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Motor Dysfunction Produced by Tacrine Administration in Rats

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CARRIERO, D. L., G. OUTSLAY, A. J. MAYORGA, J. ABERMAN, G. GIANUTSOS AND J. D. SALAMONE. *Motor dysfunction produced by tacrine administration in rats.* PHARMACOL BIOCHEM BEHAV **58**(4) 851–858, 1997.— In the present study, three experiments were conducted to provide a characterization of some of the motor effects of the anticholinesterase tacrine (1.25–5.0 mg/kg IP) in rats. In the first experiment, tacrine was found to produce tremulous jaw movements in the dose range of 1.25–5.0 mg/kg. The second experiment examined the effects of tacrine on locomotion, and it was demonstrated that tacrine produced a dose-related suppression of open-field motor activity. In the third experiment, the effects of tacrine were assessed using operant conditioning procedures. Behavioral output during lever pressing on a fixed ratio 5 schedule was recorded by a computerized system that measured response initiation time (time from offset of one response to onset of the next) and duration for each lever press. Tacrine administration substantially depressed lever pressing response rate. This deficit was largely due to a substantial increase in the average response initiation time. Analysis of the distribution of response initiation times indicated that tacrine-treated rats made relatively few responses with fast initiation times (e.g., 0–125 ms), and also that tacrine led to a dramatic increase in the number of pauses in responding (i.e., response initiation times greater than 2.5 s). Tacrine-treated rats showed a slight increase in the average initiation time for fast responses (i.e., a slight decrease in the local rate of responding), and also showed a substantial increase in the average length of pauses greater than 2.5 s. Analysis of response durations indicated that there was an overall increase in average response duration among animals that received the higher doses of tacrine. Although tacrine-induced decreases in the local rate of responding and increases in response duration contribute to the overall deficit, the major reason why tacrine-treated animals responded less was because they took much longer breaks in responding. It is possible that the tacrine-induced increases in pausing reflect a drug-induced akinesia. Thus, the present experiments indicate that tacrine impairs several aspects of motor function in the dose range tested. In view of the fact that tremor and motor slowing are classic symptoms of Parkinsonism, the present results in rats are consistent with the human literature indicating that tacrine (Cognex) can produce Parkinsonian side effects. Studies of the motor dysfunctions produced by tacrine in rats could be useful for investigating the motor side effects of tacrine in humans. © 1997 Elsevier Science Inc.

Cognex Parkinson's disease Alzheimer's disease Motor Operant Locomotion Tremor

TACRINE (Cognex) is an anticholinesterase that is currently being employed as a treatment for Alzheimer's disease. Administration of tacrine is associated with a wide variety of peripheral and central side effects (37). Some of the central side effects of tacrine are extrapyramidal motor dysfunctions; these include several Parkinsonian symptoms such as cogwheel rigidity, tremor, and bradykinesia (36,37). Consistent with the notion that tacrine can induce Parkinsonian symptoms, there is a substantial literature showing that Parkinsonism can be exacerbated by cholinergic stimulation and alleviated by muscarinic antagonism (2,13,21,31,33,35,52,54). Previous studies with animals also have shown that cholinomimetic drugs have pronounced motor effects. The muscarinic agonist pilocarpine was shown to enhance haloperidol-induced catalepsy, and also to induce catalepsy (19,29). Cholinomimetic drugs induce perioral movements in rats (4,6,7,39–41,44,45,47,50,51), and recently it was shown that tacrine also can induce these movements (32). These results suggest that a more detailed examination of the motor effects of tacrine in animal studies is warranted.

In the present study, three experiments were conducted to provide a characterization of some of the motor effects of tacrine (1.25–5.0 mg/kg IP) in rats. It was hypothesized that tacrine would produce Parkinsonian effects (i.e., tremulous

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movements and motor slowing) in the dose range tested. The first experiment was designed to examine the effects of tacrine on tremulous jaw movements [also known as vacuous jaw movements or purposeless chewing; see (17,25,32,49–51)]. Tremulous jaw movements are rapid and repetitive vertical deflections of the lower jaw, which resemble chewing but are not directed at any stimulus. Although the relation between drug-induced oral movements in rats and human clinical syndromes remains equivocal (53), it has been suggested that the tremulous, nondirected chewing-like movements in rats share important characteristics with Parkinsonian tremor (17,25, 32,45,49). Previous work has shown that tremulous jaw movements are induced by dopamine depletions (3,17,25), muscarinic agonists (4,17,44,45), and also by the anticholinesterases physostigmine and tacrine (6,7,32,39). The jaw movements induced by dopamine depletion, pilocarpine, and tacrine were found to have maximal activity within a local frequency range of 3.0–6.6 Hz (17,32,42), which is consistent with the frequency range of Parkinsonian resting tremor (1,16,22). Recent evidence indicates that tacrine-induced tremulous jaw movements can be reduced by administration of centrally acting anti-Parkinsonian drugs (7,32). The generation of tremulous jaw movements in the present study, within the dose range of 1.25–5.0 mg/kg, was used as a standard for comparison with some of the other possible motor effects of tacrine. In rats, Parkinsonian motor effects often are measured by recording locomotor activity. Dopamine antagonists and dopamine depletions have been shown to decrease locomotor activity (8,24,30). Cholinomimetic drugs also have been shown to decrease spontaneous and drug-induced locomotion (28,48). Thus, in the second experiment, the effects of tacrine on open-field locomotor activity were assessed.

The third experiment investigated the effects of tacrine on lever-pressing behavior. Lever pressing has frequently been used to assess the motor effects of muscarinic agonists (11), dopamine antagonists (18,46), and striatal dopamine depletions (9,10,46). Depletions of dopamine in the ventrolateral striatum produced substantial and persistent decreases in the number of fixed ratio 5 (FR5) lever pressing responses (46). Ventrolateral striatal dopamine depletions also produced a profound alteration of the pattern of interresponse times shown (46). The interresponse time is the time between the onset of each response, which represents the reciprocal of the local (or momentary) rate of responding. In examining the temporal characteristics of operant responding, it is important to recognize that there are two distinct components of the interresponse time. Each deflection of the lever lasts for a particular interval, which represents the response duration. Additionally, there is a time interval between the offset of one response and the onset of the next one (i.e., response initiation time). Response initiation time can further be divided into response initiations that are fast (0–1 s), those that represent short pauses (1–2.5 s), and long pauses [>2.5 s; see (9,10)]. Previous work has indicated that response initiation and duration are increased by ventrolateral striatal dopamine depletions (9,10) and dopamine antagonists (15,18,38). However, little is known about the effects of tacrine on parameters of response output such as response initiation or duration. It is important to examine the effects of drugs on detailed parameters of responding because drug-induced reductions in the total number of responses could be characterized by a number of different patterns. Decreased responding could be accompanied by increased intitiation times, increased durations, or both. The relative distributions of various temporal parameters of responding could be used to distinguish between different conditions that all suppress lever pressing. For example, response durations have been used to distinguish between the effects of extinction and neuroleptics (15), and detailed analysis of the pattern of interresponse times has been used to identify differences between the response suppressing effects of extinction and nucleus accumbens dopamine depletions (43). Therefore, the third experiment of the present work was designed to provide a detailed characterization of the effects of tacrine on the temporal parameters of FR5 lever pressing. Behavioral output during lever pressing on a FR5 schedule was recorded by a computerized system that measured response initiation time and duration for each lever press.

METHOD

Subjects

Male albino rats (total $n = 27$, Harlan–Sprague–Dawley, Indianapolis, IN) were used for these experiments. All rats were housed in a colony room with a constant temperature of 23°C and a 12-h light/dark cycle (lights on at 0700 h). Average weights at the start of the experiment were 300–325 g. These experiments were approved by the university animal care committee, which supervises the care and use of animals; consistent with university policy, all efforts were made to minimize animal suffering and the number of animals used. For the operant conditioning experiment, rats were deprived to 85% of their free-feeding body weight, while rats were kept on ad lib food and water for the other two experiments.

Drugs

Tacrine hydrochloride was obtained from Sigma Chemical Company (St. Louis, MO). This drug was dissolved in a vehicle of 0.9% saline solution for intraperitoneal (IP) injection in a volume of 1.0 ml/kg. For all experiments, the control injection consisted of 0.9 % saline (1.0 ml/kg).

Tremulous Jaw Movements

For the first experiment, observations were made in Plexiglas chambers (28 × 28 × 28 cm) atop a wire mesh floor that was 42 cm from the base. These conditions allowed for clear observation from all angles. A single observer blind to the treatment condition recorded the number of jaw movements with a mechanical hand counter over a 5-min period. Tremulous jaw movements were defined as vertical deflections of the lower jaw that were not directed at a particular stimulus. Each individual deflection of the jaw was recorded as a jaw movement. Yawning, gaping, and tongue protrusions were not considered chewing movements. Previous research involving two separate observers, including the observer used in the present study, has shown that these observation methods generate a high degree of interrater reliability [$r = 0.92$, see (32)].

Open-field Locomotor Activity

Open-field locomotor activity tests were carried out in a wooden box 45 × 45 × 18 inches, which was divided into a 5 × 5 grid (each grid 9 × 9 inches). Activity counts (crossing a dividing line from one of the grid boxes into another) were counted during a 5-min testing period. The observer was unaware of the particular experimental condition during the behavioral session.

Instrumental Behavior Procedures

For the third experiment, testing was performed in operant chambers (28 × 23 × 23 cm). Rats were deprived to 85% of their free-feeding body weights, and then were trained in 30-min sessions 5 days/week on a FR5 lever pressing schedule for 45-mg food pellets (Bioserve Inc.). Food-deprived rats were placed in an operant chamber and trained on a continuous reinforcement schedule for 1 week before being switched to a FR5 lever pressing schedule (i.e., five presses to receive one food pellet). FR5 training continued for 3 weeks before drug sessions began. A microcomputer was used to control the schedule, gather the data during the session, and measure the temporal pattern of responding. The computer recorded the number of lever press responses for the entire behavioral session. Additionally, the temporal characteristics of responding were analyzed by partitioning the session time into various components. For each response, including those that followed reinforcement, the response initiation time (i.e., time from offset of one lever press to onset of the next lever press, and from offset of the last lever press to the end of the session), and the response duration were recorded. Thus, the total session time was partitioned into two components: duration time, and initiation time. From these, the average initiation and duration times (per response) were calculated. The initiation time was further partitioned into two components: the time spent initiating fast responses (<1.0 s initiation time), and the time spent in pauses. There were two types of pauses in responding: short pauses (1.0 s to 2.5 s initiation time), and long pauses (>2.5 s). Total initiation times and average initiation times (total divided by the number of initiation times) were calculated for fast responses, short pauses, and long pauses. Each initiation time that was less than 1.0 s (i.e., fast responses) was also counted as being within one of eight time bins, each representing an interval of 125 ms (0–125 ms, 126–250 ms, 251–375 ms, etc., up to 1.0 s). Duration times also were sorted into 125 ms time bins. Similar analyses of the temporal characteristics of responding have been used previously by our laboratory (9,10).

Experiments

All three experiments were designed to have similar pharmacological methods. The same drug conditions (saline vehicle, 1.25, 2.5, and 5.0 mg/kg tacrine; IP injection) were used for all three experiments. Additionally, all three experiments employed within-subjects designs, such that each rat received all four drug treatments in a randomly varied order, with injections 1 week apart. In the first experiment, the effects of tacrine on tremulous jaw movements were assessed. Rats ($n = 6$) were injected with saline or tacrine, and then placed into the observation chamber. A 5-min observation was conducted 10–15 min after injection. A group of 10 rats was used in the second experiment, which studied the effects of tacrine on open-field locomotion. On each of the test days, rats were injected IP with saline or tacrine, and returned to their home cages. After 10 min, the rats were placed in the open-field apparatus described above, and a 5-min open-field activity test was conducted as described above. In the third experiment, rats ($n = 11$) were trained in the lever pressing task as described above. After baseline training was completed, the drug treatment sessions began. There were four drug treatments (saline vehicle, 1.25, 2.5, and 5.0 mg/kg tacrine, all injected IP), and each rat received all four treatments (one injection per week) in a randomly varied order. The 30-min operant test sessions were initiated 10 min after IP injections. Daily baseline training sessions were continued on those days that were not drug treatment days until the experiment was completed. All rats showed normal levels of responding on the baseline tests conducted between drug sessions.

Data Analysis

For Experiments 1–3, repeated measures analysis of variance (ANOVA) was used to analyze total number of locomotor activity counts, total number of tremulous jaw movements, and total number of lever-pressing responses. In all analyses using ANOVA, planned comparisons (27) were used to test for differences between each drug dose and the control condition. Raw data were log transformed prior to conducting statistical tests if the homogeneity of variance assumption for ANOVA was not met. Additional parameters of responding (average initiation time, average duration, the relative number and average length of fast responses, short pauses, and long pauses) were analyzed by the repeated measures *t*-test, with each of the three doses of tacrine being compared with the control condition as a planned comparison (27). Each dose was compared with control separately because some animals did not respond at all at the higher doses of tacrine (one nonresponder at 2.5 mg/kg; five at 5.0 mg/kg). Thus, the detailed parameters of responding could not be obtained from all animals at all doses. Consistent with the method described by Keppel [(27), pp. 146–150], the analyses of each dose of tacrine vs. control involved three planned comparisons (significance level = 0.05; approximate family-wise error = 0.15). For graphic depiction of the initiation time bins, data in each bin were expressed as a proportion of the total number of fast responses in that condition. This measure was used to correct for the treatment differences in total number of fast responses so that the relative frequency distributions of fast initiation times could be examined [see (9,10,46)]. The distributions of response initiation times were analyzed by testing for significant differences between the proportions obtained in each bin [see (5)], with each dose of tacrine being tested against saline vehicle. Because of the large number of comparisons (three comparisons × eight bins = 24), the significance level was set at $p = 0.0083$ (family-wise error of 0.2 divided by 24).

RESULTS

Experiment 1: Effects of Tacrine on Jaw Movements

Figure 1 depicts the dose-dependent induction of tremulous jaw movements by tacrine. There was a significant overall effect of tacrine on tremulous jaw movements, $F(3, 15) = 18.13$, $p < 0.0001$. Planned comparisons indicate that at doses of 1.25, 2.5, and 5.0 mg/kg tacrine, jaw movements significantly differed from the saline controls ($p < 0.05$).

Experiment 2: Effects of Tacrine on Open-field Locomotor Activity

Figure 2 shows the results of the open-field locomotor activity experiment. Tacrine administration led to a dose-related decrease in open-field locomotor activity, $F(3, 24) = 6.11$, $p < 0.0001$. Planned comparisons indicated that the 2.5 and 5.0 mg/kg doses of tacrine significantly differed from the effects of saline vehicle ($p < 0.05$).

Experiment 3: Effects of Tacrine on Lever Pressing

The effects of tacrine on total number of operant lever presses are shown in Fig. 3. Tacrine produced a dose-related

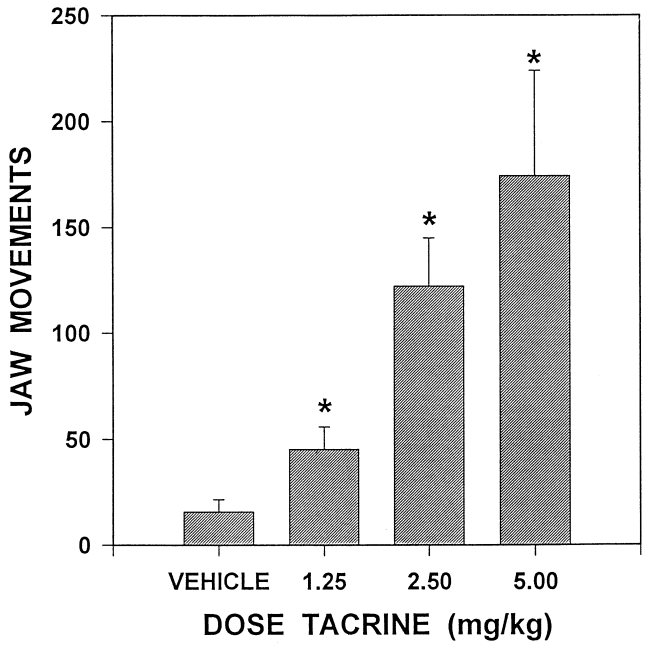

FIG. 1. Mean (±SEM) number of tremulous jaw movements in the 5-min observation time for rats that received vehicle, 1.25, 2.5, and 5.0 mg/kg tacrine (* different from vehicle, $p < 0.05$).

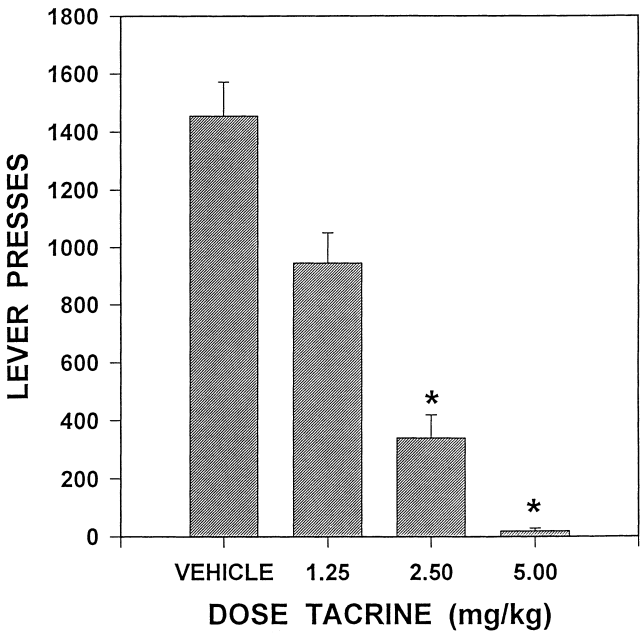

FIG. 3. Mean (±SEM) number of lever presses for the 30-min test session for rats that received vehicle, 1.25, 2.5, and 5.0 mg/kg tacrine (*different from vehicle, $p < 0.05$).

decrease in the number of lever presses, $F(3, 30) = 40.95$, $p < 0.0001$. Planned comparisons indicated that the 2.5 and 5.0 mg/kg doses significantly differed from vehicle ($p < 0.05$). Figure 4 shows the effects of tacrine on average duration of lever pressing. Tacrine produced a significant increase in duration, with significant effects at 1.25 mg/kg, $t(10) = 2.4$, $p < 0.05$, 2.5 mg/kg, $t(9) = 5.4$, $p < 0.001$, and 5.0 mg/kg, $t(5) = 4.6$, $p < 0.01$. The relative distribution of response duration times

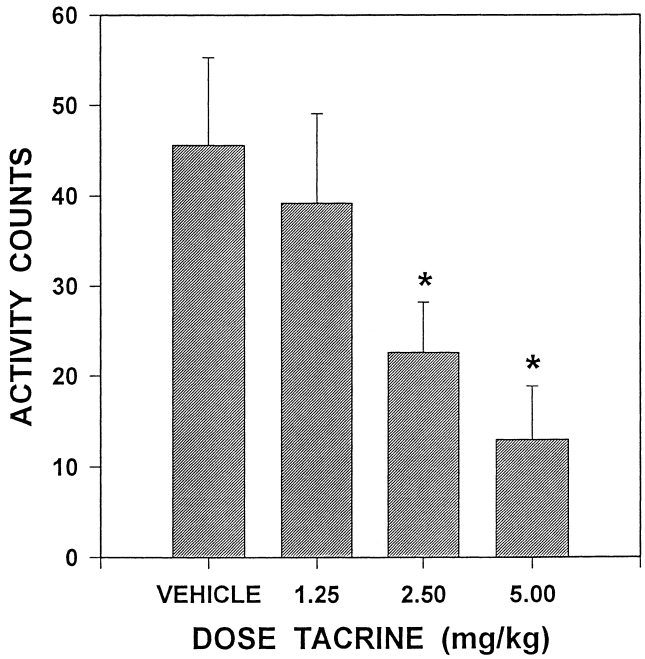

FIG. 2. Mean (±SEM) number of open field activity counts in the 5-min observation time for rats that received vehicle, 1.25, 2.5, and 5.0 mg/kg tacrine (*different from vehicle, $p < 0.05$).

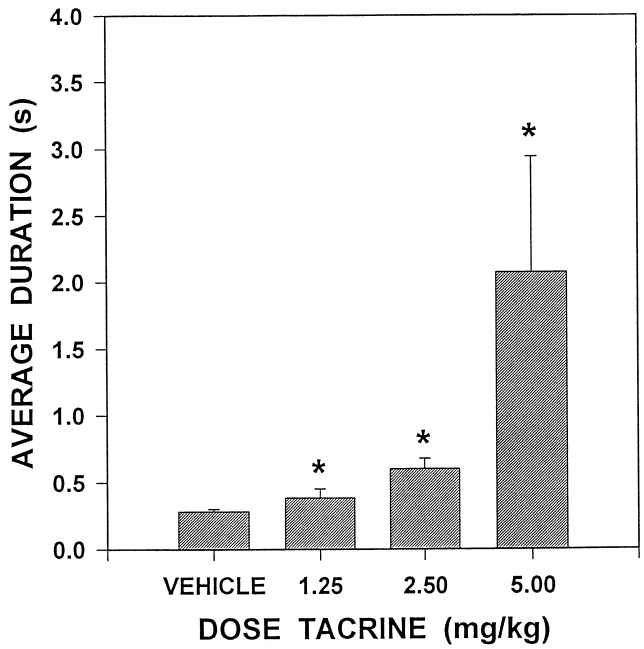

FIG. 4. Mean (±SEM) of the average response duration for rats that received vehicle, 1.25, 2.5, and 5.0 mg/kg tacrine (*different from vehicle, $p < 0.05$).

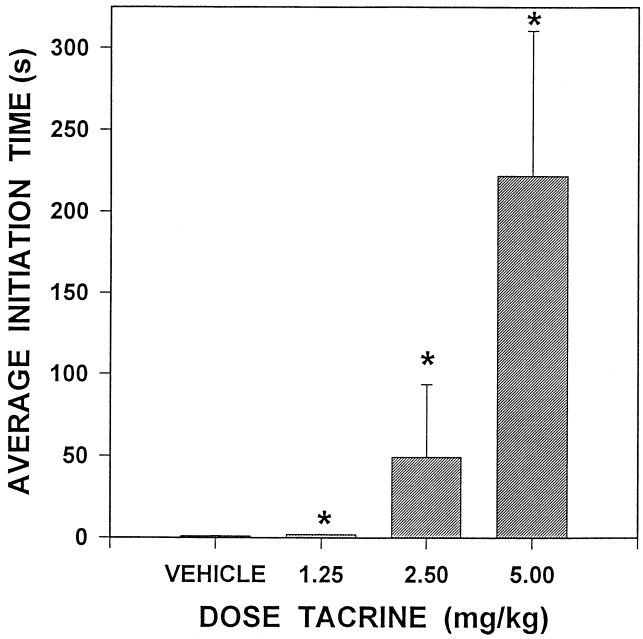

FIG. 5. Mean (±SEM) of the average response initiation time for rats that received vehicle, 1.25, 2.5, and 5.0 mg/kg tacrine (*different from vehicle, $p < 0.05$).

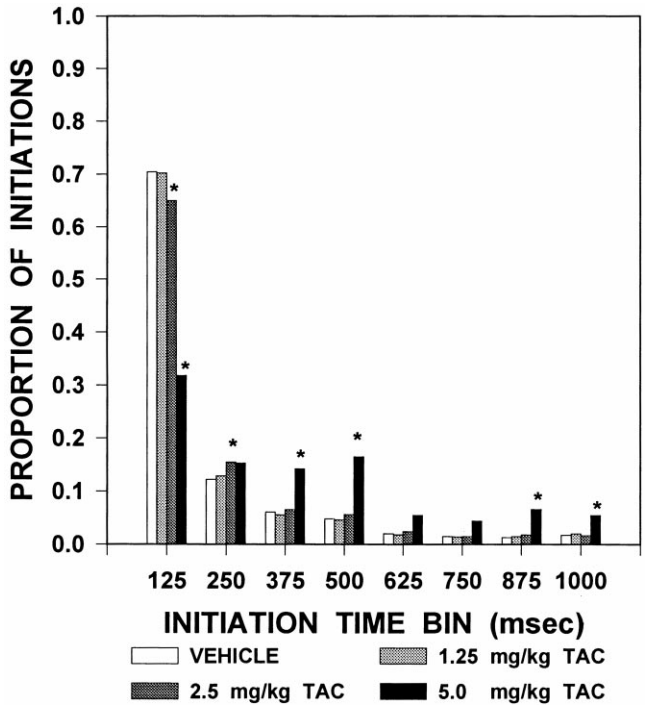

FIG. 6. Relative frequency distribution of fast initiation times (i.e., less than 1000 ms) divided into eight 125-ms time bins (0–125, 125–250, etc.; the highest value for each bin is shown on the graph). Data are expressed as the proportion of all fast initiation times at that dose (*tacrine proportion significantly different from saline proportion in that time bin, $p < 0.0083$).

within each of eight 125-ms time bins was also analyzed (data not shown). Tacrine led to relatively fewer response durations in the faster time bins (0–125 and 125–125 ms) and relatively more responses in the slower time bins. The modal duration was shifted from 125–250 ms following saline treatment to 250–500 ms after treatment with 2.5 or 5.0 mg/kg tacrine.

Figure 5 depicts the effects of tacrine on average response initiation. Tacrine produced a significant increase in average response initiation time, with significant effects at 1.25 mg/kg, $t(10) = 3.6$, $p < 0.01$), 2.5 mg/kg, $t(9) = 4.04$, $p < 0.01$, and 5.0 mg/kg, $t(5) = 8.44$, $p < 0.001$. The effects of tacrine on the components of the response initiation time are shown in Table 1. There was a significant overall decrease in the percent of lever presses with initiation times of less than 1.0 s for both the 2.5 and 5.0 mg/kg doses of tacrine. There was no significant difference in the percent of lever presses with initiation times greater than 1 s but less than 2.5 s (i.e., short pause). There was a significant increase in the percent of lever presses with initiation times greater than 2.5 s (i.e., long pause) for both the 2.5 and 5.0 mg/kg doses of tacrine relative to saline. There were only small effects of tacrine on the average length of fast responses and the average length of short pauses (see Table 1). However, tacrine produced substantial increases in the average length of long pauses, which were significant at all three doses. Figure 6 shows the relative distribution of response initiation times within each of eight 125 ms time bins (0–1000 ms, i.e., fast responses). The higher doses of tacrine led to relatively fewer response initiation times in the fastest time bin (0–125 ms) and relatively more responses in the slower time bins. Analysis of the proportions of initiation times in each time bin demonstrated that the initiation time distributions of the two higher doses of tacrine significantly differed from the proportions shown in the saline control data in several time bins (see Fig. 6).

DISCUSSION

In a dose range of 1.25–5.0 mg/kg, the anticholinesterase tacrine produced substantial effects on several different aspects of motor function. Consistent with previous reports (23,32), tacrine was shown to induce tremulous jaw movements. Significant jaw movement activity relative to the control group was observed at all three doses of tacrine administered (i.e., 1.25, 2.5, and 5.0 mg/kg). Tacrine also suppressed locomotor activity and lever pressing in the same dose range. Thus, the present study indicates that tacrine can induce tremulous movements and suppress voluntary motor activity within a roughly comparable dose range. In view of the fact that tremor and bradykinesia are classic symptoms of Parkinsonism (1,52), these effects in rats are consistent with the human literature indicating that tacrine (Cognex) can produce Parkinsonian side effects (36,37).

The present study was the first to provide a detailed characterization of the effects of tacrine on the temporal features of operant lever pressing. The operant session time was partitioned into various components so that a precise identification of the effects of tacrine could be ascertained. Tacrine produced dose-related increases in both response duration and response initiation. However, it should be emphasized that increases in response duration represented only a small portion of the total response deficit. The overall interresponse time in tacrine-treated rats was determined much more by the large increases in average initiation time (over 200 s at the highest dose) than by the small increases in duration (up to approximately 2 s). Partitioning of the initiation time also allowed for

TABLE 1

ABSOLUTE NUMBER, PERCENTAGE, AND LENGTH OF FAST RESPONSES, SHORT PAUSES, AND LONG PAUSES

Parameter	Saline ($n = 11$)	Dose Tacrine (mg/kg) 1.25 ($n = 11$)	2.5 ($n = 10$)	5.0 ($n = 6$)
Number of fast responses	1127.6 (98.2)	*722.1 (85.8)	*255.0 (64.2)	*14.3 (7.0)
Number of short pauses	208.1 (21.7)	*116.7 (13.7)	*43.2 (8.8)	*6.7 (3.4)
Number of long pauses	117.8 (11.5)	107.4 (14.9)	69.3 (14.4)	*14.3 (5.4)
Percent fast responses	77.1 (1.0)	75.5 (1.6)	*60.7 (4.7)	*31.7 (7.4)
Percent short pauses	14.2 (0.8)	12.7 (0.9)	12.3 (2.5)	15.6 (6.4)
Percent long pauses	8.7 (1.1)	11.9 (1.5)	*21.0 (2.3)	*53.2 (10.6)
Average length of fast responses (s)	0.16 (0.01)	0.16 (0.01)	*0.26 (0.06)	0.40 (0.13)
Average length of short pauses (s)	1.73 (0.02)	*1.67 (0.02)	*1.62 (0.02)	*1.82 (0.01)
Average length of long pauses (s)	8.4 (1.7)	*13.0 (2.1)	*107.5 (87.8)	*554.3 (282.3)

*$p < 0.05$, different from saline vehicle.
Means (±SEM) for each parameter are shown.

the identification of the critical features that characterize the tacrine-induced response decrements. Analysis of the distribution of initiation bins indicated that the overall pattern of the initiation of fast responses was affected by tacrine, with tacrine producing a relative decrease in the proportion of very fast (i.e, 0–125 ms) initiation times. Tacrine also produced a slight decrease in the local rate of responding, as measured by the significant increase in the average length of fast responses at the 2.5 mg/kg dose, and the strong trend towards this effect at 5.0 mg/kg. Nevertheless, the effect of tacrine on the local rate of responding was rather small in comparison to the large increase in the average length of long pauses, which was evident at all three doses. In addition, tacrine produced a temporal fragmentation of the normal pattern of responding such that there was a relative increase in the number of long pauses. Under saline conditions, more than 75% of all initiation times were less than 1.0 s (i.e., fast responses), and only about 8% were greater than 2.5 s. In contrast, after the highest dose of tacrine more than 50% of the initiation times were greater than 2.5 s. Thus, although tacrine-induced decreases in the local rate of responding and increases in response duration contributed to the overall deficit, the major contributors to the tacrine-induced decreases in responding were the increases in both the relative number and average length of pauses in responding. The precise mechanism that underlies tacrine-induced increases in pause time is not certain; however, the present data are consistent with the notion that tacrine reduces the probability of initiating voluntary movement (i.e., akinesia).

Several factors can influence operant responding for food, including motor processes and motivational factors such as appetite. However, several lines of evidence indicate that tacrine suppressed responding by affecting aspects of motor function. The first two experiments indicate that tacrine produced other motor effects, such as suppressed locomotor activity and the induction of tremulous movements, in the same dose range that reduced operant responding. In addition, the patterns of responding in tacrine-treated rats do not resemble the effects reported for motivational variables. Tacrine substantially reduced the relative number of fast responses, yet it has been reported that withdrawal of reward (i.e., extinction) leads to "bursts" of responding that are characterized by increases in the relative number of fast responses (43). Extinction does not substantially increase response duration (15), yet this parameter was increased dramatically by tacrine. Although the behavioral processes underlying drug-induced increases in response duration are not well understood, it is possible that increased response durations reflect a slower transition from the motor act of depressing the lever to the act of elevating the lever. Increases in response duration could reflect bradykinesia or catalepsy. This interpretation is consistent with studies showing that cholinomimetics induce catalepsy (19,29). It also should be recognized that lever pressing at high rates is a learned motor skill that involves considerable training, and tacrine could be interfering with higher order functions that are involved in the performance of complex and coordinated learned motor acts.

The behavioral effects of tacrine are similar to some of the effects that occur after forebrain dopamine depletion, which may give some clues as to the anatomical basis of cholinomimetic-induced motor effects. Detailed temporal analyses of responding indicated that, like tacrine-treated rats, rats with ventrolateral striatal dopamine depletions showed slight increases in duration, slight decreases in the local rate of responding, and substantial increases in the average initiation time and average length of pauses (9,10). Previous work also has shown that dopamine antagonists substantially increase response durations (15,18,38). These similarities between the behavioral effects of cholinomimetics and those of dopamine depletions or neuroleptics are consistent with previous reports indicating that there is a functional interaction between dopamine and acetylcholine, which is involved in the regulation of motor control (2,6,13,47,49). Neostriatal dopamine and acetylcholine are involved in motor functions, and evidence indicates that different striatal subregions are involved in distinct aspects of movement control (17,25,26,32,45,46). Previous work has shown that dopamine depletions in ventrolateral striatum, but not other striatal areas, can induce tremulous jaw movements (17,25). Considerable evidence indicates that muscarinic receptors in the ventrolateral striatum also mediate cholinomimetic-induced tremulous jaw movements (26, 32,45). In addition, it has been shown that local depletions of dopamine in nucleus accumbens and medial striatum can reduce locomotor activity (8,30), while ventrolateral striatal dopamine depletions severely impair lever pressing (8–10,46). Because systemic tacrine was used in the present study, the

anatomical mechanisms underlying cholinomimetic-induced reductions in locomotor activity and lever pressing remain uncertain. Nevertheless, it is reasonable to hypothesize that the regional heterogeneity of cholinergic function in striatal subregions matches the pattern previously demonstrated for dopamine. This would suggest that the locomotor activity effects of cholinomimetics are related to accumbens or medial striatal areas, while the decrease in lever pressing and the induction of tremulous jaw movements are more related to cholinergic stimulation in the ventrolateral striatum. Additional research should be performed to test this hypothesis.

Although the present study did not look specifically at memory function, other work has shown that tacrine can act to enhance performance in learning and memory tasks (12,14,20,34). The most profound enhancements have occurred in animals with impaired cholinergic function. For example, tacrine reversed the spatial discrimination learning deficits induced by hemicholinium-induced acetylcholine depletions (20). Further, tacrine has been shown to reverse scopolamine-induced amnesia in a T-maze paradigm at 3.2 mg/kg (34). However, in that study it was reported that higher doses of tacrine (5.6 and 10.0 mg/kg, IP) resulted in obvious motor problems (34). It also has been reported that tacrine could improve passive avoidance performance in animals impaired by hypoxia, with maximal effects at 5.0 mg/kg tacrine (12). Thus, it appears as though tacrine can induce motor impairments at or near the doses that also have been shown to improve memory function. Future research should focus on comparing the anatomical and neurochemical characteristics of tacrine-induced motor and cognitive effects. It is possible that such research would lead to cholinomimetic compounds that are efficacious for affecting cognitive functions yet less likely to induce motor effects.

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