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Tremulous Jaw Movements Produced by Acute Tacrine Administration: Possible Relation to Parkinsonian Side Effects

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MAYORGA, A. J., CARRIERO, D. L., COUSINS M. S., GIANUTSOS, G., AND SALAMONE, J. D. *Tremulous jaw movements produced by acute tacrine administration: Possible relation to Parkinsonian side effects.* PHARMACOL BIOCHEM BEHAV **56**(2) 273–279, 1997.—Previous work has shown that cholinomimetic drugs induce "vacuous" or non-directed jaw movements in rats. In the present study, five experiments were conducted to provide a pharmacological, anatomical and behavioral characterization of tacrine-induced vacuous jaw movements. In the first experiment, tacrine produced vacuous chewing in a dose-related manner in a range of 1.25 mg/kg to 1.0 mg/kg. This effect was reduced, also in a dose-related manner, by the co-administration of the muscarinic antagonist scopolamine in a range of 0.125 to 1.0 mg/kg, but not by *N*-methylscopolamine. The fourth experiment examined the effect of scopolamine (2.5 to 10.0 ug) injected into the ventrolateral striatum on vacuous jaw movements induced by 5.0 mg/kg tacrine. Intrastriatal injections of scopolamine completely blocked tacrine-induced jaw movements. The fifth experiment utilized a slow-motion videotaping system to analyze the temporal characteristics of vacuous chewing induced by 5.0 mg/kg tacrine. The vast majority of the movements occurred in rapid "bursts," and analysis of interresponse times (i.e., the time between each jaw movement) showed that most of the jaw movements occurred within a local frequency range of 3 to 7 Hz. Thus, tacrine-induced jaw movements are reduced by antimuscarinic treatment, and most of these movements occur in the parkinsonian tremor frequency range. Tremulous jaw movements induced by tacrine in rats appear to share some characteristics with Parkinsonian tremor. **Copyright © 1997 Elsevier Science Inc.**

Tacrine Vacuous chewing Tremor Parkinson's disease Alzheimer's disease

THE anticholinesterase tacrine (Cognex) is currently used therapeutically to improve memory function in patients with early and late onset Alzheimer's disease. This treatment is designed to elevate synaptic levels of cortical and hippocampal acetylcholine, which are substantially reduced in Alzheimer's patients (see review, ref. 26). Although tacrine has achieved limited success in this regard, this drug is also associated with extrapyramidal motor side effects in humans. These effects include various parkinsonian symptoms such as bradykinesia, cogwheel rigidity, and tremor (21,22). Tacrine has been observed to exacerbate parkinsonian symptoms in human patients (21). The induction of parkinsonian symptoms by cholinesterase inhibition is generally consistent with the substantial literature showing cholinergic involvement in idiopathic and neuroleptic-induced parkinsonism (8,18,19).

Animal studies have shown that cholinomimetic drugs produce a wide variety of motor effects (7,28). In rats, drugs that stimulate muscarinic cholinergic receptors produce a number of different orofacial movements, the most common of which is known as vacuous jaw movements (see also, vacuous or purposeless chewing; 4,5,24,28,29,33–35). This movement is typically defined as a vertical deflection of the lower jaw that is not directed at any particular stimulus. Although there is considerable discussion about the possible clinical significance of drug-induced vacuous jaw movements (9,25,37), it has been suggested that cholinomimetic-induced vacuous jaw movements share some characteristics with human parkinsonian symptoms (6,11,27,29,31,32). Vacuous jaw movements are produced by the muscarinic agonists pilocarpine, arecoline, and oxotremorine in a dose-related manner, and these movements

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are blocked by the centrally acting muscarinic antagonist scopolamine but not by *N*-methylscopolamine (28,33). The nonselective dopamine agonist apomorphine, which is effective as an antiparkinsonian agent, has been shown to reduce pilocarpine-induced vacuous jaw movements (33). Pilocarpine-induced vacuous jaw movements occur largely in bursts, with a local frequency mostly in the 3–7 Hz range (12). The induction of these movements has been linked to neostriatal mechanisms, as it has been shown that local injections of pilocarpine into the ventrolateral striatum induce vacuous jaw movements (29). The anticholinesterase physostigmine also induces vacuous jaw movements, with either systemic administration (23,24) or injections of physostigmine into the ventrolateral striatum (17) being effective. One initial report has shown that tacrine can stimulate jaw movements (15). The present study was conducted to provide a pharmacological, anatomical and behavioral characterization of tacrine-induced vacuous jaw movements.

Five experiments were conducted in order to study tacrine-induced vacuous jaw movements. The first experiment investigated the effects of different doses of tacrine (1.25–10.0 mg/kg) on vacuous jaw movements. Based upon the results of experiment 1, a single dose of tacrine (5.0 mg/kg) was selected for use in the remaining experiments. In the second and third experiments, the muscarinic antagonists scopolamine and methylscopolamine were co-administered with tacrine in order to determine if central or peripheral muscarinic blockade reduced the tacrine-induced movements. In experiment 4, scopolamine was injected into the ventrolateral striatum via chronic cannulae to assess the effects of local muscarinic blockade on the jaw movements induced by systemic tacrine. This site was chosen because previous research has shown that the ventrolateral striatum is the most effective site for induction of vacuous jaw movements by cholinomimetics (17,29) and dopamine depletions (16). In the fifth experiment, the local frequencies of tacrine-induced vacuous jaw movements were measured using a computerized analysis of slow-motion videotape from tacrine-treated rats (see also refs. 12,27).

METHODS

Subjects

Male albino rats (total $n = 41$, Harlan Sprague–Dawley, Indianapolis IN) were used for these experiments. All rats were housed in a colony room with a constant temperature of 72 F and a 12 L: 12 D cycle (lights on at 0730 h). Standard lab chow and water were available ad lib. Average weights at the start of the experiment were 300–325 g. All animal procedures were approved by the Institutional Animal Care and Use Committee.

Drugs

Tacrine hydrochloride, *n*-methylscopolamine and scopolamine hydrobromide were obtained from Sigma Chemical Company. All drugs were dissolved in a vehicle of 0.9% saline solution for both systemic and intracranial injections. Systemic injections were via the intraperitoneal route (IP) in a volume of 1.0 ml/kg.

Behavioral Observations

In the first four experiments the observation chambers consisted of Plexiglas boxes (28 × 28 × 28 cm) set atop a wire mesh floor, which were raised 42 cm above the table surface to allow for viewing from all possible angles. A mechanical hand counter was used to record numbers of chewing movements. Observations were made between 900 and 1600 h. Vacuous jaw movements were defined as vertical deflection of the lower jaw not directed at any particular stimulus. These did not include yawning or gaping. A single observer blind to study design counted each individual vertical deflection as one vacuous jaw movement, and recorded the total number of responses over a five minute observation period in experiments 1–4. Significant interrater reliability ($r = 0.92$) with this observation method was shown in pilot studies conducted along with these experiments.

In the fifth experiment, rats were placed in a clear Plexiglas tube (9 cm in diameter) to maintain their position so that a consistent view of the orofacial region could be achieved for videotaping. Each rat was recorded using a video camera (Panasonic AG-180) focused on the orofacial region for a 5 min period. A blind observer then played the videotape (Panasonic AG-1730 VCR) in slow-motion at one-sixth normal speed to observe the jaw movements as defined previously. At the point of maximal jaw opening, a blind observer pressed the space bar of the computer keyboard, and a computer program calculated various parameters of the jaw movements. These parameters included the total number of jaw movements, the total number of single jaw movements (one not preceded or followed by another movement within a one-second interval), the number of jaw movement bursts (defined as a group of at least two jaw movements with an interresponse time of less than or equal to 1.0 s), total number of jaw movements occurring in bursts, and the average burst size. The computer program converted the temporal parameters observed in slow-motion into real time and calculated the interresponse time for each jaw movement that occurred in a burst, the reciprocal of which gives the local frequency of the movements. For example, an interresponse time of 0.200 s represents a frequency of 5 Hz. The interresponse time for each jaw movement was then assigned to a 50 ms-wide time bin, and the program recorded the number of movements within each of the following interresponse time bins: 0–50, 50–100, 100–150, up to 950–1000 ms and >1000 ms. Previous experiments have demonstrated a high degree of test-retest reliability using this measurement system ($r = 0.996$ on responses in each interresponse time bin between two ratings of the same tape segment).

Surgery

For implantation of chronic guide cannulae for intracranial drug injection, all rats were anesthesized with 50.0 mg/kg sodium pentobarbital IP. Rats were placed in a stereotaxic frame with the incisor bar set 5.0 mm above the interaural line. Bilateral guide cannulae (23ga) were implanted at the following coordinates: AP-1.4 mm anterior to bregma, ML- 4.0 mm lateral to bregma, V-5.2 mm ventral to the skull surface. The cannulae were anchored to the skull using machine screws and cranioplastic cement.

Intracranial Drug Injections

The injections were made using 30 ga injectors set to extend 2.0 mm beyond the tip of the guide cannulae. The injectors were attached via PE-10 tubing to a 10 ul Hamilton syringe driven by a syringe pump. Drug solution was injected in a volume of 1.0 microliter per side at a rate of 0.5 ul per min for 2 min, and the injection cannulae were left in place for 2 min after injection to allow for drug diffusion.

Experiments

In experiment 1, rats received an IP injection of tacrine (1.25, 2.5, 5.0, 10.0 mg/kg) and were immediately placed in the observation chamber for habituation. Animals were observed 10–15 min after tacrine injection, and the number of vacuous jaw movements was recorded directly using a hand counter as described above. For this experiment, a group of rats (n = 5) was tested over a 5 week period, with each rat receiving one drug treatment per week in a randomly varied order. In experiment 2, rats were pretreated 60 min prior to observation with either 0.125, 0.25, 0.5, or 1.0 mg/kg scopolamine or saline vehicle (IP), then given tacrine 5.0 mg/kg (IP), placed in the chamber, and observed 10–15 min after tacrine injection. In this experiment, a single group of rats (n = 5) was tested over a 5 week period, with each rat receiving one drug treatment per week in a randomly varied order. For experiment 3, rats were pretreated with either saline vehicle, or *N*-methylscopolamine (0.5 and 1.0 mg/kg; all injections IP) 60 min before observation, and then were injected with 5.0 mg/kg tacrine IP, placed in the chamber, and observed 10–15 min after tacrine injection. A group of rats (n = 6) was tested over a 3 week period for this experiment, with each rat receiving one drug treatment per week in a randomly varied order. For experiment 4, rats received intracranial injections of 2.5, 5.0, 10.0 ug scopolamine or saline in 1.0 ul volume into the ventrolateral striatum, 1 wk after implantation of the guide cannulae. The injection process lasted two minutes, then drug was allowed to diffuse for 2 min, after which each animal was injected with 5.0 mg/kg tacrine IP. The rats were then immediately placed in the observation chamber and observed 10–15 min after tacrine injection. A separate group of rats was used for each drug treatment (n = 5 per group) in this experiment, and each rat was randomly assigned to receive only one drug treatment. In experiment 5, the slow-motion videotape system was used to characterize the temporal pattern of the jaw movements. Rats (n = 5) were given 5.0 mg/kg tacrine IP and placed in the Plexiglas tube. Ten minutes later rats were videotaped for a 5 min period. Videotapes were analyzed as described above. A new set of rats was used for each of these experiments.

Data Analysis

In experiments 1, 2 and 3, each rat received all drug treatments in a randomly varied order. Thus, repeated measures analysis of variance (ANOVA) was used to analyze the data. For experiment 4, separate groups of rats were used for each drug treatment; thus, a between-groups ANOVA was used. In all experiments, post-hoc comparisons between drug-treated and control groups were conducted by using the Dunnett's test. Various descriptive statistics were used for experiment 5.

RESULTS

Dose-response Analysis of Tacrine-Induced Vacuous Jaw Movements

Figure 1 shows the dose-response curve for tacrine-induced vacuous jaw movements obtained in the first experiment. Curve-fitting analyses of these dose-response data indicate that the ED50 for the induction of vacuous jaw movements by tacrine is approximately 2.6 mg/kg. ANOVA demonstrated that there was a significant overall effect of tacrine on vacuous jaw movements [$F(4, 16) = 19.0$, $p < .001$] . Using Dunnett's test to analyze differences between each dose of tacrine and the vehicle treatment, it was observed that the 2.5, 5.0 and 10.0 mg/kg doses all produced levels of jaw movement that significantly differed from the vehicle treatment ($p < 0.05$).

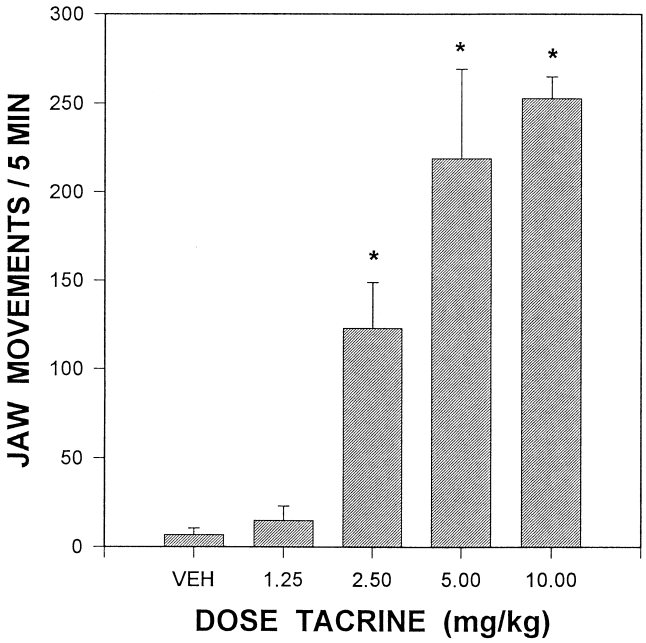

FIG. 1. Mean (+ SEM) number of jaw movements induced by various doses of tacrine are shown. (* different from vehicle, $p < 0.05$).

Effect of Systemic Scopolamine and Methylscopolamine on Tacrine-Induced Movements

The second experiment studied the effect of co-administration of scopolamine on tacrine-induced vacuous jaw movements. As shown in Fig. 2, scopolamine produced a dose-related decrease in the vacuous jaw movements induced by 5.0 mg/kg tacrine. ANOVA revealed a significant overall effect of scopolamine dose [$F(4, 16) = 3.69$, $p < 0.05$], and post-hoc comparisons indicated that the 0.5 and 1.0 mg/kg doses of scopolamine plus tacrine significantly differed from tacrine plus vehicle. In the third experiment, the effects of *N*-methylscopolamine on tacrine-induced movements were assessed. It can be seen in Fig. 3 that doses of 0.5 and 1.0 mg/kg methylscopolamine had no suppressive effect upon tacrine-induced jaw movements [$F(2, 10) = 3.96$, $p > 0.05$).

Injections of Scopolamine Directly into Ventrolateral Striatum

The fourth experiment examined the effects of local intrastriatal injections of scopolamine on the vacuous jaw movements induced by systemic (5.0 mg/kg) tacrine. As shown in Fig. 4, injections of scopolamine into the ventrolateral striatum produced a dose related decrease in tacrine-induced jaw movements. ANOVA demonstrated a significant effect of dose [$F(3, 16) = 29.98$, $p < 0.001$], and post-hoc comparisons showed that co-administration of either 2. 5, 5.0 or 10.0 ug per side of scopolamine suppressed tacrine-induced jaw movements relative to vehicle plus tacrine.

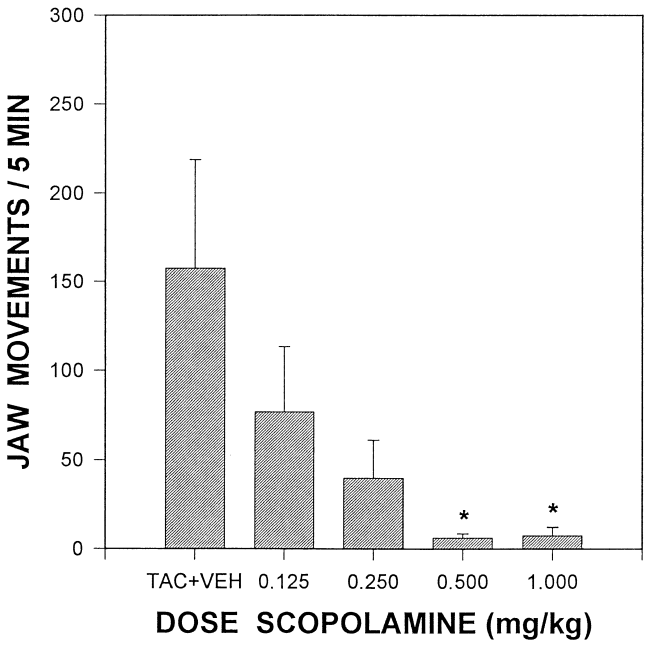

FIG. 2. This figure shows the effect of scopolamine on tacrine-induced movements. Mean (+ SEM) number of jaw movements induced by various doses of scopolamine co-administered with 5.0 mg/kg tacrine are shown. All rats received injections of tacrine, and the control condition (TAC+VEH) involved injections of 5.0 mg/kg tacrine plus vehicle. (* different from tacrine plus vehicle, $p < 0.05$).

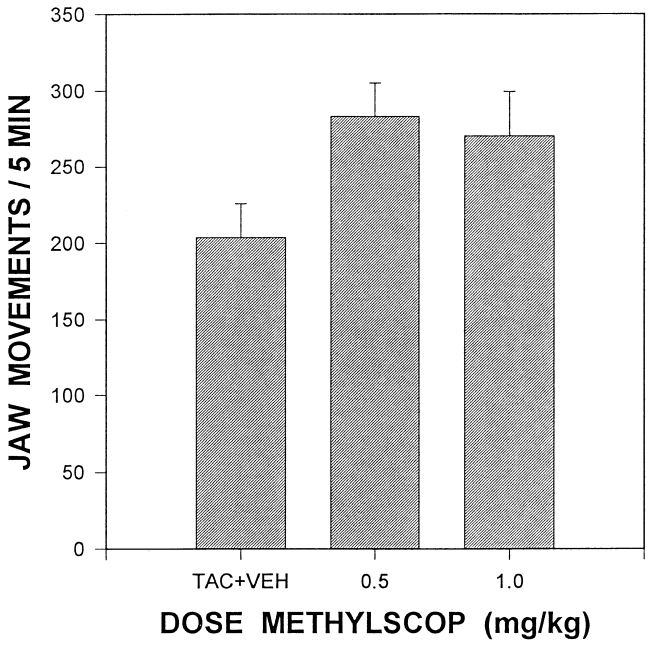

FIG. 3. This figure shows the effect of methylscopolamine (METHYLSCOP) on tacrine-induced movements. Mean (+ SEM) number of jaw movements induced by various doses of methylscopolamine co-administered with 5.0 mg/kg tacrine are shown. All rats received injections of tacrine, and the control condition (TAC+VEH) involved injections of 5.0 mg/kg tacrine plus vehicle.

Analysis of the Temporal Characteristics of Jaw Movement

In the fifth experiment, a computerized slow-motion videotape analysis system was used to provide a temporal characterization of the jaw movements induced by 5.0 mg/kg tacrine. Table 1 lists the descriptive statistics for some of the parameters of movement analyzed by the computer program. It can be seen that the vast majority of vacuous jaw movements (approximately 99%) occurred in "bursts" (i.e., with interresponse times of less than 1.0 s) Fig. 5 is a frequency distribution histogram showing the distribution of jaw movement interresponse times that were less than 1000 ms; the period from 0-1000 ms is separated into 20 time bins that are each 50 msec wide. As shown in this figure, most of the jaw movements occur with interresponse times in the 150–300 ms range, and the peak of the distribution was in the 200–250 ms bin. Because the interresponse time is the reciprocal of the frequency, Fig. 5 also has a line depicting the 3–7 Hz frequency range (142–333 ms interresponse time); it can be seen that most of the interresponse times are in the 3–7 Hz range.

General Observations

Rats injected with tacrine also showed signs of peripheral parasympathetic activity (e.g., salivation, diarrhea). Although methylscopolamine did not reduce tremulous jaw movements, it was noted that both methylscopolamine and scopolamine reduced parasympathetic activity. Occasional muscle twitches were sometimes observed in the body, neck and face of tacrine-treated rats. Co-treatment with scopolamine did not appear to reverse this effect, and it is likely that these muscle twitches represent a peripheral nicotinic action of tacrine directly on neuromuscular junctions. In the first three experiments, injections of 5.0 mg/kg tacrine generally produced high levels of jaw movement activity (e.g., 160–240 movements/5 min); however, in experiment 4, rats that had chronic cannulae implanted generally showed lower levels of jaw movement activity with this dose of tacrine.

DISCUSSION

Systemic administration of tacrine led to a dose-related increase in vacuous jaw movements. Although 1.25 mg/kg tacrine was ineffective at producing a jaw movement response, all three of the higher doses (2.5, 5.0 and 10.0 mg/kg) induced significant increases in vacuous jaw movements relative to the vehicle control condition. The ED50 for tacrine-induced jaw movements was approximately 2.6 mg/kg. Previous work has indicated that physostigmine induces vacuous jaw movements in the range of 0.2-0.4 mg/kg (refs. 23,24; also, unpublished observations), which indicates that tacrine is about 5–10 times

TABLE 1

MEAN (± SEM) OF VARIOUS PARAMETERS OF JAW MOVEMENT ACTIVITY INDUCED BY 5.0 mg/kg TACRINE AS MEASURED BY THE SLOW-MOTION VIDEOTAPE METHOD (n = 5)

Parameter	Mean	SEM
Total jaw movements	173.4	48.8
Single jaw movements	1.6	0.5
Movements in bursts	171.8	58.4
Number of bursts	20.6	6.4
Average burst size	8.4	0.8

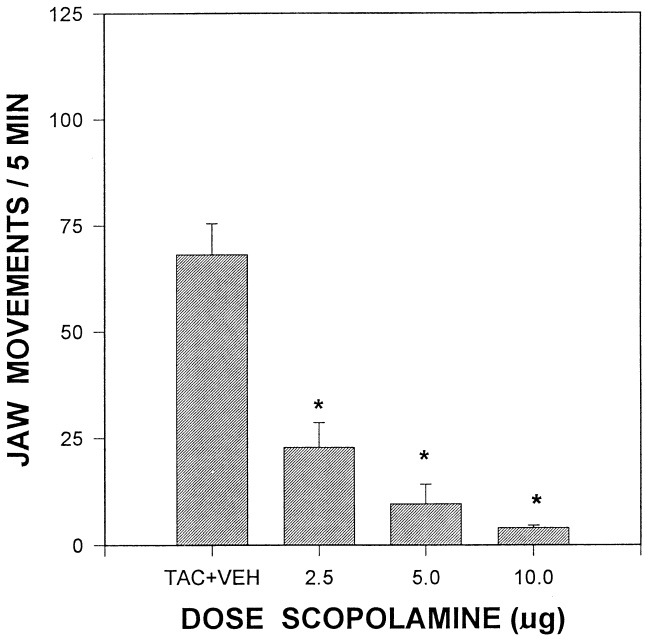

FIG. 4. The effects of scopolamine injected into the ventrolateral striatum on tacrine-induced movements are shown. Data represent mean (+ SEM) number of jaw movements induced by various doses of intrastriatal scopolamine co-administered with 5.0 mg/kg tacrine. All rats received injections of tacrine, and the control condition (TAC+ VEH) involved injections of 5.0 mg/kg tacrine plus vehicle. (*different from vehicle plus tacrine, $p < 0.05$).

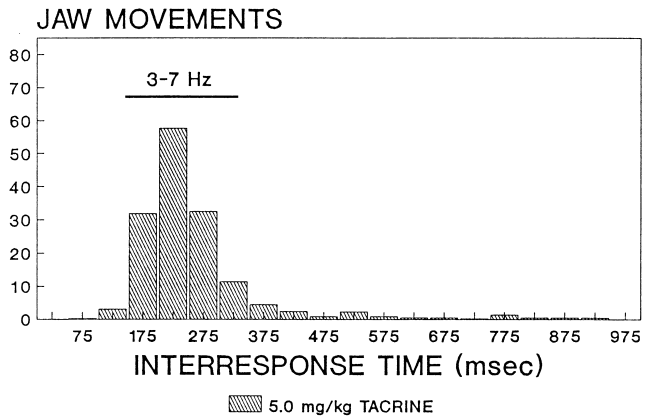

FIG. 5. This figure is a frequency distribution histogram showing the number of jaw movement interresponse times that are distributed into twenty 50-msec time bins. The midpoint of every other interresponse time bin is labelled on the *x*-axis (i.e., 75 msec, 175 ms etc.) Data shown are the mean number of jaw movement interresponse times in each time bin for rats treated with 5.0 mg/kg tacrine (n = 5). The interresponse times corresponding to the parkinsonian tremor frequency range (3–7 Hz) are shown.

less potent than physostigmine for producing jaw movements. This difference between these two drugs is consistent with their relative potencies for inhibition of acetylcholinesterase (40).

Considerable evidence indicates that cholinomimetic-induced vacuous jaw movements are dependent upon stimulation of central muscarinic receptors. Vacuous jaw movements are induced by a variety of muscarinic agonists (28). Peripheral or central nicotinic stimulation does not induce vacuous jaw movements (24,34). Previous research with physostigmine has indicated that physostigmine-induced vacuous jaw movements are blocked by the muscarinic antagonists scopolamine and atropine (23). In the present study, it was shown that tacrine-induced vacuous jaw movements were completely blocked by the muscarinic antagonist scopolamine. Yet the quaternary analogue of scopolamine, *N*-methylscopolamine, failed to reduce vacuous jaw movements when administered at a relatively high dose (1.0 mg/kg). Because methylscopolamine does not penetrate the blood-brain barrier well, these results are consistent with the notion that the blockade of tacrine-induced jaw movements by scopolamine is related to antagonism of central muscarinic receptors. Consistent with the notion that tacrine-induced vacuous jaw movements are produced by muscarinic stimulation in the brain, it also was shown that local injections of low doses of scopolamine directly into the ventrolateral striatum completely blocked the jaw movements induced by systemic tacrine. These data are consistent with previous work indicating that the ventrolateral striatum is a critical brain site for the induction of vacuous jaw movements by cholinomimetics (17,29) and striatal dopamine depletion (16). Kelley et al. (17) injected physostigmine into ventromedial, dorsolateral and ventrolateral striatum, and reported that the ventrolateral striatum was the most effective site for induction of jaw movements. In previous work from our laboratory, it was observed that ventrolateral striatal injections of pilocarpine substantially increased vacuous jaw movements, whereas ventromedial injections were ineffective (29). Also, it was demonstrated that the ventrolateral striatum was the only striatal site at which neurotoxic depletions of dopamine induced vacuous jaw movements (16). Future research will be necessary to determine which muscarinic receptor is involved in the production of vacuous jaw movements, although anatomical evidence does indicate that the preponderance of postsynaptic receptors in the striatum are of the m4 subtype (38).

It is appropriate to consider if the vacuous jaw movements induced by tacrine represent a form of cholinomimetic-induced tremulous activity. According to Findley and Gresty (10), tremor is defined as "a periodic oscillation of a body member." Several cholinomimetic drugs are known to be tremorogenic agents, and the anticholinesterase physostigmine has been shown to enhance parkinsonian tremor (8). Analyses of the temporal characteristics of vacuous jaw movements in the present study demonstrated that these movements occur mostly in the 3–7 Hz frequency range. Although there are a number of tremulous phenomena that are related to parkinsonism, the most common is a resting tremor that occurs in the 3–7 Hz range (1,11). The peak frequency of jaw movements produced by 5.0 mg/kg tacrine was 4–5 Hz (i.e., 200–250 ms interresponse time). Using a different type of behavioral and computer method, See and Chapman (30) observed that the anticholinesterase physostigmine also increased jaw movement activity in the 4–5 Hz frequency range. Additional studies from our laboratory have shown that jaw movements induced by pilocarpine (12) or reserpine plus a low dose of apomorphine (27) also show similar frequency characteristics. These results suggest that, as well as being called "vacuous," or non-directed, the vertical jaw movements induced by cholinomimetics or dopamine depletion can appropriately be referred to as "tremulous."

Tacrine has been reported to produce parkinsonian symptoms in human patients (21). Moreover, there is a substantial

literature showing acetylcholine/dopamine interactions, as well as cholinergic involvement in idiopathic and neuroleptic-induced parkinsonism (2,3,8,18,19). Muscarinic antagonists are routinely used as antiparkinsonian drugs, especially for the treatment of neuroleptic-induced parkinsonism (18,19,36). Cholinomimetics have been shown to induce or exacerbate parkinsonian symptoms (8,13,20). Although parkinsonian tremor typically involves the hand, it also can involve the jaw (1,14,36). Parkinsonian jaw tremors have been described as an "up-and-down" movement of the lower jaw (1). Physostigmine has been shown to exacerbate a type of parkinsonian oral tremor (i.e., "rabbit syndrome") in neuroleptic-treated patients (39). These findings, taken together with the present results, suggest that cholinomimetic-induced jaw movements in rats share some characteristics with parkinsonian tremor. Possibly, studies of tacrine-induced jaw movements in rats could yield insights into the anatomy, neurochemistry, or pathophysiology of tremulous motor activity. In addition, it is possible that studies of vacuous jaw movements could assist in the development of novel treatments for idiopathic, neuroleptic- or tacrine-induced parkinsonian symptoms.

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