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Effects of H1 Antagonists on Cholinomimetic-Induced Tremulous Jaw Movements: Studies of Diphenhydramine, Doxepin, and Mepyramine

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CARLSON, B. B., J. T. TREVITT AND J. D. SALAMONE. *Effects of H1 antagonists on cholinomimetic-induced tremulous jaw movements: Studies of diphenhydramine, doxepin, and mepyramine.* PHARMACOL BIOCHEM BEHAV **65**(4) 683–689, 2000.—In several previous studies, tremulous jaw movements in rats have been used to assess the effects of antiparkinsonian drugs and atypical antipsychotics. Because antihistamines such as diphenhydramine are used as antiparkinsonian agents, and atypical antipsychotic drugs such as clozapine and olanzapine have high affinity for histamine H1 receptors, the present study investigated the effects of H1 antagonists on cholinomimetic-induced jaw movements. Diphenhydramine, doxepin, and mepyramine (all injected IP 2.5–20.0 mg/kg) were assessed for their ability to block the jaw movements induced by 5.0 mg/kg of the anticholinesterase tacrine. Within this dose range, only diphenhydramine produced a robust and significant reduction in jaw movement activity. Thus, diphenhydramine was subjected to further testing, which employed procedures previously used to assess the effects of other antitremorogenic drugs, such as clozapine. Diphenhydramine did not induce jaw movement activity. In addition to suppressing jaw movement activity after acute injections, diphenhydramine also suppressed tacrine-induced jaw movements after repeated (14-day) administration. In summary, the present results show that diphenhydramine suppresses cholinomimetic-induced jaw movements, an effect that is similar to other antiparkinsonian or antitremor drugs such as anticholinergics, L-DOPA, DA antagonists, and clozapine. Nevertheless, doxepin produced only mild effects, and mepyramine, which has a higher affinity and selectivity than diphenhydramine for H1 receptors, failed to suppress cholinomimetic-induced jaw movements. These results suggest that diphenhydramine suppresses tremulous movements through a mechanism that does not depend upon antagonism of histamine H1 receptors. © 2000 Elsevier Science Inc.

H1 antagonists Cholinomimetic-induced tremulous jaw movements Diphenhydramine Doxepin Mepyramine

TREMULOUS jaw movements in rats have been suggested as a possible model of the tremor related to parkinsonism (41,42,44,48,49). Tremulous jaw movements (also known as vacuous jaw movements or vacuous chewing) are vertical deflections of the lower jaw that resemble chewing, but are not directed at any particular stimulus (18,24,49,56). Tremulous jaw movements can be induced by reserpine (4,43,49), dopamine (DA) depletions in the ventrolateral striatum (18,24), muscarinic agonists (5,7–39,40,43,44,51,52), and anticholinesterases such as physostigmine or tacrine (8,11,25,29). Similar jaw movements are induced by acute or subchronic injections of dopamine antagonists (16,24,48,49). The jaw movements induced by cholinomimetics and DA depletions occur mostly in bursts, and the local frequency of movements within these bursts occurs with a peak between 3–7 Hz (12,18,29,41), similar to the frequency range that is reported for parkinsonian tremor (1). As discussed in detail in a recent review, tremulous jaw movements in rats meet a reasonable set of validation criteria for use as an animal model of parkinsonian tremor (44). The ability of cholinomimetic drugs to induce tremulous movements in rats is consistent with the literature showing that cholinomimetic drugs induce or exacerbate parkinsonian symptoms in humans (2,15,23,34). The anticholinesterase tacrine can produce parkinsonian side effects, including tremor, in patients with Alzheimer's disease (36). Furthermore, tacrine-induced jaw movements in rats can be reduced by antiparkinsonian or antitremor drugs that have a variety of distinct pharmacological profiles, including L-DOPA, apomorphine, bromocriptine, amantadine, benztropine, and clozapine (13,54–56).

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TABLE 1

BINDING AFFINITIES (INHIBITION CONSTANTS) FOR HISTAMINE H_1-RECEPTORS AND MUSCARINIC ACETYLCHOLINE RECEPTORS IN BOVINE CEREBRAL CORTEX [FROM (27)]

	Inhibition of ^{3}H-QNB Binding (K_{1a} nM)	Inhibition of ^{3}H-Mepyramine Binding (K_{1b} nM)	K_1 Value Ratio (K_{1a}/K_{1b})
Diphenhydramine	280 ± 50	14 ± 2	20
Doxepin	40 ± 2	0.12 ± 0.02	330
Mepyramine	30,000 ± 2000	0.24 ± 0.03	130,000

Diphenhydramine has been used for several decades as a treatment for idiopathic and neuroleptic-induced parkinsonism (7,35). Although diphenhydramine has several different pharmacological effects, it is primarily referred to as an "antihistamine" [e.g., (35)]. Receptor binding data show that diphenhydramine binds with high affinity to the histamine H1 receptor (27). Other drugs that can have antiparkinsonian or antitremor effects also show moderately high affinity for the H1 receptor. For example, the atypical antipsychotic clozapine has been shown to bind to H1 receptors in addition to DA, muscarinic, and several subtypes of serotonin receptors (45). Several recent studies have demonstrated that clozapine has antiparkinsonian effects, and is particularly effective at suppressing tremor in patients with idiopathic Parkinson's disease (3,6,9,17,19,20). Previous work has shown that clozapine can suppress tacrine-induced jaw movements in rats (54,56); however, it is not clear if this effect is dependent upon the blockade of histamine H1 receptors. Thus, the present experiments investigated the effects of the H1 antagonists diphenhydramine, doxepin, and mepyramine on tacrine-induced jaw movements in rats.

In the first three experiments, the ability of diphenhydramine, doxepin, and mepyramine (i.e., pyrilamine) to suppress the jaw movements induced by 5.0 mg/kg tacrine were assessed. Diphenhydramine was selected because this drug is known to act as an antiparkinsonian agent (7,35). Doxepin and mepyramine were studied because these drugs have a higher affinity for the H1 receptor than diphenhydramine (27,53), and also because these drugs have a higher selectivity than diphenhydramine for the H1 receptor relative to other receptors [(27); see Table 1). Although diphenhydramine is known for its antimuscarinic properties as well as its antihistamine effects, doxepin has moderate muscarinic affinity compared to its affinity for the H1 receptor, while mepyramine has little or no affinity for muscarinic receptors (27). Doxepin and mepyramine both readily penetrate into the brain, and mepyramine often is used as an H1 ligand for receptor binding or imaging studies (14,27,33,57,58). A previous study indicated that a single low dose of mepyramine (5.0 mg/kg) did not suppress pilocarpine-induced jaw movements (51), but the present experiment was intended to provide a more extensive dose–response analysis. Based upon the results of the first group of experiments, diphenhydramine was subjected to additional assessment using the jaw movement model. Rats were administered diphenhydramine for 14 consecutive days, were observed for possible induction of jaw movements on day 13, and then were challenged with an injection of tacrine on day 14. This procedure has been used in several previous studies to assess the effects of repeated admininstration of clozapine and olanzapine on tacrine-induced tremulous jaw movements (10,54,55).

METHOD

Subjects

Male Sprague–Dawley rats (Harlan–Sprague–Dawley, Indianapolis, IN) were used in these experiments (total $n = 59$). The rats were 310–450 g during the course of the experiment, and had ad lib access to lab chow and water. All animals were group housed in a colony that was maintained at approximately 23°C, and had a 12 L:12:D cycle (lights on at 0700 h). The animal research protocols used were approved by the Institutional Animal Care and Use Committee.

Drugs

Tacrine was obtained from Sigma Chemical Co. (St. Louis, MO). Diphenhydramine was obtained from Research Biochemicals International (RBI; Natick, MA). Both drugs were dissolved in 0.9% saline, which also served as the vehicle control. Drug doses were based upon previous published reports and extensive pilot work (41,56). All experiments used the following doses: saline vehicle, 2.5, 5.0, 10.0, and 20.0 mg/kg. The dose of tacrine in all tremulous jaw movement studies was 5.0 mg/kg. All drugs were administered by IP injection.

Experimental Procedures—Tremulous Jaw Movements

Observations of animals took place in a 27 × 17.5 × 17-cm clear Plexiglas chamber with a wire mesh floor. To allow viewing of the animal from several angles, the chamber was elevated 42 cm above the table top. Tremulous jaw movements were defined as rapid vertical deflections of the lower jaw that resemble chewing, but are not directed at any particular stimulus. Each individual deflection of the jaw was recorded using a mechanical hand counter. The observer was unaware of the experimental treatment of the animal being observed. Separate studies using these methods with two observers demonstrated an interrater reliability of $r = 0.92$ ($p < 0.05$).

Experiments 1, 2, and 3: Effects of Acute Diphenhydramine, Doxepin, and Mepyramine on Tacrine-induced Jaw Movements

Separate groups of rats were used to assess the effects of acute diphenhydramine ($n = 10$), doxepin ($n = 7$), and mepyramine ($n = 7$) treatment on tacrine-induced jaw movements. On test days, each animal received an IP injection of 5.0 mg/kg tacrine (10 min before testing) to induce tremulous jaw movements, as well as one of the following doses of diphenhydramine, doxepin, or mepyramine: vehicle, 2.5, 5.0, 10.0, and 20.0 mg/kg IP (immediately after tacrine injection). Within each separate drug study, a repeated measures design was used [see also (10,13,55,56)]. Animals in each study re-

ceived all drug treatments in a randomly varied order, across the 5-week period, with one injection per week. Rats were placed in the observation chamber immediately after tacrine injection to allow for habituation to the observation chamber. Animals were observed for tremulous jaw movements for a 5-min period after a 10 min habituation.

Experiments 4 and 5: Effects of Repeated Diphenhydramine on Tremulous Jaw Movement Activity

Separate groups of rats ($n = 7$ per dose) were used to assess the effects of repeated diphenhydramine treatment on the production and suppression of tremulous jaw movements. Each animal received one of the following doses of diphenhydramine daily for 14 consecutive days: vehicle, 2.5, 5.0, 10.0, and 20.0 mg/kg IP. Animals received the same dose across all 14 days. Animals were tested on days 13 and 14. On day 13, after the IP injection of diphenhydramine, animals were immediately placed in a Plexiglas observation chamber and allowed to habituate for 10 min. Animals were then observed for tremulous jaw movements for a 5-min period after the 10-min habituation. The testing protocol for day 14 followed the same pattern as that for day 13, with the exception that in addition to the diphenhydramine injection, rats were given an injection of tacrine (5.0 mg/kg) prior to being placed in the observation chamber. The day 13 test assessed the effects of repeated diphenhydramine administration on the induction of vacuous jaw movements. The day 14 test assessed the effects of repeated diphenhydramine administration on tacrine-induced jaw movements.

Data Analysis

For Experiments 1–3, jaw movement data were analyzed using a repeated-measures analysis of variance (ANOVA), with dose as the repeated measure. Day 13 data (diphenhydramine alone, Experiment 4) were analyzed using a between-subjects analysis of variance (ANOVA), with dose as the independent variable, and number of tremulous jaw movements as the dependent variable. If there was an overall significant ANOVA, planned comparisons using the overall error term were used to assess the differences between each drug condition and the control condition, keeping the total number of comparisons to the number of conditions minus one (26). Day 14 data (tacrine challenge day, Experiment 5) were analyzed in a similar fashion. ED_{50}s were calculated using a commercially available program (GraphPad Prism).

RESULTS

Experiments 1–3: Effects of Acute Diphenhydramine, Doxepin, and Mepyramine on Tacrine-induced Jaw Movements

Figure 1 shows dose–response curves for the effect of diphenhydramine, doxepin, and mepyramine on tacrine-induced jaw movements. Diphenhydramine produced a significant reduction of tacrine-induced tremulous jaw movements, $F(4, 36) = 13.4$, $p < 0.001$ (see Fig. 1), with an ED_{50} of 7.73 mg/kg. Planned comparisons revealed that 10.0 and 20.0 mg/kg diphenhydramine significantly reduced tacrine-induced jaw movements. Doxepin failed to produce a significant suppression of jaw movement activity, $F(4, 24) = 2.6$, NS (see Fig. 1), although there was a tendency for this drug to suppress jaw movements in some animals at the highest dose. In view of the tendency to show some suppression of jaw movements at the highest dose, orthogonal analysis of trend was conducted to test for a significant linear effect of dose. With this analysis, there was a significant linear trend, $F(1, 6) = 9.3$, $p < 0.05$, with doxepin. Mepyramine failed to reduce tacrine-induced jaw movements at any dose up to 20.0 mg/kg, $F(4, 24) = 0.81$, NS. In all three studies, correlational analyses indicated that the jaw movement responses induced by tacrine (i.e., tacrine plus vehicle) did not systematically vary over the 5-week test period, suggesting that tacrine-induced jaw movements did not show tolerance or sensitization under the conditions employed in the present investigation. Animals treated with tacrine plus diphenhydramine, doxepin, or mepyramine did not show signs of ataxia, incoordination, or seizures, although some of the animals showed signs of mild sedation (i.e., head down, eyes partly closed).

Experiments 4 and 5: Effects of Repeated Diphenhydramine on Tremulous Jaw Movement Activity

With repeated administration, diphenhydramine failed to induce tremulous jaw movements on day 13, $F(1, 33) = 2.66$,

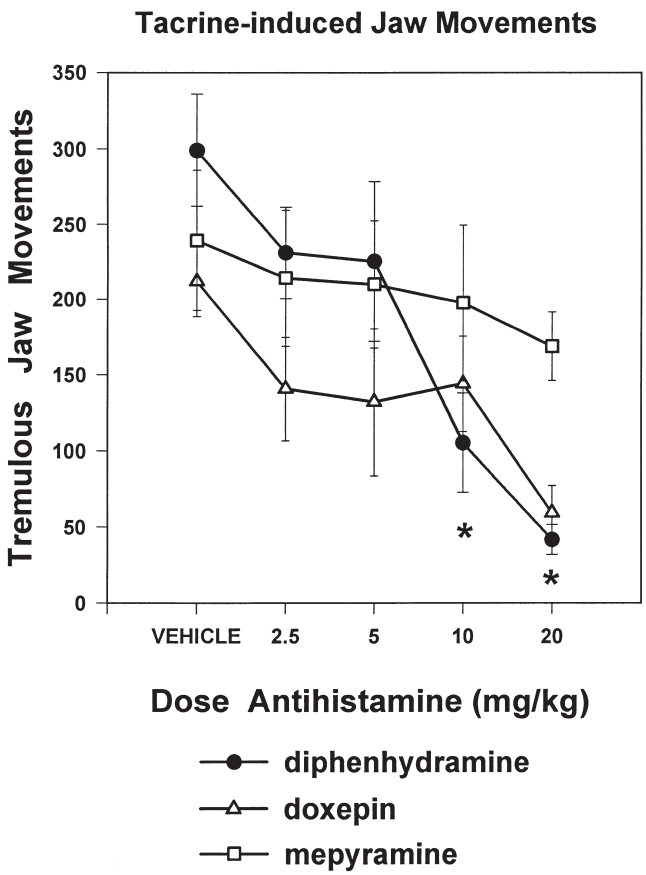

FIG. 1. Effects of various antihistamines on tacrine-induced jaw movements. Mean (±SEM) number of tremulous jaw movements (per 5 min) after administration of 5.0 mg/kg tacrine plus different doses of diphenhydramine (dashed line), doxepin, and mepyramine are shown. All rats received tacrine, and the control condition on the graph (VEHICLE) represents tacrine plus vehicle. *$p < 0.05$, diphenhydramine different from tacrine plus vehicle, planned comparison.

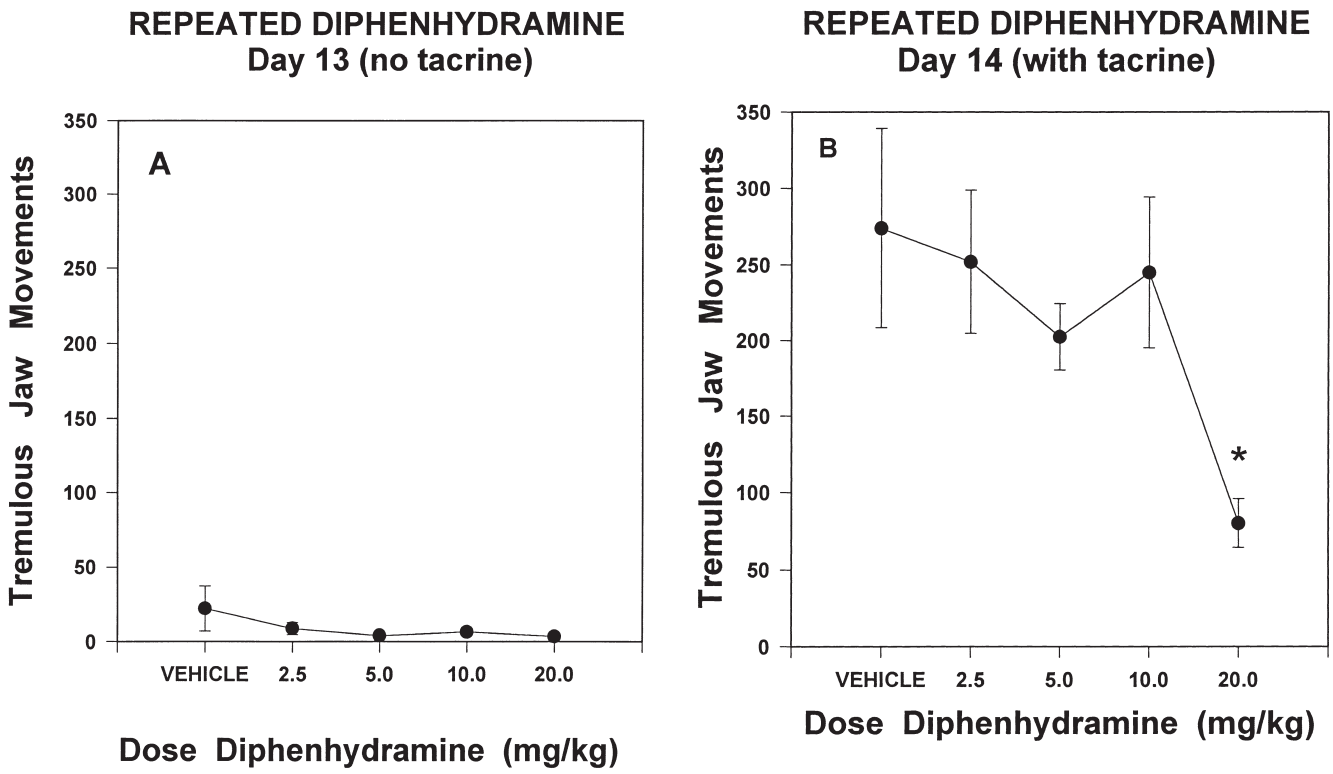

FIG. 2. (A) Mean (±SEM) number of jaw movements per 5 min during the day 13 observation, after injection of vehicle or various doses of diphenhydramine. (B) Mean (±SEM) number of jaw movements per 5 min during the day 14 observation, after injection of vehicle or various doses of diphenhydramine; all rats also received a challenge dose of 5.0 mg/kg tacrine to induce jaw movements. *$p < 0.05$, different from tacrine plus vehicle, planned comparison.

NS; see Fig. 2a). On day 14, diphenhydramine significantly suppressed tacrine-induced jaw movements, $F(1, 33) = 7.674$, $p < 0.01$; see Fig. 2b), with an ED_{50} of 16.9 mg/kg. Planned comparisons revealed that the 20.0 mg/kg dose of diphenhydramine significantly reduced tacrine-induced jaw movements.

DISCUSSION

In Experiment 1, diphenhydramine significantly reduced tacrine-induced tremulous jaw movements, with an estimated ED_{50} value of approximately 7.73 mg/kg. Repeated injections of diphenhydramine did not induce jaw movements after 13 days of administration. As shown in Experiment 5, repeated 14-day administration of diphenhydramine also resulted in a suppression of tacrine-induced jaw movements, with an ED_{50} of approximately 16.9 mg/kg. The higher ED_{50} value observed after 14 days of diphenhydramine treatment suggests that there may be tolerance to the suppressive effect of diphenhydramine on tacrine-induced jaw movements, which is consistent with previous reports of tolerance to some of the effects of diphenhydramine (46). Nevertheless, despite the tolerance that may develop with repeated injections, the present results indicate that diphenhydramine can suppress tacrine-induced jaw movements under both acute and repeated drug treatment conditions. As noted above, it has been suggested that suppression of cholinomimetic-induced tremulous jaw movements can be used as a model for assessing antiparkinsonian drugs. In this context, the present results are consistent with human clinical data showing that diphenhydramine has antiparkinsonian effects (7,35). Previous work has shown that several other antiparkinsonian drugs, including L-DOPA, bromocriptine, apomorphine, amantadine, and benztropine, all suppress tacrine-induced jaw movements (13). In rats, diphenhydramine was less potent than apomorphine, but more potent than amantadine or L-DOPA, for suppression of tacrine-induced jaw movements (13); these results are generally consistent with the clinically effective doses reported in the literature. The atypical antipsychotic clozapine, which is known to have antitremorogenic properties, also has been shown to suppress cholinomimetic-induced jaw movement after both acute and repeated injections (10,54,56). Thus, the present results, together with previous studies, indicate that a variety of antiparkinsonian or antitremor drugs with distinct pharmacological characteristics all act to suppress tacrine-induced jaw movements.

Although diphenhydramine reliably suppresses tacrine-induced jaw movements, the neurochemical basis of this effect is unclear. Diphenhydramine is typically labeled as an "antihistamine"; however, this drug has a variety of other neurochemical actions. Binding studies indicate that diphenhydramine also binds to muscarinic receptors, and displays only a modest selectivity for H1 receptors compared to muscarinic receptors (i.e., about 20-fold, Table 1) (27). The results of Experiments 2 and 3 suggest that H1 antagonism is not the critical action of diphenhydramine that results in a suppression of jaw movement activity. Doxepin has a much higher affinity for H1 receptors than diphenhydramine, and although doxepin does

bind to muscarinic receptors, doxepin is more selective than diphenhydramine for the H1 receptor relative to muscarinic receptors (i.e., about 330-fold selectivity, Table 1) (27). In Experiment 2, there was a tendency for doxepin to suppress jaw movements at the highest dose in some animals, and a significant dose-related trend was observed. Nevertheless, despite the potent antihistamine effects of doxepin, this drug did not produce a significant overall suppression of tacrine-induced jaw movements in the dose range tested. The third drug tested was mepyramine, which has an extremely high affinity for H1 receptors, and is one of the most selective compounds known in terms of binding to the H1 receptor relative to muscarinic receptors (i.e., 130,000-fold selectivity, Table 1) (27). As demonstrated in Experiment 3, mepyramine failed to suppress tacrine-induced jaw movements, even in doses up to 20.0 mg/kg. Mepyramine does have central nervous system effects at or below the doses tested in the present study. For example, doses of mepyramine as low as 1.0–5.0 mg/kg were shown to enhance the seizure-inducing effects of amygdala kindling in rats (58), and a dose of 3.0 mg/kg in rats produced analgesia (21). Thus, considering the overall pattern of effects shown in Experiments 1–3, it appears as though H1 antagonism per se does not result in a suppression of tacrine-induced jaw movements. Rather, diphenhydramine appears to suppress tacrine-induced jaw movements through actions other than histamine H1 antagonism. Considering that tacrine-induced jaw movements have been proposed as a model for human parkinsonian tremor, the present results also suggest that the antiparkinsonian effects of diphenhydramine in humans are not directly due to the antihistaminergic effects of this drug.

It is likely that the muscarinic antagonist properties of diphenhydramine are critical for the action of this drug in suppressing tacrine-induced jaw movements, and this effect may also be important for the human antiparkinsonian effects of this drug. Cholinomimetic-induced jaw movements are dependent upon stimulation of central muscarinic receptors (29,43). Several different muscarinic antagonists have been shown to suppress cholinomimetic-induced jaw movements, including nonselective compounds such as scopolamine, atropine, benztropine (13,29,43), and relatively selective antagonists such as methoctramine and AFDX-116 (30,50). Research with selective muscarinic antagonists has shown that suppression of cholinomimetic-induced jaw movements appears to be related to blockade of M2 or M4 receptor subtypes (30,50). A combination of anatomical and pharmacological evidence suggests that postsynaptic muscarinic M4 receptors in ventrolateral neostriatum mediate the jaw movement suppression produced by muscarinic antagonists (30). Receptor binding studies involving nonselective muscarinic ligands have shown that diphenhydramine binds with relatively high affinity to muscarinic receptors (27), although there is little information on any subtype-specific binding. Taking all this information into account, it is reasonable to suggest that diphenhydramine suppresses tacrine-induced jaw movements because of muscarinic antagonist effects. In view of the fact that several muscarinic antagonists are known to be antiparkinsonian in human patients (7,31,35), the anticholinergic properties of diphenhydramine may also explain the human antiparkinsonian effects of this drug. Future binding studies should examine the subtype-specific binding characteristics of diphenhydramine to determine if the antiparkinsonian effects of this drug are related to blockade of a specific subtype of muscarinic receptor.

Atypical antipsychotic drugs such as clozapine and olanzapine also suppress tacrine-induced jaw movements, and the present results shed light on the possible mechanism of action for the motor effects of these drugs. In procedures that are very similar to the ones employed in the present work, both acute and repeated daily injections of clozapine and olanzapine suppressed tacrine-induced jaw movements (10,54–56). Clozapine and olanzapine have a broad range of neurochemical effects, including actions on histamine$_1$, muscarinic, alpha$_1$ and alpha$_2$, and 5-HT$_{1A}$, 5-HT$_{2A}$, 5-HT$_{2C}$, 5-HT$_6$ and 5-HT$_7$ receptors (28,32,45,47). Because of the broad receptor binding profiles of clozapine and olanzapine, the specific mechanism underlying the suppressive effects of these drugs on tacrine-induced jaw movements in rats has remained somewhat uncertain. There is independent evidence to suggest that blockade of muscarinic or 5-HT$_{2A/2C}$ receptors could lead to the suppression of tacrine-induced jaw movements (51,56); nevertheless, the role of H1 antagonism in the effects of clozapine and olanzapine could not be discounted. The inability of the highly selective H1 antagonist mepyramine to suppress tacrine-induced jaw movements in the present study suggests that clozapine and olanzapine do not suppress tacrine-induced jaw movements due to H1 antagonism. This observation places additional emphasis on the importance of muscarinic and serotonergic effects of atypical antipsychotics for understanding the unique motor properties of these drugs.

In summary, the mixed antihistamine/anticholinergic drug diphenhydramine suppressed tacrine-induced tremulous jaw movements after either acute or repeated daily injections. In view of the proposed relation between tremulous jaw movements in rats and parkinsonian tremor in humans, the present results are consistent with the known antiparkinsonian characteristics of diphenhydramine. Doxepin, which is somewhat more selective than diphenhydramine for H1 receptors relative to muscarinic receptors, failed to produce a significant suppression of tacrine-induced jaw movements, although there was a trend toward suppression at the higher dose. It is possible that the muscarinic and serotonergic antagonist properties of doxepin (14,22,27) contributed to this tendency to suppress jaw movements. Finally, the highly selective H1 antagonist mepyramine, which has little or no affinity for muscarinic receptors, had no suppressive effects on tacrine-induced jaw movements. These results suggest that diphenhydramine does not suppress tacrine-induced jaw movements due to blockade of H1 receptors, but instead due to other neurochemical actions, such as muscarinic antagonism.

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