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Effects of Acute and Repeated Clozapine Injections on Cholinomimetic-Induced Vacuous Jaw Movements

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CHESLER, E. J. AND J. D. SALAMONE. *Effects of acute and repeated clozapine injections on cholinomimetic-induced vacuous jaw movements.* PHARMACOL BIOCHEM BEHAV **54**(3) 619-624, 1996.—Three studies were undertaken to investigate the effects of the atypical neuroleptic clozapine on the vacuous jaw movements induced by cholinergic stimulation in rats. In the first experiment, acute clozapine injections (4.0-16.0 mg/kg) produced a dose-related suppression of the vacuous jaw movements induced by 0.4 mg/kg physostigmine. In the second experiment, acute injections of clozapine (2.0-16.0 mg/kg) also suppressed vacuous jaw movements induced by 4.0 mg/kg pilocarpine in a dose-related manner. The third experiment was designed to compare the effects of acute and repeated administration of 16.0 mg/kg clozapine. In this experiment, there were three groups: one that received 4.0 mg/kg pilocarpine, a second group that received pilocarpine plus an acute injection of 16.0 mg/kg clozapine, and a third group that received injections of 16.0 mg/kg clozapine for 14 consecutive days, including the final day in which they also were injected with pilocarpine. For the third experiment, animals were assessed for the sedative effects of clozapine as well as vacuous jaw movements. The results indicated that either acute or repeated injections of 16.0 mg/kg clozapine reduced vacuous jaw movements relative to rats that received pilocarpine alone, and the two clozapine-treated groups did not differ from each other. The sedation ratings indicated that acute injections of 16.0 mg/kg clozapine produced substantial drowsiness and sedation, whereas rats that had received clozapine for 14 days did not show substantial sedation. These results indicate that clozapine can suppress cholinomimetic-induced vacuous jaw movements. The suppressive effects of clozapine on pilocarpine-induced vacuous jaw movements do not show tolerance within the 14-day period of repeated injections, whereas the sedative effects of clozapine do show tolerance. Thus, these results demonstrate that the suppression of pilocarpine-induced vacuous jaw movements by clozapine is not merely an artifact of clozapine-induced sedation. Because pilocarpine-induced vacuous jaw movements share some characteristics with human parkinsonian symptoms, the present results are consistent with previous reports indicating that repeated injections of clozapine produce anti-parkinsonian effects.

Vacuous chewing Purposeless chewing Acetylcholine Dopamine Serotonin Tremor
Parkinson's disease Atypical neuroleptic

A NUMBER of different pharmacological and neurochemical conditions can lead to the production of vacuous jaw movements in rats (4,5,18,22,40,43,44). These movements (also known as vacuous or purposeless chewing), are characterized by rapid vertical deflections of the lower jaw that resemble chewing but are not directed at any stimulus. Injections of dopamine (DA) antagonists such as haloperidol and sulpiride have been shown to induce vacuous jaw movements (33-35,43,44). Striatal DA depletions exacerbated haloperidol-induced vacuous jaw movements (13), and DA depletions localized to the ventrolateral striatum were shown to induce vacuous jaw movements (18). As well as being related to DA depletions and DA antagonism, substantial evidence indicates that vacuous jaw movements are produced by muscarinic cholinergic stimulation. Thus, vacuous jaw movements have been shown to be induced by a variety of muscarinic agonists (33,39), as well as the anticholinesterase physostigmine (33). Direct injections of physostigmine or pilocarpine into the ventrolateral striatum also produce vacuous jaw movements (20,40). Although the potential clinical significance of vacu-

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ous jaw movements remains unclear (51), it has been suggested that drug-induced perioral movements in rats may be useful as animal models of extrapyramidal movement disorders (10,12, 18,30,35,40,43,48). Several studies have indicated that vacuous jaw movements involve an interaction between acetylcholine and DA that is similar to the interaction shown in Parkinsonism (1,4,9,18,31,33,37,40,43,44). Vacuous jaw movements induced by pharmacological depletion of DA tend to occur in bursts, with a local frequency in the same range as Parkinsonian tremor [i.e., 3–7 Hz; see (17,37)].

Although several different conditions have been shown to induce vacuous jaw movements, evidence indicates that administration of the atypical neuroleptic clozapine fails to induce vacuous jaw movements (14,19). In fact, one study has shown that clozapine actually decreases pilocarpine-induced vacuous jaw movements (45). The behavioral pharmacology of clozapine has become an important area of research, because this drug has a unique biochemical, behavioral and clinical profile in comparison with other antipsychotic drugs (27,29,36,41). Clozapine is much less likely than other antipsychotic drugs to induce motor side effects such as tardive dyskinesia or parkinsonism (29,36). Some evidence indicates that clozapine treatment can reduce symptoms of tardive dyskinesia (36) and Meige syndrome (50). Recent studies also have indicated that clozapine has antiparkinsonian effects in patients with idiopathic Parkinson's disease (3,6,32). Therefore, the present series of experiments was undertaken to investigate the effects of clozapine on cholinomimetic-induced vacuous jaw movements. In the first experiment, acute clozapine injections (4.0–16.0 mg/kg) were studied for their effects upon the vacuous jaw movements induced by 0.4 mg/kg physostigmine. In the second experiment, acute injections of clozapine (2.0–16.0 mg/kg) were given to replicate the previous study indicating that clozapine could reduce pilocarpine-induced vacuous jaw movements. The third experiment was designed to compare the effects of acute and repeated administration of 16.0 mg/kg clozapine. In this experiment, there were three groups: one that received 4.0 mg/kg pilocarpine, a second group that received pilocarpine plus an acute injection of 16.0 mg/kg clozapine, and a third group that received injections of 16.0 mg/kg clozapine for 14 consecutive days, including the final day in which they also were injected with pilocarpine. The effects of repeated clozapine were studied in the third experiment because normal clinical practice involves repeated administration of the drug. For the third experiment, animals also were assessed for the sedative effects of clozapine, because considerable evidence indicates that sedation is a major side effect of acute clozapine administration in humans (36), and it is possible that clozapine-induced alterations of vacuous jaw movements could be an artifact of the sedative effects produced by acute clozapine injections.

METHOD

Subjects

Male Sprague–Dawley rats were obtained from Harlan Sprague–Dawley (Indianapolis, IN). Rats were 325–450 g during the course of the experiment, and were group housed in a colony that was maintained at approximately 23°C. The colony had a 12 L : 12 D cycle (lights on 0700 h), and all rats had ad lib access to lab chow and water.

Drugs

Clozapine was obtained thanks to the courtesy of Sandoz Pharmaceuticals. Pilocarpine and physostigmine were obtained from Sigma Chemical Co. A 0.3% tartaric acid vehicle was used for dissolving clozapine, while 0.9% saline was the vehicle for injections of pilocarpine and physostigmine. Intraperitoneal injections were used for all experiments. Doses of pilocarpine and physostigmine, and the postinjection times for behavioral observations, were selected on the basis of previous research [(5,39,40,45); also, pilot data].

Behavioral Observations

Rats were observed in 30 × 30 × 30 cm Plexiglas chambers with a wire mesh floor that was elevated 42 cm from the table top to allow for viewing of the rats from underneath. All observations were conducted from 1200 to 1700 h. Vacuous jaw movements are defined as rapid vertical deflections of the lower jaw that resemble chewing but are not directed at any stimulus. A blinded observer recorded each individual vertical deflection of the jaw using a mechanical counter. In Experiment 3, an observer noted the presence or absence of behavioral characteristics of sedation (e.g., eyes closed, head down, curled up in a ball, flattened posture, ataxia, problems with limb placement, lack of alertness, general appearance of sleepiness). The rats were assessed according to a sedation rating [4—awake, active: enganged in locomotion, rearing or head movements; 3—awake, inactive: eyes fully open, head up, no locomotion or rearing, normal posture; 2—moderate sedation: eyes partly closed, head somewhat down; 1—heavy sedation: eyes mostly closed, head mostly or entirely down, flattened posture, lack of normal limb placement; 0—asleep; see also (38)]. Previous studies involving two observers that used this scale have shown significant interrater reliability [Spearman correlation = 0.89; see (38)].

Experiments

In Experiment 1, there were four experimental conditions. All rats (n = 6) received 0.4 mg/kg physostigmine, and the four conditions were: physostigmine plus tartaric acid vehicle, physostigmine plus 4.0 mg/kg clozapine, physostigmine plus 8.0 mg/kg clozapine, and physostigmine plus 16.0 mg/kg clozapine. Injections of tartaric acid vehicle or clozapine were given 50 min before behavioral testing, while injections of physostigmine were given 10 min before behavioral testing. Immediately after injections of physostigmine, rats were placed into the observation chamber for a 10 min habituation period; behavioral observations were conducted 10–15 min after injection of physostigmine. Each rat received all four drug treatments in a randomly varied order, with 1 week between each drug treatment.

In Experiment 2, there were five experimental conditions. All rats (n = 5) received 4.0 mg/kg pilocarpine, and the five conditions were: pilocarpine plus tartaric acid vehicle, pilocarpine plus 2.0 mg/kg clozapine, pilocarpine plus 4.0 mg/kg clozapine, pilocarpine plus 8.0 mg/kg clozapine, and pilocarpine plus 16.0 mg/kg clozapine. Injections of tartaric acid vehicle or clozapine were given 50 min before behavioral testing, while injections of pilocarpine were given 10 min before behavioral testing. Immediately after injections of pilocarpine, rats were placed into the observation chamber for a 10-min habituation period; behavioral observations were conducted 10–15 min after injection of pilocarpine. Each rat received all four drug treatments in a randomly varied order, with 1 week between each drug treatment.

For Experiment 3, there were three drug treatment conditions. As in Experiment 2, all rats received injections of 4.0 mg/kg pilocarpine. In Experiment 3, the rats were randomly

assigned to one of three different drug treatment groups (n = 6 per group): one group received tartaric acid vehicle for 13 days and on the test day received tartaric acid vehicle plus pilocarpine, a second group received tartaric acid vehicle for 13 days and received an acute injection of 16.0 mg/kg clozapine on the test day followed by injection of pilocarpine, and a third group received injections of 16.0 mg/kg clozapine for 13 consecutive days, and then on the test day they also were injected with 16.0 mg/kg clozapine followed by pilocarpine. Injections of tartaric acid vehicle or clozapine were given 50 min before behavioral testing, and rats were observed for the sedative effects of clozapine in a 15-s observation period immediately prior to injections of pilocarpine. Injections of pilocarpine were given 10 min before behavioral testing. Immediately after injections of pilocarpine, rats were placed into the observation chamber for a 10-min habituation period; observations of vacuous jaw movements were conducted 10–15 min after injection of pilocarpine.

Data Analyses

For Experiments 1 and 2, the effects of drug treatments on vacuous jaw movements were assessed using repeated measures analysis of variance (ANOVA). Simple one-way ANOVA was used in Experiment 3. In each experiment, Dunnett's multiple comparison test was used to assess difference between each group that received clozapine and the control group (i.e., the group that received physostimine or pilocarpine plus tartaric acid vehicle). Nonparametric analyses were used for assessing the sedative effects in Experiment 3.

RESULTS

The results of Experiment 1 are shown in Fig. 1. Clozapine produced a dose-related decrease in vacuous jaw movements induced by physostigmine. Repeated measures ANOVA demonstrated a significant effect of drug treatment, $F(3, 15) = 3.58$, $p < 0.05$. Post hoc comparisons with Dunnett's test indicated that only the 16.0 mg/kg dose of clozapine significantly reduced vacuous jaw movements relative to the effects of physostigmine alone. Figure 2 shows the results of Experiment 2. Clozapine produced a dose-related decrease in vacuous jaw movements induced by pilocarpine. Repeated measures ANOVA demonstrated a significant effect of drug treatment, $F(4, 16) = 4.98$, $p < 0.05$. Post hoc comparisons with Dunnett's test indicated that only the 16.0 mg/kg dose of clozapine significantly reduced vacuous jaw movements relative to the effects of pilocarpine alone.

The effects of acute and repeated daily injections of clozapine on pilocarpine-induced vacuous jaw movements are shown in Fig. 3. ANOVA demonstrated that there was a significant overall treatment effect, $F(2, 15) = 5.48$, $p < 0.05$. Post hoc analyses with Dunnett's test indicated that both acute and

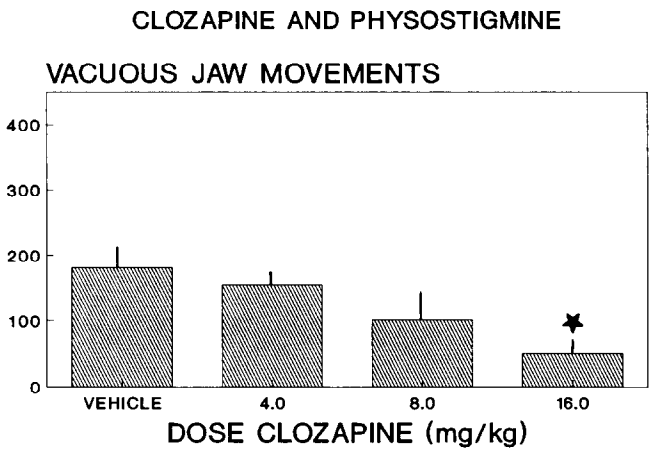

FIG. 1. In this experiment, all rats received 0.4 mg/kg physostigmine. Data shown are mean (±SEM) vacuous jaw movements induced by 0.4 mg/kg physostigmine plus vehicle (VEHICLE), and physostigmine plus various doses of clozapine (*different from physostigmine plus vehicle, $p < 0.05$).

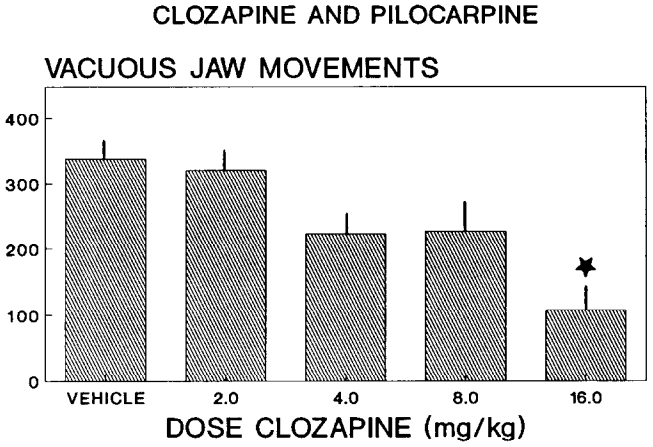

FIG. 2. In this experiment, all rats received 4.0 mg/kg pilocarpine. Data shown are mean (±SEM) vacuous jaw movements induced by 4.0 mg/kg pilocarpine plus vehicle (VEHICLE), and pilocarpine plus various doses of clozapine (*different from pilocarpine plus vehicle, $p < 0.05$).

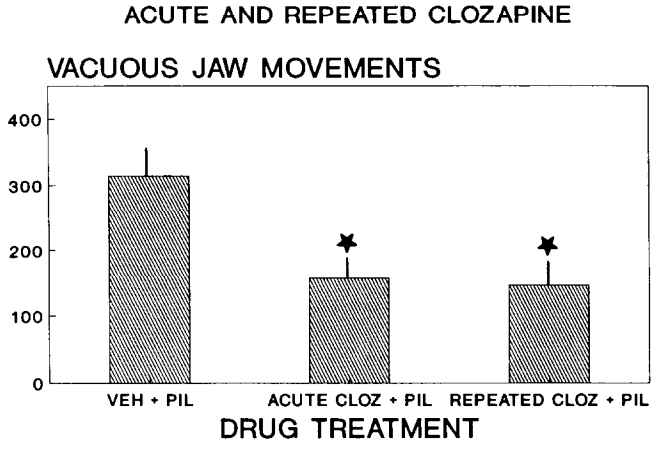

FIG. 3. Mean (±SEM) vacuous jaw movements induced by acute injections of 4.0 mg/kg pilocarpine plus vehicle (VEH + PIL), 4.0 mg/kg pilocarpine plus acute injection of 16.0 mg/kg clozapine (ACUTE CLOZ + PIL), and 4.0 mg/kg pilocarpine plus repeated injections of 16.0 mg/kg clozapine (REPEATED CLOZ + PIL); *different from pilocarpine plus vehicle, $p < 0.05$.

repeated treatment with clozapine resulted in a significant reduction in pilocarpine-induced vacuous jaw movements relative to pilocarpine alone. However, the two clozapine-treated groups did not differ from each other as determined by the Tukey test. The results of the sedation tests indicate that acute injections of 16.0 mg/kg clozapine produced significant sedation, whereas on the 14th day of clozapine injection there was not a significant sedative effect. The number of rats with sedation (i.e., sedation score = 1 or 2) was 0 out of 6 for the group that received vehicle, 6 out of 6 of the group that received acute clozapine, and 1 out of 6 of the group that received repeated clozapine. Based upon the Fisher exact test, the group that received acute clozapine differed significantly ($p < 0.05$) from both the vehicle-treated group and the repeated clozapine group.

DISCUSSION

Clozapine produced a dose-related suppression of the vacuous jaw movements induced by pilocarpine and physostigmine. These results are consistent with the previous report of Stewart et al. (45), who demonstrated that clozapine injected in doses of 1-20 mg/kg produced a dose related suppression of vacuous jaw movements induced by pilocarpine. In that study, it was demonstrated that other DA antagonists, including trifluoperazine, sulpiride, SCH 23390, pimozide, and thioridazine all failed to suppress pilocarpine-induced vacuous jaw movements [but see also (23)]. The present results demonstrate that the inhibitory effects of clozapine on vacuous jaw movements are not unique to pilocarpine-induced movements; clozapine can reduce the vacuous jaw movements induced by cholinesterase inhibition as well as direct stimulation of muscarinic receptors. In addition, the results of Experiment 3 demonstrate that repeated as well as acute administration of clozapine can suppress pilocarpine-induced vacuous jaw movements. One of the major reasons for undertaking Experiment 3 was to determine if clozapine-induced suppression of vacuous jaw movements showed rapid tolerance. Some of the behavioral effects of clozapine, such as the suppression of lever pressing, do, in fact, show relatively rapid tolerance (52). In a recent study, it was shown that 6.0 mg/kg clozapine suppressed lever pressing substantially in the first few days of administration, but showed rapid tolerance within the 14-day repeated injection period (38). In that study, it also was demonstrated that clozapine produced significant sedative effects in the first 10 days of administration, but this effect, like suppression of lever pressing, showed substantial tolerance. Clozapine is known to produce substantial sedative effects in humans, and sedation has been reported to be the most common side effect of clozapine (7,36). Like the sedative effects in rats, clozapine-induced sedation in psychotic patients generally shows relatively rapid tolerance (24,25). The sedative effects of clozapine in rats involve a general appearance of sleepiness (i.e., head down, flat posture, eyes closed), as well as ataxia and problems with limb placement; these effects are distinct from the extrapyramidal motor effects ususally produced by typical antipsychotic drugs such as haloperidol [see also (21,38)]. The results of Experiment 3 indicate that acute administration of 16.0 mg/kg clozapine produced substantial sedation, but by the 14th day of injection these effects were significantly reduced. It was noted by the observer that during the vacuous jaw movement tests, the rats that received acute clozapine and pilocarpine had their heads down, whereas the rats that received repeated clozapine and pilocarpine did not have their heads down. Thus, the results of Experiment 3 demonstrate that the sedative effect of clozapine shows relatively rapid tolerance, whereas clozapine-induced suppression of pilocarpine-induced vacuous jaw movements shows no signs of tolerance within the 14-day injection period. These results demonstrate that the suppression of pilocarpine-induced vacuous jaw movements by clozapine is not merely an artifact of clozapine-induced sedation.

As noted above, clozapine has a unique profile of motor effects compared to the typical antipsychotic drugs. Typical antipsychotic DA antagonists produce motor side effects such as parkinsonism, dystonia and tardive dyskinesia (26,28,49). In constrast, clozapine has little or no propensity for producing these motor effects (29,36). Some reports indicate that clozapine can actually improve motor function in Parkinson's disease patients (3,6,32). Administration of clozapine for 1 month reduced global parkinsonian scores in patients with idiopathic Parkinson's disease (3). Clozapine also has been reported to have some beneficial effects on Parkinsonian tremor (11,32). These reports of antiparkinsonian effects of clozapine are particularly interesting in view of the potential clinical significance of vacuous jaw movements in rats. It has been suggested that vacuous jaw movements in rats share characteristics with human Parkinsonian symptoms (5,17, 36,39,42). Human Parkinsonism, like vacuous jaw movements, can be produced or exacerbated by cholinomimetic drugs (9,15,31). Thus, the ability of clozapine to reduce pilocarpine-induced vacuous jaw movements in rats may be related to the anti-Parkinsonian effects of clozapine. This would suggest that the ability of drugs to reduce pilocarpine-induced vacuous jaw movements could be used as a behavioral test for the anti-parkinsonian actions of novel clozapine-like antipsychotic drugs.

The neurochemical basis of clozapine's effects on vacuous jaw movements is unclear. Future research involving acute and long-term administration of clozapine could be useful for understanding the neurochemical properties of this drug. In addition to having DA antagonist effects, clozapine is known to have a variety of other neurochemical actions, including both muscarinic and serotonergic antagonism (27,42). These muscarinic and serotonergic effects of clozapine may contribute to the ability of clozapine to reduce pilocarpine-induced vacuous jaw movements. Muscarinic antagonists reduced the vacuous jaw movements induced by systemic or intrastriatal injections of pilocarpine (33,39,40) and physostigmine (20, 33), as well as those movements induced by DA antagonists (33,43), and pharmacological depletion of DA (36). Evidence also indicates that serotonin is involved in vacuous jaw movements. The serotonin agonist *m*-chlorophenylpiperazine induces vacuous jaw movements in rats (22,46), and this effect was antagonized by the serotonin antagonists methiothepin and minanserin, as well as the muscarinic antagonists benzhexol and scopolamine (46). Pilocarpine-induced vacuous jaw movements were shown to be reduced by depletion of serotonin (47). Thus, clozapine has two actions, muscarinic antagonism and serotonin antagonism, each of which has been shown to reduce vacuous jaw movements. As well as being involved in the generation of vacuous jaw movements in rats, DA, acetylcholine, and serotonin mechanisms are potentially important for motor syndromes related to basal ganglia dysfunction in humans. Muscarinic antagonism is a common treatment for Parkinsonian symptoms (26,27), and the serotonin antagonist ritanserin has demonstrated some anti-Parkinsonian effects (15). For some time it has been suggested that acetylcholine/DA interactions are important for motor control (2,9,37,42,43). More recently, serotonin/DA interactions have been emphasized (8,22,27,29). The unique ability of clozapine to produce little in the way of extrapyramidal

motor effects, and to possess some degree of anti-Parkinsonian activity may, in fact, be related to a three-way interaction between the dopaminergic, muscarinic and serotonergic effects of this important drug.

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REFERENCES

1. Adams, R. D.; Victor, M. Tremors, myoclonus, spasms, and tics. Principles of neurology. New York: McGraw-Hill; 1981:69-77.
2. Agid, Y.; Guyenet, P.; Glowinski, J.; Beaujouan, J. C.; Javoy, F. Inhibitory influence of the nigrostriatal dopamine system on the striatal cholinergic neurons of the rat. Brain Res. 86:488-492; 1975.
3. Arevalo, G. J.; Gershanik, O. S. Modulatory effect of clozapine on levodopa response in Parkinson's disease: A preliminary study. Movement Disord. 8:349-354; 1993.
4. Baskin, P.; Salamone, J. D. Vacuous jaw movements in rats induced by acute reserpine administration: Interactions with different doses of apomorphine. Pharmacol. Biochem. Behav. 46: 793-797; 1993.
5. Baskin, P.; Gianutsos, G.; Salamone, J. D. Repeated scopolamine injections sensitize rats to pilocarpine-induced vacuous jaw movements and enhance striatal muscarinic receptor binding. Pharmacol. Biochem. Behav. 49:437-442; 1994.
6. Bernardi, F.; Del Zompo, M. Clozapine in idiopathic Parkinson's disease. Neurol. 40:1151; 1990.
7. Burke, M.; Sebastian, C. Treatment of clozapine sedation. Am. J. Psychiatry 150:1900-1901; 1993.
8. Casey, D. E. Serotonergic and dopaminergic aspects of neuroleptic-induced extrapyramidal syndromes in nonhuman primates. Psychopharmacology (Berlin) 112:S55-S59; 1993.
9. Duvoisin, R. C. Cholinergic-anticholinergic antagonism in parkinsonism. Arch. Neurol. 17:124-136; 1967.
10. Ellison, G.; See, R. Rats administered chronic neuroleptics develop oral movements which are similar in form to those in humans with tardive dyskinesia. Psychopharmacology (Berlin) 98: 564-566; 1989.
11. Friedman, J. H.; Lannon, M. C. Clozapine-responsive tremor in Parkinson's disease. Movement Disord. 5:225-229; 1990.
12. Glassman, R. B.; Glassman, H. N. Oral dyskinesia in brain-damaged rats withdrawn from neuroleptic: Implication for models of tardive dyskinesia. Psychopharmacology (Berlin) 69:19-25; 1980.
13. Gunne, L. M.; Growden, J.; Glaeser, B. Oral dyskinesia in rats following brain lesions and neuroleptic administration. Psychopharmacology (Berlin) 77:134-139; 1982.
14. Gunne, L. M.; Andersson, U.; Bondesson, U.; Johansson, P. Spontaneous chewing movements in rats during acute and chronic antipsychotic drug administration. Pharmacol. Biochem. Behav. 25:897-901; 1986.
15. Harbaugh, R. E.; Roberts, D. W.; Coombs, D. W.; Saunders, R. L.; Reeder, T. M. Preliminary report: Intracranial cholinergic drug infusion in patients with Alzheimer's disease. Neurosurgery 15:514-518; 1984.
16. Hirsch, E.; Auff, E.; Birkmayer, W.; Schnaberth, G.; Riederer, P. Ritanserin in the treatment of Parkinson's disease. In: Nappi, G.; Caraceni, T., eds. Parkinsonism: Diagnosis and treatment. New York: Laurel House; 1989:199-203.
17. Hunker, C. J.; Abbs, J. H. Uniform frequency of Parkinsonian resting tremor in the lips, jaw, tongue, and index finger. Movement Disord. 5:71-77; 1990.
18. Jicha, G.; Salamone, J. Vacuous jaw movements and feeding deficits in rats with ventrolateral striatal dopamine depletion: Possible relation to Parkinsonian symptoms. J. Neurosci. 11: 3822-3829; 1991.
19. Johansson, P.; Casey, D. E.; Gunne, L. M. Dose-dependent increases in rat spontaneous chewing rates during long-term administration of haloperidol but not clozapine. Psychopharmacol. Bull. 22:1017-1019; 1986.
20. Kelley, A. E.; Bakshi, V. P.; Delfs, J. M.; Lang, C. G. Cholinergic stimulation of the ventrolateral striatum elicits mouth movements in rats: Pharmacological and regional specificity. Psychopharmacology (Berlin) 99:542-549; 1989.
21. Koek, W.; Colpaert, F. C. Inhibition of methylphenidate-induced behaviors in rats: Differences among neuroleptics. J. Pharmacol. Exp. Ther. 267:181-191; 1993.
22. Kostrzewa, R. M.; Brus, R.; Perry, K. W.; Fuller, R. W. Age-dependence of a 6-hydroxydopamine lesion on SKF 38393 and *m*-chlorophenylpiperazine-induced oral activity responses of rats. Brain Res. 76:87-93; 1993.
23. Levin, E. D.; Ellison, G. D.; See, R. E.; South, D.; Young, E. D_1 and D_2 dopamine receptor interactions with pilocarpine-induced oral activity in rats. Pharmacol. Biochem. Behav. 33:501-505; 1989.
24. Lieberman, J.; Kane, J.; Johns, C. Clozapine: Guidelines for clinical management. J. Clin. Psychiatry 50:329-338; 1989.
25. Lindstrom, L. H. The effect of long term treatment of clozapine in schizophrenia: A retrospective study of 96 patients treated with clozapine for up to 13 years. Acta. Psychiatr. Scand. 77:524-529; 1988.
26. Marsden, C. D.; Tarsy, D. Baldessarini, R. J. Spontaneous and drug-induced movement disorders in psychotic patients. In: Bendon, D. F.; Blumer, D., eds. Psychiatric aspects of neurological disease. New York: Grune and Stratten; 1975:219-266.
27. Matsubara, A.; Matsubara, R.; Kusumi, I.; Koyama, T.; Yamashita, I. Dopamine D_1, D_2, and serotonin$_2$ receptor occupation by typical and atypical antipsychotic drugs in vivo. J. Pharmacol. Exp. Ther. 266:498-508; 1993.
28. McEvoy, J. P. The clinical use of anticholinergic drugs as treatment for extrapyramidal side effects of neuroleptic drugs. J. Clin. Psychopharmacol. 3:288-301; 1983.
29. Meltzer, H. Y. Clinical studies on the mechanism of action of clozapine: The dopamine-serotonin hypothesis of schizophrenia. Psychopharmacology (Berlin) 99:s18-s27; 1989.
30. Neisewander, J. L.; Lucki, I.; McGonigle, P. Neurochemical changes associated with the persistence of spontaneous oral dyskinesia in rats following chronic reserpine treatment. Brain Res. 558:27-35; 1991.
31. Noring, U.; Povlesen, U. J.; Casey, D. E.; Gerlach, J. Effect of a cholinomimetic drug (RS 86) in tardive dyskinesia and drug-related Parkinsonism. Psycholpharmacology (Berlin) 84:569-571; 1984.
32. Pakkenberg, H.; Pakkenberg, B. Clozapine in the treatment of tremor. Acta Neurol. Scand. 73:295-297; 1986.
33. Rupniak, N. M. J.; Jenner, P.; Marsden, C. D. Cholinergic modulation of perioral behavior induced by chronic neuroleptic administration to rats. Psychpharmacology (Berlin) 79:226-230; 1983.
34. Rupniak, N. M. J.; Jenner, P.; Marsden, C. D. Pharmacological characterization of spontaneous or drug-induced purposeless chewing movements in rats. Psychopharmacology (Berlin) 85:71-79; 1985.
35. Rupniak, N. M. J.; Jenner, P.; Marsden, C. D. Acute dystonia induced by neuroleptic drugs. Psychopharmacology (Berlin) 88: 403-419; 1986.
36. Safferman, A.; Lieberman, J. A.; Kane, J. M.; Szymanski, S.; Kinon, B. Update on the clinical efficacy of clozapine. Schizophr. Bull. 17:247-261; 1991.
37. Salamone, J. D.; Baskin, P. B. Vacuous jaw movements induced by reserpine and low-dose apomorphine: Possible model of Parkinsonian tremor. Pharmacol. Biochem. Behav. 53:179-183; 1996.
38. Salamone, J. D.; Cousins, M. S.; Maio, C.; Champion, M.; Turski, T.; Kovach, J. Different behavioral effects of haloperidol, clozapine and thioridazine in an instrumental lever pressing/feeding procedure. Psychopharmacology (Berlin) (in press).

39. Salamone, J. D.; Lalies, M. D.; Channell, S. L.; Iversen, S. D. Behavioral and pharmacological characterization of the mouth movements induced by muscarinic agonists in the rat. Psychopharmacology (Berlin) 88:467–471; 1986.
40. Salamone, J. D.; Johnson, C. J.; McCullough, L. D.; Steinpreis, R. E. Lateral striatal cholinergic mechanisms involved in oral motor activities in the rat. Psychopharmacology (Berlin) 102:529–534; 1990.
41. Schmauss, M.; Wolff, R.; Erfurth, A.; Ruther, E. Tolerability of long term clozapine treatment. Psychopharmacology (Berlin) 99: s105–s108; 1989.
42. Snyder, S. H.; Banerjee, S. P; Yamamura, H. I.; Greenberg, D. Drugs, neurotransmitters and schizophrenia. Science 184:1243–1253; 1974.
43. Steinpreis, R. E.; Baskin, P. P.; Salamone, J. D. Vacuous jaw movements induced by subchronic administration of haloperidol: Interactions with scopolamine. Psychopharmacology (Berlin) 111: 99–105; 1993.
44. Steinpreis, R. E.; Salamone, J. D. The effects of acute haloperidol and reserpine administration on vacuous jaw movements in three different age groups of rats. Pharmacol. Biochem. Behav. 46:405–409; 1993.
45. Stewart, B. R.; Jenner, P.; Marsden, C. D. The pharmacological characterization of pilocarpine-induced chewing in the rat. Psychopharmacology (Berlin) 97:228–234; 1988.
46. Stewart, B. R.; Jenner, P.; Marsden, C. D. Induction of purposeless chewing behaviour in rats by 5-HT agonist drugs. Eur. J. Pharmacol. 162:101–107; 1989.
47. Stewart, B. R.; Rose, S.; Jenner, P.; Marsden, C. D. Pilocarpine-induced purposeless chewing behaviour in rats is dependent on intact central stores of 5-HT. Eur. J. Pharmacol. 142:173–176; 1987.
48. Stoessl, A. J.; Martin-Iversen, M. T.; Barth, T. M.; Dourish, C. T.; Iversen, S. D. Effects of ageing on the behavioural responses to dopaminergic agonists: Decreased yawning and locomotion, but increased stereotypy. Brain Res. 495:20–30; 1989.
49. Tarsy, D. Neuroleptic-induced extrapyramidal reactions: Classification, description and diagnosis. Clin. Neuropsychopharmacol. 6:s9–s26; 1983.
50. Van Putten, T.; Wirshing, W. C.; Marder, S. R. Tardive Meige syndrome responsive to clozapine. J. Clin. Psychopharmacol. 10: 381–382; 1990.
51. Waddington, J. L. Spontaneous orofacial movements induced in rodents by very long-term neuroleptic drug administration: Phenomenology, pathophysiology and putative relationship to tardive dyskinesia. Psychopharmacology (Berlin) 101:431–447; 1990.
52. Wiley, J. L.; Compton, A. D.; Porter, J. H. Differential effects of clozapine and pimozide on fixed-ratio responding during repeated dosing. Pharmacol. Biochem. Behav. 48:253–257; 1994.