Pergamon

Pharmacology Biochemistry and Behavior, Vol. 49, No. 2, pp. 437–442, 1994

0091-3057/94 $6.00 + .00

0091-3057(94)E0178-K

BRIEF COMMUNICATION

Repeated Scopolamine Injections Sensitize Rats to Pilocarpine-Induced Vacuous Jaw Movements and Enhance Striatal Muscarinic Receptor Binding

PATRICIA P. BASKIN,* GERALD GIANUTSOS† AND JOHN D. SALAMONE*[1]

*Department of Psychology and †Section of Pharmacology and Toxicology,
The University of Connecticut, Storrs, CT 06269-1020

Received 22 October 1993

BASKIN, P. P., G. GIANUTSOS AND J. D. SALAMONE. *Repeated scopolamine injections sensitize rats to pilocarpine-induced vacuous jaw movements and enhance striatal muscarinic receptor binding.* PHARMACOL BIOCHEM BEHAV 49(2) 437–442, 1994.—This experiment was conducted to determine if repeated administration of the muscarinic antagonist scopolamine could increase pilocarpine-induced vacuous jaw movements and also enhance muscarinic receptor binding. Rats received daily injections of either scopolamine (0.5 mg/kg IP) or saline for 14 days. On day 15 rats received no injections of scopolamine, but did receive injections of pilocarpine (1.0, 2.0 or 4.0 mg/kg IP) or saline. After administration of pilocarpine or saline, all rats were observed for vacuous jaw movements and rearing behavior. The day after pilocarpine injections, rats were sacrificed and samples of tissue from the lateral neostriatum were removed to assess muscarinic receptor binding using ^{3}H-QNB as the ligand. Analyses of the vacuous jaw movement data indicated that there was a significant dose-related increase in vacuous jaw movements induced by pilocarpine, and also that there was a significant enhancement of pilocarpine-induced vacuous jaw movements in rats pretreated with repeated scopolamine injections. There was not a significant scopolamine × pilocarpine interaction, suggesting that pretreatment with scopolamine produced an apparent parallel shift in the pilocarpine dose–response curve. Pilocarpine significantly suppressed rearing behavior, and scopolamine pretreatment significantly enhanced the suppression of rearing produced by pilocarpine. Analysis of the receptor binding data indicated that there was a significant increase in the number of muscarinic receptor sites (B_{max}) in rats that received repeated scopolamine injections as compared to saline-treated rats. These results demonstrate that repeated administration of scopolamine sensitizes rats to the induction of vacuous jaw movements produced by pilocarpine, and also indicate that vacuous jaw movements may be a useful behavioral procedure for assessing striatal muscarinic supersensitivity.

Oral movements Basal ganglia Parkinsonism Acetylcholine Tremor

IN rats, a variety of pharmacological conditions are known to produce vacuous jaw movements (10,20,24,25). These movements are characterized by a rapid vertical deflection of the lower jaw that resembles chewing behavior but is not directed at any particular stimulus. Vacuous jaw movements have been reported to result from chronic (20,32) or acute administration of dopamine receptor antagonists (8,10,21,22,28,29). Acute administration of the monoamine-depleting agent reserpine was shown to increase vacuous jaw movements (2,29). In addition, neurotoxic depletion of dopamine in the ventrolateral striatum was shown to increase vacuous jaw movements (10). Considerable evidence indicates that there is an acetylcholine/dopamine interaction in the production of vacuous jaw movements, and that muscarinic cholinergic stimulation leads to a

[1] To whom requests for reprints should be addressed.

pronounced induction of vacuous jaw movements. The vacuous jaw movements induced by repeated administration of haloperidol were shown to be reduced by coadministration of the muscarinic antagonists atropine and scopolamine (20). Systemic administration of a number of muscarinic agonists induced vacuous jaw movements (20,24). These cholinomimetic-induced vacuous jaw movements are blocked by central muscarinic antagonism (20,24,30,31). Injections of pilocarpine or physostigmine directly into the ventrolateral striatum also induced vacuous jaw movements (11,25). The vacuous jaw movements induced by intrastriatal injections of cholinomimetics were blocked by muscarinic antagonists (11,25).

Most studies of the effects of muscarinic antagonists on vacuous jaw movements have focussed on the ability of acute administration of muscarinic antagonists to reverse the vacuous jaw movements induced by dopamine antagonists or cholinomimetics. Few studies have investigated the effects of repeated injections of muscarinic antagonists. Previous work has shown that repeated administration of scopolamine (SCOP) reduced the vacuous jaw movements induced by haloperidol (28). In addition, removal of SCOP treatment after several days of injection was shown to cause a rebound increase in haloperidol-induced vacuous jaw movements (28). Administration of SCOP alone for 2 weeks did not significantly increase vacuous jaw movements. The present experiment was designed to determine if repeated administration of scopolamine could alter the ability of the muscarinic agonist pilocarpine to induce vacuous jaw movements. Rats received daily injections of either SCOP (0.5 mg/kg IP) or saline for 14 days, which is the same treatment used previously (28). On day 15, rats received no injections of scopolamine, but did receive injections of various doses of pilocarpine to assess the dose-response curve for pilocarpine-induced vacuous jaw movements in rats that had received either SCOP or saline pretreatment. Rearing behavior also was measured to observe the effects of SCOP treatment upon an aspect of motor activity that did not involve perioral movements. After the behavioral testing, samples of tissue from the lateral neostriatum were analyzed for muscarinic binding to determine if repeated SCOP injections led to muscarinic receptor supersensitivity.

METHOD

Subjects

The subjects were 73 male Sprague-Dawley rats obtained from Harlan Sprague-Dawley (Indianapolis, IN). 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 0700 h). Standard lab chow and water were available ad lib. Average weights at the start of the experiment were 310–360 g.

Drugs

(−)Scopolamine hydrobromide (SCOP) and pilocarpine nitrate were obtained from Sigma Chemical Company. Both drugs were dissolved in a 0.9% saline vehicle solution. All injections were made intraperitoneally (IP) in a volume of 1.0 ml/kg.

Behavioral Observations

Observation chambers consisted of a Plexiglas box (28 × 28 × 28 cm) placed on a wire mesh floor. The floor of the chamber was elevated 42 cm from the surface of the table on which it was placed to allow clear observation of behaviors from all angles, including underneath. All observations were made between 1300 and 1700 h. Mechanical counters were used to record the frequency of vacuous jaw movements and rearing during a 5-min observation period. Vacuous jaw movements were defined as rapid vertical deflections of the lower jaw that resembled chewing but were not directed at any particular stimulus. A single observer who was unaware of the drug treatments counted each individual vertical deflection of the jaw as one vacuous jaw movement response, and counted the total number of these responses for the entire 5-min observation period. Previous studies of interrater reliability have indicated that the use of this method of observation and definition for vacuous jaw movements typically results in greater than 90% agreement between observers.

General Procedures

Rats were randomly assigned to receive daily IP injections of either SCOP (0.5 mg/kg) or saline during a 14-day pretreatment period. These daily injections of SCOP or saline vehicle were given 4–6 h after the onset of the light part of the light : dark cycle. On day 15, all rats were injected with either pilocarpine (1.0, 2.0, or 4.0 mg/kg) or saline 10 min prior to behavioral testing. After these injections animals were placed in the observation chambers to allow pretest habituation. An observer unaware of the drug conditions counted the number of vacuous jaw movements (as defined above) and rearing responses during the 5-min observation period (10–15 min after injection).

Tissue Preparation and Muscarinic Binding Assay

On day 16, all rats were decapitated and the brains were removed and frozen. A 1.2 mm coronal section was cut with a freezing microtome at the level of the neostriatum. Using a 16 ga. stainless steel tube, three tissue samples were cut from the lateral striatum on both sides (see Fig. 1). These six samples from the lateral striatum of each rat (three per side) were combined for use in the muscarinic binding assay. The lateral striatum was chosen for this dissection because previous work indicated that the ventral portion of the lateral striatum is closely related to the production of vacuous jaw movements

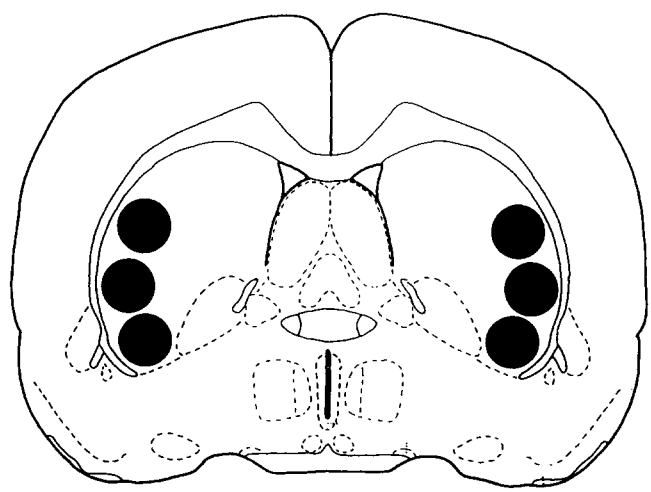

FIG. 1. Coronal section through rat brain at the level of the neostriatum. The three circles on each side indicate approximate locations of lateral striatal tissue samples.

(10,25). Pilot data indicated that small samples including only the ventrolateral striatum were too small to generate accurate binding data by Scatchard analysis. Therefore, large tissue samples of the lateral striatum that included ventral as well as more dorsal areas were used. Tissue samples were subjected to a muscarinic binding assay using ^{3}H-quinuclidinyl benzilate (^{3}H-QNB), a nonspecific muscarinic antagonist, as the ligand. Muscarinic binding was determined in each striatal sample according to previously described methods (1,34). In brief, tissue samples were homogenized in 100 volumes of 0.32 M sucrose and centrifuged at 1000 × *g* for 10 min. The supernatant was further centrifuged at 48,000 × *g* for 20 min, and the resulting pellet was resuspended in ice-cold 0.05 M Na/K phosphate buffer (pH = 7.4), recentrifuged and resuspended in fresh buffer. Aliquots containing 50 μl of tissue homogenate were incubated at 25°C with ^{3}H-QNB for 1 h. At least four different QNB concentrations (in most cases, five concentrations; 0.025, 0.05, 0.1, 0.2, and 0.4 nM), run in duplicate determinations, were used for the quantitation of binding parameters for each sample. Bound QNB was separated from free by filtration through Whatman GF/B filters using a 24-sample Brandel Cell Harvester, and then washed three times with ice-cold buffer. Radioactivity on the filters was measured by liquid scintillation spectrometry. Radioactivity remaining after incubation with atropine sulfate (10 μM; approximately 3000 × K_i) was used to determine nonspecific binding. Protein values were determined by the method of Lowry (14), and samples typically had approximately 20 μg protein.

Data Analysis

Behavioral data were square root transformed before analysis to reduce the heterogeneity of variance across groups. A *t*-test was performed between the SCOP and saline pretreated rats that received saline on day 15 to determine directly if SCOP pretreatment alone had any effect on vacuous jaw movements or rearing. A 2 × 3 factorial analysis of variance (ANOVA) was conducted to assess the effects of drug treatments (2 pretreatment conditions × 3 doses of pilocarpine) on vacuous jaw movements and rearing. For the biochemical measures, binding curves were plotted and Scatchard analysis was performed. Animals from which insufficient data was available to calculate a Scatchard analysis (three rats) were eliminated from further biochemical analyses. Linear regression analysis with the LIGAND computerized package was carried out to determine K_d and B_{max} values for each rat. Initial statistical analyses indicated that the day 15 (i.e., pilocarpine) treatments had no effect on muscarinc binding. Thus, the rats were collapsed into two groups (SCOP vs. saline pretreatment) and the *t*-test was used to assess any effects of pretreatment on binding activity. The binding data analyzed were from individual animals (i.e., nonpooled binding data), and the negative log of the K_d (pK_d) was used as the index of affinity. The Pearson product-moment correlation coefficient was used to determine the relations between neurochemical and behavioral data.

RESULTS

Figure 2 depicts the effects of various drug treatments of vacuous jaw movements. There was no significant difference in vacuous jaw movements between SCOP pretreated rats that received saline on day 15 and saline pretreated rats that received saline on day 15, $t(16) = -1.16$, NS). Figure 2 shows that pilocarpine produced a dose-related increase in vacuous jaw movements, and factorial ANOVA demonstrated that

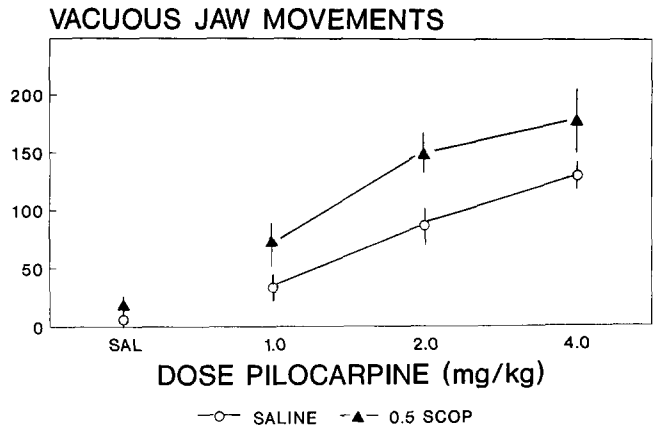

FIG. 2. Mean (±SEM) vacuous jaw movements per 5-min observation period for rats that received pretreatments of SCOP or saline on days 1-14, and injections of saline (SAL), 1.0 mg/kg, 2.0 mg/kg, or 4.0 mg/kg pilocarpine on day 15.

there was a significant effect of pilocarpine dose on vacuous jaw movements, $F(2, 49) = 35.19$, $p < 0.0001$. There was a significant effect of SCOP pretreatment on vacuous jaw movements, $F(1, 49) = 18.71$, $p < 0.0001$, and in Fig. 2 it can be seen that SCOP pretreated rats showed higher levels of vacuous jaw movements compared to saline pretreated rats. There was not a significant pretreatment × pilocarpine dose interaction, $F(2, 49) = 0.4$, NS. In Fig. 3, the effects of various drug treatments on rearing behavior are shown. There was no significant difference in rearing behavior between SCOP pretreated rats that received saline on day 15 and saline pretreated rats that received saline on day 15, $t(16) = -1.46$, NS). Pilocarpine produced a dose-related decrease in rearing, and factorial ANOVA demonstrated that there was a significant effect of pilocarpine dose on rearing, $F(2, 49) = 14.07$, $p < 0.0001$. There was a significant effect of SCOP pretreatment on vacuous jaw movements, $F(1, 49) = 4.07$, $p < 0.05$, and Fig. 3 shows that SCOP pretreated rats had a greater pilocarpine-induced suppression of rearing compared to saline

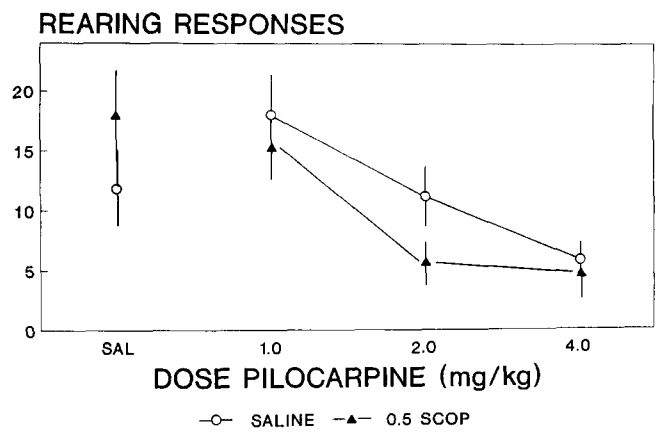

FIG. 3. Mean (±SEM) rearing responses per 5-min observation period for rats that received pretreatments of SCOP or saline on days 1-14, and injections of saline, 1.0 mg/kg, 2.0 mg/kg, or 4.0 mg/kg pilocarpine on day 15.

pretreated rats. There was not a significant pretreatment × pilocarpine dose interaction, $F(2, 49) = 0.96$, NS. The results of the muscarinic binding assay are shown in Table 1. Pretreatment with SCOP significantly increased receptor number as measured by the B_{max}, $t(68) = -2.68$, $p < 0.01$. In contrast, there was no significant effect of SCOP pretreatment on receptor affinity as measured by the pK_d, $t(68) = -1.51$, NS. Correlational analyses indicated that there were no significant correlations between vacuous jaw movements and B_{max} within each of the four different groups (i.e., four different day 15 treatments) that had received SCOP pretreatment. Collapsing across both SCOP and vehicle-pretreated animals, there was a significant correlation between the number of vacuous jaw movements and the number of receptor sites (i.e., B_{max}) amoung rats that had received 2.0 mg/kg pilocarpine, $r(19) = 0.52$, $p < 0.05$, but not amoung rats that received other doses of pilocarpine or saline.

DISCUSSION

Consistent with other reports (24,25,30,31), the present experiment demonstrated that vacuous jaw movements were increased in a dose-dependent fashion following acute administration of pilocarpine. The induction of vacuous jaw movements by acute administration of pilocarpine was potentiated by repeated pretreatment with the muscarinic antagonist SCOP. Pretreatment with SCOP also enhanced the pilocarpine-induced suppression of rearing behavior. Thus, the two major motor effects of pilocarpine recorded in the present experiment were increases in vacuous jaw movements and decreases in rearing, and pretreatment with SCOP for 14 days enhanced both effects of pilocarpine. The lack of pretreatment × pilocarpine dose interaction, coupled with the significant effect of SCOP, suggest that SCOP pretreatment produced an apparent parallel shift in the pilocarpine dose-response curve for each behavior. SCOP pretreatment did not significantly affect vacuous jaw movements or rearing behavior in rats that were not injected with pilocarpine. In addition to altering the behavioral effects of pilocarpine administration, SCOP pretreatment resulted in significant increases in the number of muscarinic receptor sites. Taken together, these results are consistent with the notion that repeated administration of the muscarinic antagonist SCOP results in behavioral and biochemical markers of striatal muscarinic supersensitivity (9).

TABLE 1

EFFECTS OF PRETREATMENT ON STRIATAL MUSCARINIC BINDING ACTIVITY

	Pretreatment Condition	
Binding Parameter	Saline	SCOP
Receptor number (B_{max}, pmol/mg protein)		
mean	0.74	0.80*
SD	0.09	0.07
Affinity (pK_d)		
mean	10.03	9.97
SD	0.14	0.16

SD = standard deviation.
*$p < 0.01$, t-test.

Alterations of muscarinic receptor density in response to pharmacological challenges have previously been reported. Chronic administration of organophosphates, a class of potent anticholinesterases, decreased muscarinic receptor binding (7). Injections of the direct muscarinic agonist oxotremorine also decreased striatal muscarinic binding (3). These previous results indicate that muscarinic receptors are capable of downregulating as a result of chronic overstimulation. Our own results are in agreement with other biochemical studies showing that subchronic administration of muscarinic antagonists such as SCOP or atropine leads to an increase in muscarinic receptor density (B_{max}) without significant changes in affinity (pK_d) (3,15,23). The small increase in B_{max} observed in the present study (8.1%) is modest compared to some previous reports. However, in those previous studies the doses of SCOP used to induce muscarinic supersensitivity were considerably higher than those used in the present work (10.0 mg/kg in ref. 3; 1.0 mg/kg in ref. 23). In addition, it is possible that the increases in nonspecific (i.e., both M_1 and M_2) muscarinic binding as measured by QNB may have obscured somewhat larger changes that could have taken place in a particular subtype of muscarinic receptor.

In the present study, the lateral striatum was the locus at which muscarinic receptor binding was assessed. This site was chosen for biochemical analysis because the striatal region in general shows a high degree of muscarinic binding (13,18,19), and because the neostriatum is a basal ganglia area that is important for motor function. In addition, the lateral striatum is the subregion of neostriatum that is most closely related to motor function. The lateral striatum of the rat is the striatal region that receives the greatest innervation from sensorimotor cortex (17,33). The ventral portion of the lateral striatum is the site at which dopamine depletions produce the most severe deficits in food intake and lever pressing (5,10,26,27). Moreover, the ventral part of the lateral striatum has been strongly implicated in the production of oral motor activity (10,11,12,25). Depletion of striatal dopamine in the ventrolateral striatum increased vacuous jaw movements, whereas depletions in other striatal areas were ineffective (10). Local injections of physostigmine or pilocarpine into the ventral portion of the lateral striatum were shown to induce vacuous jaw movements (11,25). Thus, the present results demonstrated that repeated injections of SCOP increased the number of muscarinic receptor sites in the the brain area (lateral striatum) that has been most closely associated with the production of vacuous jaw movements.

It has been suggested that drug-induced perioral movements in rats may be related to human motor syndromes such as tardive dyskinesia (6) or acute dystonia (22). Considerable evidence indicates that cholinergic hyperfunction and dopaminergic hypofunction are closely related to the production of vacuous jaw movements in rats (2,10,24,25,28,29). In particular, it has been observed that vacuous jaw movements are produced by striatal dopamine depletions (10), by acute administration of dopamine receptor antagonists (8,10,21,22, 28,29) and by acute administration of reserpine (2,29). Thus, it has been noted that vacuous jaw movements in rats share some characteristics with human Parkinsonian symptoms (10,25,28). Muscarinic antagonists are used as treatments for idiopathic and drug-induced parkinsonism, and clinical evidence indicates that withdrawal of anticholinergic drugs after chronic anticholinergic administration can reduce symptoms

of tardive dyskinesia (4) but enhance neuroleptic-induced dystonic or parkinsonian symptoms (16). In a previous report, removal of SCOP treatment after several days of injection was shown to cause a rebound increase in haloperidol-induced vacuous jaw movements (28). The present results indicate that withdrawal of SCOP after repeated SCOP pretreatment acted to enhance pilocarpine-induced vacuous jaw movements. Therefore, the present results are consistent with the notion that some of the pharmacological characteristics of vacuous jaw movements in rats are similar to dystonia or parkinsonism, both of which tend to increase after anticholinergic withdrawal. The present results, together with the previous report by Steinpreis et al. (28), suggest that increased muscarinic receptor density produced by chronic anticholinergic treatment could affect the extrapyramidal motor effects of dopamine antagonists and muscarinic agonists.

ACKNOWLEDGEMENTS

Many thanks to Gale Morrow for performing the muscarinic receptor binding assays.

REFERENCES

1. Bartholomew, P. M.; Gianutsos, G.; Cohen, S. D. Differential cholinesterase inhibition and muscarinic receptor changes in CD-1 mice made tolerant to malathion. Toxicol. Appl. Pharmacol. 81: 147-155; 1985.
2. 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.
3. Ben-Barak, J.; Gazit, H.; Silman, I.; Dudai, Y. In vivo modulation of the number of muscarinic receptors in rat brain by cholinergic ligands. Eur. J. Pharmacol. 74:73-81; 1981.
4. Burnett, G. B.; Prange, A. J.; Wilson, I. C.; Jolliff, L. A.; Creese, I. C.; Snyder, S. H. Adverse effects of anticholinergic antiparkinsonian drugs in tardive dyskinesia. Neuropsychobiology 6:109-120; 1980.
5. Cousins, M. S.; Sokolowski, J. D.; Salamone, J. D. Different effects of nucleus accumbens and ventrolateral striatal dopamine depletions on instrumental response selection in the rat. Pharmacol. Biochem. Behav. 46:943-951; 1993.
6. 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.
7. Gazit, H.; Silman, I.; Dudai, Y. Administration of organophosphate causes a decrease in muscarinic receptor levels in rat brain. Brain Res. 174:351-356; 1981.
8. 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.
9. Herman, Z. S.; Slomiska-Zurek, J. Central cholinergic supersensitivity after long-term atropine administration. Psychopharmacology (Berlin) 64:337-340; 1979.
10. 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.
11. 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.
12. Kelley, A. E.; Lang, C. G.; Gauthier, A. M. Induction of oral stereotypy following amphetamine microinjection into a discrete subregion of the striatum. Psychopharmocology (Berlin) 95:556-559; 1988.
13. Kuhar, M. J.; Yamamura, H. I. Localization of cholinergic muscarinic receptors in the rat brain by light microscopic radioautography. Brain Res. 110:229-243; 1976.
14. Lowry, O. H.; Rosenbrough, N. J.; Farr, A. L.; Randall, R. J. Protein measurement with the Folin phenol reagent. J. Biol. Chem. 193:265-275; 1951.
15. Majocha, R.; Baldessarini, R. J. Tolerance to an anticholinergic agent is paralleled by increased binding to muscarinic receptors in rat brain and increased behavioral response to a centrally acting cholinomimetic. Life Sci. 35:2247-2255; 1984.
16. 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.
17. McGeorge, A. J.; Faull, R. L. M. The organization of the projection from the cerebral cortex to the striatum in the rat. Neuroscience 29:503-537; 1989.
18. Nastuk, M. A.; Graybiel, A. M. Patterns of muscarinic cholinergic binding in the striatum and their relation to dopamine islands and striosomes. J. Comp. Neurol. 237:176-194; 1985.
19. Nastuk, M. A.; Graybiel, A. M. Autoradiographic localization and biochemical characteristics of M_1 and M_2 muscarinic binding sites in the striatum of the cat, monkey and human. J. Neurosci. 8:1052-1062; 1988.
20. 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.
21. 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.
22. Rupniak, N. M. J.; Jenner, P.; Marsden, C. D. Acute dystonia induced by neuroleptic drugs. Psychopharmacology (Berlin) 88: 403-419; 1986.
23. Russell, R. W.; Ehlert, F. J.; Hwa, J. J. Relationship between behaviorally augmented tolerance and upregulation of muscarinic receptors in the CNS: Effects of chronic administration of scopolamine. Psychopharmacology (Berlin) 88:33-39; 1986.
24. 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 88:467-471; 1986.
25. 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.
26. Salamone, J. D.; Kurth, P.; McCullough, L. D.; Sokolowski, J. D.; Cousins, M. S. The role of brain dopamine in response initiation: Effects of haloperidol and regionally specific dopamine depletions on the local rate of instrumental responding. Brain Res. 628:218-226; 1993.
27. Salamone, J. D.; Mahan, K.; Rogers, S. Ventrolateral striatal dopamine depletions impair feeding and food handling in rats. Pharmacol. Biochem. Behav. 44:605-610; 1993.
28. 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.
29. 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.
30. Stewart, B. R.; Jenner, P.; Marsden, C. D. Pharmacological characterization of pilocarpine-induced chewing in the rat. Psychopharmacology (Berlin) 97:228-234; 1988.

31. Stewart, B. R.; Jenner, P.; Marsden, C. D. Assessment of the muscarinic receptor subtype involved in the mediation of pilocarpine-induced purposeless chewing behaviour. Psychopharmacology (Berlin) 97:228–234; 1989.
32. 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.
33. Webster, K. E. Cortico-striatal interrelations in the albino rat. J. Anat. 95:523–543; 1961.
34. Yamamura, H. L.; Snyder, S. H. Muscarinic cholinergic binding in rat brain. Proc. Natl. Acad. Sci. USA 71:1725–1729; 1974.