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Cholinergic Modulation of Oral Activity in Drug-Naive and Chronic Haloperidol-Treated Rats

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SEE, R. E. AND M. A. CHAPMAN. *Cholinergic modulation of oral activity in drug-naive and chronic haloperidol-treated rats.* PHARMACOL BIOCHEM BEHAV **39**(1) 49–54, 1991.—The cholinergic agonists pilocarpine, physostigmine, oxotremorine, and arecoline were administered IP at various doses to rats. Oral activity was assessed in these animals with a computerized video analysis system that determined the number and form of jaw openings and closings (computer scored movelets "CSMs"). The different cholinergic drugs produced distinctive changes in the number of CSMs at various amplitudes and in the frequency distribution of CSMs as determined by fast fourier analysis. Rats treated for 28 weeks with haloperidol showed a previously described, late onset oral dyskinesia characterized by increases in small amplitude CSMs, decreases in CSM slope, increased energy at the 1–3 Hz range and decreased energy at the 5–7 Hz range. Administration of pilocarpine (1.0 mg/kg) reversed all of these effects, while the anticholinergic drug, scopolamine (0.05 mg/kg), had no effect. These results indicate that different cholinomimetics can uniquely alter oral activity in rats and that symptoms of late onset, neuroleptic-induced oral dyskinesia are modified by a cholinergic agonist.

Animal model Oral movements Cholinergic drugs Tardive dyskinesia Dystonia Haloperidol

CENTRAL cholinergic function has been extensively studied in relation to extrapyramidal control of motor activity. It has long been established that dopamine and acetylcholine closely interact in the basal ganglia and that various neuroleptic-induced movement disorders, including acute dystonia and tardive dyskinesia may be due in part to alterations in the balance between these two neurotransmitters (6, 10, 17).

Several previous studies have focused on orofacial movements in rodents as an indication of central cholinergic function. "Purposeless" (nondirected) chewing has been induced in rodents by a variety of cholinergic drugs such as the muscarinic receptor agonist pilocarpine (18,21) and the cholinesterase inhibitor, physostigmine (14,15). These movements can be reversed by administration of a cholinergic antagonist such as scopolamine (16, 18, 22). Cholinomimetics have also been shown to induce other forms of oral activity such as yawning, tongue protrusion, and jaw tremor (18, 22, 24). Cholinergic agonists and antagonists have also been tested in several animal models of neuroleptic-induced oral movements. Rupniak et al. (15,16) have reported that the cholinergic agonists pilocarpine and physostigmine increase chewing jaw movements in neuroleptic-treated rats. Since these movements are increased by cholinergic agonists and decreased by scopolamine, it has been presented as a possible rodent model of neuroleptic-induced acute dystonia (17). However, some reports indicate that late-onset chewing movements in rats respond to cholinergic drugs in a manner more consistent with the pharmacological profile of tardive dyskinesia (23, 25, 26).

In several previous studies utilizing a computerized video analysis system, it has been shown that unique patterns of oral activity can be objectively measured in rats given a variety of drugs, including dopamine agonists and antagonists (5,7). Using this approach, it has been found that continuous, long-term administration of neuroleptics leads to a pattern of oral movement changes that is analogous in several respects to late onset oral dyskinesias seen in humans treated with neuroleptics (2, 3, 19, 20). The present study was designed with the specific goal of comparing the oral movements seen after administration of several cholinergic agonists reported to increase purposeless chewing and to test the effects of a cholinergic agonist and a cholinergic antagonist on oral activity in rats administered chronic haloperidol.

METHOD

This study consisted of two experiments. Experiment 1 examined the acute effects on oral movements of several cholinergic agonists at different doses. Experiment 2 examined the effects of a single dose of pilocarpine and a single dose of sco-

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polamine in chronic haloperidol-treated rats. Subjects in both experiments were female, Sprague-Dawley rats maintained on a 12-h light/dark cycle with continuous access to food and water. All behavioral testing took place during the dark phase of the cycle. In Experiment 1, rats (weight 205–320 g) were group housed (3–4 per cage) while in Experiment 2, rats (weight 264–348 g) were singly housed. Drug doses were based on previous studies (15, 18, 22) and initial pilot data.

Computerized Assessment of Oral Movements

Rats were habituated to being placed in plastic tubes (5.7 cm dia., 19.0 cm length) resting inside a soundproof chamber. Before the onset of testing, all rats were habituated to the tube in four 5-min sessions over a 2-week time period. Animals showed higher baseline oral activity in the tube when compared to oral activity seen in an open testing environment (8, 19, 20), but they habituate well to the test apparatus and showed minimal struggling during the brief 5-min session. Rats were placed in the tube 1–2 min prior to the beginning of a 5-min data collection session. At the end of the tube was a 3.3 cm hole through which the rat's head protruded. Prior to being placed in the tube, small spots were painted on the upper and lower jaws of the rat using a UV sensitive dye. A video camera with a UV filter was positioned in front of the rat and connected to a computer equipped with a movement detection circuit (MM board, Biotronics Design), which monitored only the two painted spots. This circuit calculated the distance between the upper and lower spots at a rate of 60 times per second. Oral activity was thus recorded as individual openings or closings of the jaws or "computer scored movelets" (CSMs). A computer program analyzed the data for each file and classified each CSM according to amplitude as determined by the number of TV rasters covered by the CSM. The distribution of CSM amplitudes was divided into 5 categories according to the number of rasters covered: 2, 3, 4–5, 6–9, ≥10. The corresponding distances in mm were 0.6, 0.9, 1.2–1.5, 1.8–2.7, ≥3.0. The slope of each CSM (amplitude/duration) was determined as well. The data from the computerized jaw movement apparatus were also subjected to fast fourier transform (FFT) as previously described (3). This computerized system has been extensively validated in previous studies (2, 3, 19, 20).

Experiment 1: Cholinergic Agonists

A crossover, random order design was utilized such that each rat in a test group received each dose of drug as a single IP injection. Each drug administration was followed by an interval of 3–4 days. Each independent group (N = 7–9) was tested with a single drug at 3 different doses and with saline. Drugs used (dose range in mg/kg) included the cholinergic agonists pilocarpine (0.5, 1.0, 2.0), oxotremorine (0.1, 0.5, 1.0), physostigmine (0.05, 0.2, 0.5), and arecoline (4.0, 8.0, 16.0). The delay between injection and computerized assessment of oral activity for each drug was as follows: oxotremorine—20 min, pilocarpine—15 min, physostigmine—15 min, arecoline—5 min. Another group of animals (N = 8) was given the cholinergic antagonist scopolamine (0.1 mg/kg), the peripheral antagonist methyl scopolamine (0.1 mg/kg), or saline followed 15 min later by pilocarpine (2.0 mg/kg) and testing for oral activity 15 min after pilocarpine.

Experiment 2: Chronic Haloperidol Treatment

This experiment consisted of two groups, chronic haloperidol (N = 8) and their controls (N = 8). Chronic haloperidol was administered as previously described (2). Briefly, rats were anesthetized with halothane and a subcutaneous injection of lidocaine HCl (2%) at the incision site. Thin-walled silastic reservoirs (constructed from Dow-Corning silastic sheeting) containing haloperidol base (100 mg) were subcutaneously implanted through an incision made in the skin lateral to the vertebral column. Release rates of these implants is approximately 0.23 mg/day (thus giving a dose of 0.92–0.66 mg/kg/day for rats weighing 250–350 grams). After 16 weeks of continuous administration, the implants were removed and fresh reservoirs were implanted to ensure continuous drug delivery. Control animals were implanted with an empty reservoir.

Oral movements were assessed every 4 weeks using the automated scoring method. Beginning at week 28, these rats were tested with the computerized system 20 min after acute injections of saline, pilocarpine (1.0 mg/kg), or scopolamine (0.05 mg/kg). These drugs were administered in a counterbalanced order, with a three-day interval between each test. This test yielded 6 groups: control-saline (Con-Sal), control-pilocarpine (Con-Pil), control-scopolamine (Con-Sco), haloperidol-saline (Hal-Sal), haloperidol-pilocarpine (Hal-Pil), and haloperidol-scopolamine (Hal-Sco).

Drugs

The following compounds were purchased from commercial sources: physostigmine sulfate, arecoline hydrobromide (Research Biochemicals Inc.); scopolamine hydrobromide, methyl scopolamine bromide, pilocarpine HCl (Sigma Chemical). Oxotremorine was generously donated by Dr. Bjorn Ringdahl. Haloperidol was generously donated by McNeil Pharmaceutical.

Data Analysis

The Kruskal-Wallis one-way analysis of variance was used for measures of CSM amplitudes and CSM slopes. If the H value was associated with $p<0.05$, specific comparisons were made with the Mann-Whitney U-test for individual comparisons. Significant differences were defined at $p<0.05$, $p<0.01$, $p<0.005$, and $p<0.001$. For fast fourier analysis, the absolute energy at a particular frequency was converted to the percent of total energy across all frequency bands. Repeated measures analyses of variance were used for statistical analysis of FFT data. If the value of F was significant at $p<0.05$, specific post hoc comparisons were made with the Newman-Keuls test for individual comparisons. Significant differences were defined at $p<0.05$ and $p<0.01$.

RESULTS

Experiment 1: Cholinergic Agonists

All of the cholinergic agonists produced peripheral signs of cholinergic stimulation, particularly at the highest dose of each drug. These effects included piloerection, defecation, tremor, excessive salivation, lachrymation and urination. Figure 1 shows CSMs/min for amplitude category 6–9 following various doses of the cholinergic agonists. We have previously found this category of CSMs to correspond best with human observer rated vacuous chewing movements (20). Administration of pilocarpine dose-dependently increased CSMs in this amplitude range (Kruskal-Wallis test for overall group differences, $H = 13.30$, $p<0.005$). These increases were significant for doses of 0.5 ($p<0.05$), 1.0 ($p<0.01$), and 2.0 ($p<0.005$). Pilocarpine also significantly increased CSMs of amplitude 4–5 ($H = 11.68$, $p<0.01$) at doses

TABLE 1

SHIFTS IN PERCENTAGE OF TOTAL ENERGY AT VARIOUS FREQUENCIES FOLLOWING CHOLINERGIC AGONIST ADMINISTRATION

Drug	Hz	Dose 0	Low	Medium	High
Pilocarpine	5	7.0 ± 0.8	7.6 ± 0.6	7.8 ± 0.5	8.4 ± 1.4*
	6	7.7 ± 0.9	8.5 ± 1.3	9.4 ± 0.8*	9.5 ± 1.8*
Physostigmine	2	14.0 ± 1.8	12.9 ± 2.3	11.4 ± 2.8	10.3 ± 0.9*
	4	9.0 ± 0.8	8.2 ± 0.5	8.4 ± 1.2	10.6 ± 2.3*
	5	6.7 ± 0.8	6.5 ± 0.5	7.5 ± 2.2	8.3 ± 1.0*
Oxotremorine	1	17.7 ± 2.7	16.5 ± 1.6	14.5 ± 2.3*	14.6 ± 2.4*
	2	12.9 ± 1.8	11.7 ± 0.7	11.0 ± 0.7*	10.9 ± 1.5*
	3	13.0 ± 1.5	11.4 ± 1.1	10.4 ± 0.4†	12.0 ± 1.7
	8	4.3 ± 0.7	4.5 ± 0.3	5.1 ± 0.3*	4.9 ± 0.7
	9	3.8 ± 0.7	4.0 ± 0.4	4.6 ± 0.3*	4.4 ± 0.6
	10	4.1 ± 0.7	4.7 ± 0.7	5.3 ± 0.4†	5.1 ± 0.6*
	11	3.0 ± 0.6	3.5 ± 0.6	3.9 ± 0.5*	3.7 ± 0.6

Values are means ± S.D. (*$p<0.05$ and †$p<0.01$, Newman-Keuls test.)

of 1.0 ($p<0.05$) and 2.0 ($p<0.005$), but did not significantly increase CSMs at any other amplitude category. Pilocarpine also increased the average CSM slope for amplitude 4–5 ($H=7.53$, $p<0.05$) and 6–9 ($H=12.50$, $p<0.01$), indicating a faster rise time for each opening and closing of the jaws. This increase was significant at the high dose for CSM slopes of amplitude 4–5 ($p<0.05$) and 6–9 ($p<0.005$) and at the middle dose for amplitude 6–9 ($p<0.05$).

Physostigmine dose-dependently increased CSMs at amplitude 6–9 ($H=16.39$, $p<0.001$) with significant increases at doses of 0.2 ($p<0.05$) and 0.5 ($p<0.005$) (Fig 1). In contrast to pilocarpine, physostigmine also increased CSMs at all other amplitude categories. This was particularly true at the high dose of 0.5, at which CSMs were significantly increased at all amplitude categories (specific comparisons at amplitude categories 2, 3, 4–5, and 6–9; $p<0.005$) except amplitude≥10 (n.s.). At the high dose of physostigmine, CSM slope was also significantly increased at amplitude categories 2, 4–5, 6–9 and≥10 ($p<0.05$ to $p<0.005$).

Oxotremorine significantly increased CSMs only of amplitude 2 ($H=13.49$, $p<0.005$)) at a dose of 0.5 ($p<0.05$) and 1.0 ($p<0.05$). Arecoline showed no increase in number of CSMs or slope at any amplitude category measured. At the high dose of arecoline (16.0 mg/kg), animals showed a tendency towards gaping with their jaws remaining in a wide-open position.

Fast fourier analysis results for significant effects of cholinergic agonist treatment are summarized in Table 1 (for significant post hoc comparisons refer to Table 1). Pilocarpine dose-dependently shifted the percentage of energy with significant increases at frequencies of 5 Hz, $F(3,31)=3.41$, $p<0.05$ and 6 Hz, $F(3,31)=3.62$, $p<0.05$. Physostigmine significantly decreased the percentage of energy at a frequency of 2 Hz, $F(3,27)=4.35$, $p<0.05$, while significantly increasing the percentage at frequencies of 4 Hz, $F(3,27)=4.31$, $p<0.05$ and 5 Hz, $F(3,27)=2.96$, $p<0.05$. Oxotremorine also significantly decreased the percentage in the lower frequency range [1 Hz, $F(3,27)=3.24$, $p<0.05$; 2 Hz, $F(3,27)=3.97$, $p<0.05$; 3 Hz, $F(3,27)=5.13$, $p<0.01$] and increased the percentage at fre-

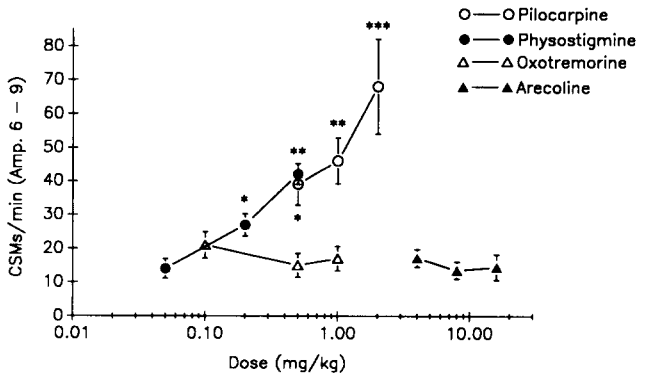

FIG. 1. Frequency (mean ± SEM) of CSMs/min of amplitude 6–9 following acute cholinergic agonists (N = 7–8 per group). Mean number of CSMs in the combined control conditions (N = 30) was 19.6 ± 2.4. (Significantly different from control: *$p<0.05$, **$p<0.01$, ***$p<0.005$, Mann-Whitney U-test.)

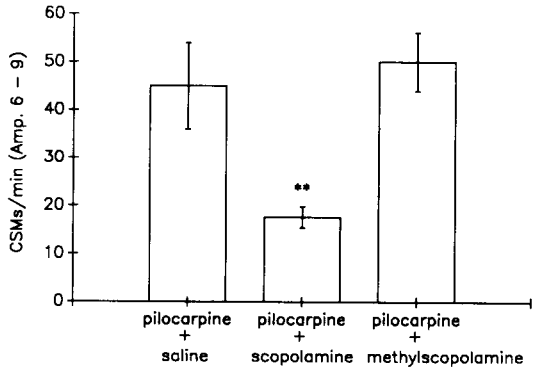

FIG. 2. Effects of IP injections of saline, scopolamine (0.1 mg/kg), or methylscopolamine (0.1 mg/kg) 15 minutes prior to injection with pilocarpine (2.0 mg/kg) on CSMs/min (mean ± SEM) of amplitude 6–9. Testing for oral activity was conducted 15 min after pilocarpine injection. (**$p<0.01$ compared to pilocarpine + saline, Mann-Whitney U-test.)

quencies of 8 to 11 Hz [8 Hz, $F(3,27)=2.91$, $p<0.05$; 9 Hz, $F(3,27)=3.87$, $p<0.05$; 10 Hz, $F(3,27)=5.09$, $p<0.01$; 11 Hz, $F(3,27)=3.08$, $p<0.05$]. Interestingly, these effects were most significant at the medium dose of 0.5 mg/kg.

Figure 2 shows that concurrent administration of scopolamine (0.1 mg/kg) significantly blocked the pilocarpine-induced (2.0 mg/kg) increase in CSMs at amplitude 6–9 [$F(2,26)=7.34$, $p<0.005$; specific comparison for pilocarpine + saline and pilocarpine + scopolamine, $p<0.01$]. In contrast, administration of the peripheral anticholinergic, methylscopolamine (0.1 mg/kg), did not significantly alter the number of CSMs induced by pilocarpine. Both antagonists blocked the peripheral effects of pilocarpine (defecation, piloerection, salivation).

Experiment 2: Chronic Haloperidol Administration

Animals administered chronic haloperidol were not significantly different from control animals on oral movement measurements during the first 16 weeks of the study. As previously reported (2), the total number of CSMs in the haloperidol-treated group were slightly decreased, but this was not significant at any time. However, fast fourier analysis showed that by week 20 there was a change in the energy distribution such that the haloperidol treated-group was significantly decreased at frequencies of 5 Hz, $F(1,14)=17.75$, $p<0.005$, 6 Hz, $F(1,14)=12.06$, $p<0.005$ and 7 Hz, $F(1,14)=4.64$, $p<0.05$ and increased (n.s.) in the 1–3 Hz range. By week 24, a significant increase at 1 Hz was found, $F(1,14)=4.85$, $p<0.05$. This same shift in FFT distribution of CSMs has been reported in previous studies that have utilized chronic haloperidol and fluphenazine (2,19).

At 28 weeks, all animals were tested with saline, pilocarpine (1.0 mg/kg), and scopolamine (0.05 mg/kg). Comparison of Con-Sal and Hal-Sal revealed two characteristic CSM patterns previously seen in chronic haloperidol studies (2, 19, 20). Hal-Sal showed a significant increase in the number of the smallest CSM category (amplitude 2) when compared to Con-Sal ($H=8.46$, $p<0.05$; Mann-Whitney U-test, $p<0.05$) and a significant decrease in CSM slope at amplitude 6–9 ($H=17.74$, $p<0.005$; Mann-Whitney U-test, $p<0.05$). Administration of pilocarpine abolished these effects, and produced a significant increase in CSMs of amplitude 6–9 ($H=11.51$, $p<0.05$; Mann-Whitney U-test, $p<0.05$).

Figure 3 shows the effects of acute injections on the energy distribution in the chronic haloperidol animals at 28 weeks. Data are shown as percent of Con-Sal. Significant main effects were seen at the following frequencies: 2 Hz, $F(5,44)=2.68$, $p<0.05$; 3 Hz, $F(5,44)=5.32$, $p<0.001$; 5 Hz, $F(5,44)=8.01$, $p<0.001$; 6 Hz, $F(5,44)=12.64$, $p<0.0001$; 7 Hz, $F(5,44)=7.03$, $p<0.001$; 8 Hz, $F(5,44)=2.69$, $p<0.05$. The Hal-Sal group showed a similar pattern to that seen at weeks 20 and 24, with increases at 1–3 Hz and decreases at 5–7 Hz (significantly less than Con-Sal at 6 Hz, $p<0.05$). Administration of pilocarpine (Hal-Pil) produced a dramatic shift in FFT distribution, resulting in significant increases at 5 and 6 Hz ($p<0.01$) and decreases at 1–3 Hz (comparison of Hal-Sal to Hal-Pil, $p<0.05$ at 3 Hz). No significant differences were found in the Hal-Sco group when compared to either Con-Sal or Hal-Sal. Administration of pilocarpine to the control animals produced a similar pattern of increased CSMs at amplitude 6–9 ($p<0.05$) and increased percentage of energy at 6 and 7 Hz ($p<0.05$) while scopolamine had no effect.

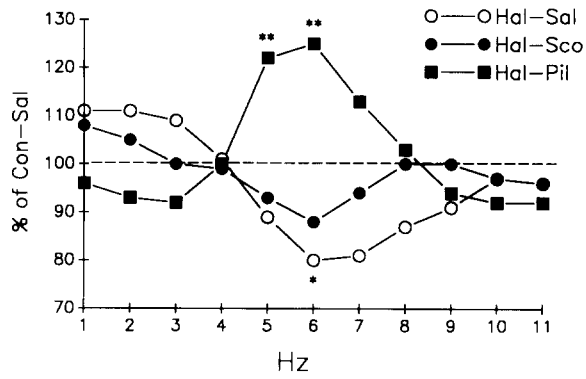

FIG. 3. Fast fourier frequency distribution for CSMs as % of control-saline (Con-Sal) in chronic haloperidol-treated rats 20 minutes after IP administration of saline, pilocarpine (1.0 mg/kg) or scopolamine (0.05 mg/kg). (*$p<0.05$ and **$p<0.01$, Newman-Keuls test.)

DISCUSSION

The results from the present study replicate prior findings that cholinergic agonists increase oral movements in rats (14–18, 21, 22). Although previous evidence suggests that different cholinergic agonists vary considerably in their ability to increase the number of observed oral movements (18,22), it has been argued that activation of central cholinergic activity by different agonists results in oral movements that are indistinguishable in form by simple observation (21). However, our results indicate that cholinergic agonists can produce uniquely different effects on the number and form of oral movements as assessed by detailed computer analysis. Pilocarpine and physostigmine were most potent at increasing the total number of CSMs, with pilocarpine preferentially increasing medium-sized CSMs and physostigmine increasing CSMs in all CSM categories. Fast fourier analysis showed that these two drugs primarily increased the percentage of CSMs in mid-range frequencies (4–6 Hz), with decreases in the lower range (1, 2 Hz). On the other hand, oxotremorine increases only the smallest CSMs (amplitude 2) and the FFT pattern revealed an increase at the 8–11 Hz range, which reflected the well-established tremorogenic nature of oxotremorine (13,22). Arecoline did not significantly change the number of CSMs in any category, although it did produce noticeable signs of increased cholinergic tone. Interestingly, the cholinergic agonist carbachol has also been reported to not significantly alter the frequency of oral movements (18).

All of the cholinergic agonists used in this study had clear effects on cholinergic activity and all are known to have central nervous system activity. The role of central cholinergic activity for the induction of oral movements has been previously demonstrated (18,21) and was further seen in the present study by the ability of scopolamine, but not methylscopolamine, in blocking pilocarpine-induced increases in CSMs. The differential effects on oral activity observed in the present study may thus be due to activation of various populations of central cholinergic receptors. Since physostigmine is a cholinesterase inhibitor, it should result in greater stimulation of all cholinergic receptors by a general enhancement of acetylcholine activity [although there is evidence for direct receptor effects by cholinesterase inhibitors (14)]. On the other hand, it has been suggested that pilocarpine-induced oral movements are mediated specifically through muscarinic M-2 receptors (22). Both oxotremorine and arecoline are nonselective muscarinic receptor agonists (14,23). Recent studies with oxotremorine and several oxotremorine analogs have suggested that differences in in vivo responses to muscarinic agonists, including oral tremor, may reflect regional differences in receptor reserve (13). Such a mechanism, in addition to activation of specific receptor subtypes, may account for the differen-

tial oral movement patterns induced by various cholinergic agonists.

Clinical use of cholinergic drugs have shown that cholinergic agonists may intensify symptoms of dystonia but ameliorate symptoms of tardive dyskinesia (6, 10, 17) [although many reports indicate a paradoxical response to cholinergic agonists and antagonists in tardive dyskinesia (9,11)]. Administration of both acute cholinergic agonists and repeated neuroleptics to rodents have been reported to produce changes in oral activity that model acute dystonia based on the similarity of oral movement responses to the clinical profile (16,17). However, a number of studies suggest a greater similarity to a tardive dyskinesia model following prolonged neuroleptics (4, 19, 20, 26). In previous studies utilizing this computerized movement analysis system (3, 19, 20), it has been found that chronic administration of continuous haloperidol increases small amplitude CSMs during drug administration and decreases the slope of CSMs, a pattern seen in the present study. Following termination of haloperidol treatment, CSMs of larger amplitude categories increase in a form of withdrawal dyskinesia. In addition, fast fourier analysis has shown that chronic neuroleptics produce a pattern of increases at 1–3 Hz and decreases at 5–7 Hz. This same pattern (increased energy at the lower frequencies) has been reported in fast fourier analysis of both orofacial dyskinesia and dyskinetic movements of the extremities in TD patients (1, 12, 27). Thus, although caution must be exercised in drawing analogies from animal data to clinical TD, the long-term effects of continuous haloperidol administration in rats appears to show some similarities to tardive dyskinesia. In contrast, chronic administration of intermittent haloperidol injections (once weekly) produces a syndrome of oral movement changes during drug treatment characterized by an increase in CSMs of amplitude 6–9 and an increase in energy at 5–7 Hz (19). This pattern, which is similar to the cholinergic-induced CSMs of the present study, appear more indicative of a dystonia-like effect rather than a tardive dyskinesia-like pattern.

The animals treated with continuous chronic haloperidol for 28 weeks in this study also exhibited changes in oral movements characterized by an increase in the 1–3 Hz range and decrease in the 5–7 Hz range. As in Experiment 1, administration of pilocarpine produced an increase in the number of CSMs of amplitude of 6–9 and a shift in the percentage of energy with decreases at 1–3 and increases at 5–7 Hz. Thus, although pilocarpine increased oral movements, it did not exacerbate the tardive dyskinesia-like pattern of the haloperidol-treated animals. This seems to indicate that the cholinergic agonist-induced changes in oral activity are indeed more dystonia-like in pharmacological profile (17). Pilocarpine may actually ameliorate the late onset dyskinesia pattern found in continuous haloperidol treated rats or simply mask this pattern by increasing the number of movements in the 5–7 Hz range. The anticholinergic scopolamine, at a dose that potently blocks pilocarpine-induced chewing (22), did not alter CSMs appreciably on any measure in either the control or haloperidol-treated rats. Anticholinergic treatment has been reported to reverse neuroleptic-induced orofacial movements that appear soon after initiation of neuroleptic administration (16). However, following treatment with prolonged neuroleptics, Waddington (26) has reported the lack of responsivity to the anticholinergic procyclidine on orofacial movements.

The findings of the present study indicate that the well-documented enhancement of oral movements in rats by cholinergic agonists can be characterized as dystonic in nature as previously suggested (17,21). But the type of oral movements induced by pilocarpine are not characteristic of the oral dyskinesia seen after prolonged continuous haloperidol and in fact alter many of the symptoms noted, including the increase in small amplitude CSMs, the decreased slope of CSMs, and the pattern of frequency distribution. Testing of oral activity in chronic neuroleptic animals with various types of cholinergic agonists is underway in order to further characterize the pharmacology of this animal model of late onset oral dyskinesia.

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