD patients show improved picture recognition after IV or oral administration of physostigmine, the present data demonstrating a positive effect of 5-HT antagonists on DMTS performance suggests that the use of 5-HT antagonists may be an alternative or complementary neurotransmitter approach to the treatment of memory dysfunction.

It is not known whether the effects of alterations in serotonergic activity exert a direct influence on information processing or if it is an indirect effect via modulation of other neurotransmitter systems. The interaction between the serotonergic nervous system and other neurotransmitter systems is well established (5), and recent results show that the 5-HT antagonists can potentiate the effects of compounds that restore neurotransmitter function that is impaired by exposure to hypoxia [DeNoble, (17)]. This would suggest that the activity of 5-HT antagonists is due, at least in part, to effects on other neurotransmitter systems.

Collective evidence from multidisciplines has supported the role of ACh in the mediation of cognitive deficits of the AD type. Numerous preclinical reports have appeared in the literature in which an anticholinergic challenge resulting in a performance deficit was partially or completely reversed by cholinomimetic drugs (2, 7, 29). A major drawback of tests that rely on the ability of a potential therapeutic agent to reverse the effects of an anticholinergic challenge is that drug candidates may have specific procholinergic effects without having any direct effect on cognitive function.

In that regard, the evaluation of putative cognitive enhancers in tasks that eliminate a specific pharmacological intervention(s) or produce more global CNS alterations may be advantageous. For example, exposure to hypoxia before or after learning has been used to produce memory impairments in animals (15, 16, 30, 31) and in humans, in which the effects of mild hypoxia include impairment in memory function (23). Further research has shown that exposure to hypoxia can produce a rapid onset of reversible brain dysfunction that results in memory loss similar to that seen in senile dementia (28). Hypoxia-induced neurotransmitter changes provide the most probable mechanism of impaired performance, since oxygen is used in the synthesis of several neurotransmitters shown to be involved in memory function. Specifically, dopamine and epinephrine syntheses are dependent on a combination of tyrosine and oxygen, and 5-HT synthesis is dependent on tryptophan and oxygen. Tyrosine hydroxylation is impaired when oxygen concentrations are reduced in a brain synaptosome preparation, suggesting that a rate-limiting step in the synthesis of catecholamines is the availability of oxygen (13,14). Further, it has also been demonstrated that hypoxia reduces ACh synthesis in vitro (21) and in vivo (19,20). Taken together, these results demonstrate that the effects of hypoxia on neurotransmitter function are less specific than a pharmacological challenge such as scopolamine, and hypoxia produces alterations in several neurotransmitters that have a major influence on cognitive function.

Previous research with rodents has shown that the acetylcholinesterase inhibitors (19,20), 5-HT_2 antagonists (30), and neurotransmitter release enhancers (16,20) will ameliorate the effects of hypoxia on performance. The present experiment extends these findings by demonstrating that 5-HT antagonists will reduce the effects of hypoxia on performance of a DMTS task in squirrel monkeys. While there have been numerous reports of performance deficits induced by pharmacological intervention (6,29) or by normal aging (7,8) in primates, the effect of mild-grade hypoxia on performance has not received experimental attention. In the present study, an individualized hypoxia level was obtained to produce performance deficits, which was shown to be reliable within subjects across several weeks of testing. The hypoxia-induced performance deficit was confined to the hypoxia session, reduced by 5-HT antagonists and not by amphetamine pretreatment.

The results of the present study combined with previous literature on 5-HT antagonists effects on performance suggest that 5-HT antagonists alone or as an adjunct therapy with other purported cognitive enhancers should be considered.

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