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Vacuous Jaw Movements Induced by Acute Reserpine and Low-Dose Apomorphine: Possible Model of Parkinsonian Tremor

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SALAMONE, J. D. AND P. BASKIN. *Vacuous jaw movements in rats induced by acute reserpine and low-dose apomorphine administration: Possible model of parkinsonian tremor.* PHARMACOL BIOCHEM BEHAV **53**(1) 179–183, 1996.— Coadministration of the monoamine-depleting agent reserpine with a low dose of apomorphine has been shown to result in high levels of vacuous jaw movements in rats. Two experiments were conducted to study the pharmacologic and motoric characteristics of the vacuous jaw movements induced by 5.0 mg/kg reserpine plus 0.1 mg/kg apomorphine. The first experiment was undertaken to determine whether the vacuous jaw movements induced by reserpine plus apomorphine could be reduced by coadministration of the muscarinic antagonist scopolamine. Injections of scopolamine produced a dose-related decrease in vacuous jaw movements induced by reserpine plus apomorphine, with the two highest doses (0.5 and 1.0 mg/kg scopolamine) producing significant differences relative to the control group that received reserpine plus apomorphine. In the second experiment, a slow-motion videotape system was used to study the temporal characteristics of the vacuous jaw movements induced by reserpine and apomorphine, and to study the effects of 1.0 mg/kg scopolamine on these movements. Most of the vacuous jaw movements shown by rats treated with reserpine and apomorphine occurred in rapid bursts of jaw movement. Analysis of the interresponse times (i.e., time between each jaw movement) showed that most of the jaw movements had a local frequency in the range of 2.86–6.67 Hz. Cotreatment with scopolamine significantly affected several measures of jaw movements. Thus, the vacuous jaw movements induced by reserpine plus apomorphine can be reversed by anticholinergic treatment, and these movements tend to occur as periodic oscillations of the lower jaw with a frequency of 3–7 Hz. Vacuous jaw movements in rats share some characteristics with parkinsonian symptoms and may represent an animal model of parkinsonian tremor.

Dopamine Striatum Acetylcholine Motor Purposeless chewing Vacuous chewing Parkinsonism Tremor

DOPAMINE (DA) antagonists have been shown to induce a variety of oral movements in rats (9,12–14,16,17,22,24,25, 29,30,33,36). One type of neuroleptic-induced movement that has frequently been reported in the literature is known as "vacuous jaw movements" [14,27,28; also known as "purposeless chewing," see (25)]. Vacuous jaw movements are characterized by rapid vertical deflections of the lower jaw that resemble chewing, but are not directed at any particular stimulus (3,4,27–30). Several studies have shown that vacuous jaw movements are induced by administration of DA antagonists (24,25,29,30). Although some research has indicated that chronic administration of DA antagonists is necessary for producing perioral movements (9,13), a large number of studies conducted under a variety of different conditions have reported that acute or subchronic administration of DA antagonists can produce vacuous jaw movements (12,16,25,26,29,30).

Additional research has demonstrated that depletion of DA can also induce or exacerbate vacuous jaw movements. Neurotoxic depletion of striatal DA enhanced neuroleptic-induced vacuous jaw movements (14). Local injections of the neurotoxic agent 6-hydroxydopamine (6-OHDA) directly into the ventrolateral striatum produced vacuous jaw movements and accentuated those induced by haloperidol (16). Administration of the monoamine-depleting agent reserpine can induce oral activities including vacuous jaw movements (4,22,30). It was recently reported that acute administration of 5.0 mg/kg reserpine could induce vacuous jaw movements in three different age groups of rats (30). Acute injections of reserpine

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were shown to induce vacuous jaw movements in a dose-related manner, with significant effects at 2.5 and 5.0 mg/kg (4). The vacuous jaw movements induced by 5.0 mg/kg reserpine were reduced by coadministration of high doses (0.5–1.0 mg/kg) of the DA agonist apomorphine (4). A low dose of apomorphine (0.1 mg/kg), which was thought to act presynaptically to decrease DA release or reduce DA synthesis (7,11,35), actually enhanced vacuous jaw movements induced by reserpine (4). This combined administration of reserpine plus the low dose of apomorphine produced very high levels of vacuous jaw movements, which were substantially greater than the magnitude of the effect typically produced by other DA-related treatments such as haloperidol, reserpine, or 6-OHDA (4,16,29). Thus, the coadministration of reserpine and a low dose of apomorphine appears to be a useful model system for obtaining high levels of vacuous jaw movements in rats.

The present studies were designed to investigate further the vacuous jaw movements induced by acute administration of reserpine plus apomorphine. In the first experiment, different doses of scopolamine (0.25, 0.5, and 1.0 mg/kg) were coadministered with 5.0 mg/kg reserpine and 0.1 mg/kg apomorphine to determine whether muscarinic antagonism reversed the effects of reserpine and apomomorphine on vacuous jaw movements. This first experiment was undertaken because several reports from both the basic and clinical literatures indicate that DA and acetylcholine interact in the regulation of movement (5,8,18,20,21,23,24,29). In the second experiment, a slow-motion videotape system was used to study the temporal characteristics of the vacuous jaw movements induced by reserpine and apomorphine, and to study the effects of 1.0 mg/kg scopolamine on these movements. Previous work has employed automated analyses of small amplitude oral movements that resulted from chronic neuroleptic administration (9). The present work involved the direct observation of large amplitude vertical deflections of the lower jaw after acute drug treatments. This computerized analysis allowed for the determination of the temporal organization and local frequency of the jaw movements.

METHODS

Subjects

The subjects were 55 male Sprague–Dawley rats obtained from Harlan Sprague-Dawley (Indianapolis, IN). All rats were single-housed in a colony room with an ambient temperature of 72°F and a 12 L : 12 cycle (lights on at 0700 h). Standard lab chow and water were available ad lib. Animals were maintained in the colony room until the average weights at the start of the experiment were 400–500 g.

Drugs

The drugs used in these experiments were obtained from Sigma Chemical Company (St. Louis, MO). Reserpine was dissolved in a warm 0.3% tartaric acid vehicle solution, and the IP injection volumes for reserpine were 2.0 ml/kg. Apomorphine was dissolved in a 0.1% ascorbic acid solution, and IP injections of apomorphine were in a volume of 1.0 ml/kg. Scopolamine was dissolved in 0.9% saline.

Behavioral Observation Procedures

For Experiment 1, the 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 above the surface of the table on which it rested to allow clear observation of behaviors from all angles, including from underneath. All observations were made between 1230 and 1600 h. In Experiment 1, mechanical counters were used to record the frequency of vacuous jaw movements during a 5-min observation period conducted 90–95 min postinjection of reserpine. 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 blind observer counted each individual vertical deflection of the jaw as one vacuous jaw movement response, and recorded the total number of these jaw movements 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 usually results in > 90% agreement between different observers.

In Experiment 2, the rats were put in clear Plexiglas tubes (9 cm in diameter) that restricted locomotion so that a profile of the oral region could be videotaped consistently. A video camera (Panasonic AG-180, Secaucus, NJ) was used to record the head region of a rat placed in the clear Plexiglas tube, and each rat was recorded for a 5-min period. After the tape was recorded, a blind observer played back the videotape (Panasonic AG-1730 tape player) in slow motion at one-sixth normal speed, and the session was observed for vacuous jaw movements. To avoid fatigue in the analysis of the videotaped movements, the observer broke down the 5-min observation period into five 1-min periods, and observed each 1-min period separately with a short break in between (each 1-min period = 6 min of observation at slow motion). A vacuous jaw movement was defined in the same manner described before. Each time a jaw opening occurred (defined as the point of maximal jaw opening), a blind observer pressed the space bar of the computer keyboard, and a computer program recorded various parameters of jaw movements. These parameters included the total number of vacuous jaw movements (each individual jaw opening), total number of single jaw movements (a movement that was not preceded or followed by another jaw movement within a 1.0-s interval), number of bursts of jaw movement (a burst being defined as a group of at least two jaw movements that were within 1.0 s of each other), total number of jaw movements occurring in bursts, and average burst size. In addition, the program converted the temporal parameters observed in slow motion from the videotape back into real time, and calculated the interresponse time (IRT) for each jaw movement that occurred within a burst, as defined earlier. The IRT is the reciprocal of the local rate of vacuous jaw movements. Thus, an IRT of 0.250 s represented a local frequency of 4.0 jaw movements/s (i.e., 4 Hz). The IRT for each vacuous jaw movement was then assigned to a 50-ms-wide IRT bin, so that the computer recorded the number of movements occurring within each of the following IRT bins: 0–50, 50–100, and 100–150 ms, up to 950–1000 ms, and > 1000 ms. Multiple observations of the same tape sequence demonstrated a high degree of reliability (e.g., correlations > 0.9 when compared across the IRT bins in separate observations) with this measurement system.

Experiment 1

In Experiment 1, all animals first received an IP injection of reserpine (5.0 mg/kg) 90 min before the time at which behavioral observations would begin. One hour before the onset of behavioral testing, rats received IP injections of either 1.0 ml/kg saline or 0.25, 0.5, or 1.0 mg/kg scopolamine. Ten

minutes before behavioral observations began, all rats received IP injections of 0.1 mg/kg apomorphine. Thus, all rats received both reserpine and apomorphine, and there were four treatment groups (reserpine + apomorphine + saline; reserpine + apomorphine + 0.25 mg/kg scopolamine; reserpine + apomorphine + 0.5 mg/kg scopolamine; reserpine + apomorphine + 1.0 mg/kg scopolamine; n = 10 per group). Immediately after injection of apomorphine, animals were placed in the apparatus for 10 min habituation before observation from 90–95 min after reserpine injection. Rats were observed only 10 min after apomorphine injection, because this drug has a very short duration of action. All animals were observed for the number of vacuous jaw movements shown during the 5-min observation period.

Experiment 2

In experiment 2, the slow-motion videotape system was used to characterize the temporal pattern of vacuous jaw movement activity. Rats were randomly assigned to two groups (5.0 mg/kg reserpine + 0.1 mg/kg apomorphine + saline, n = 7; 5.0 mg/kg reserpine + 0.1 mg/kg apomorphine + 1.0 mg/kg scopolamine, n = 8). The drug administration procedures used were the same as those employed in Experiment 1. The videotaped observation method described earlier was used to measure vacuous jaw movements within the 5-min observation period.

Data Analysis

We used a simple one-way analysis of variance (ANOVA) to assess the effects of drug treatments on vacuous jaw movements in Experiment 1. Significant omnibus analyses were subjected to post hoc comparisons using the Tukey multiple comparisons test (α = 0.05). Parameters of vacuous jaw movements obtained from the videotaped observation system in Experiment 2 were analyzed using Student's t-test.

RESULTS

Experiment 1

A dose-response curve depicting the effects of scopolamine treatment on the vacuous jaw movements induced by 5.0 mg/kg reserpine plus 0.1 mg/kg apomorphine is presented in Fig. 1. Injections of reserpine plus apomorphine resulted in a robust vacuous jaw movement response, and nine of 10 rats that received reserpine, apomorphine, and saline showed more than 25 jaw movements during the observation period. There was a significant overall effect of drug treatment on vacuous jaw movements [$F(3, 36) = 4.2, p < 0.05$]. Post hoc analysis of these data revealed that treatment with either 0.5 or 1.0 mg/kg scopolamine in combination with reserpine plus apomorphine significantly decreased vacuous jaw movements relative to control rats that received reserpine, apomorphine, and saline. No significant effects were observed for 0.25 mg/kg scopolamine treatment compared to controls.

Experiment 2

Table 1 summarizes the results of Experiment 2. Administration of scopolamine significantly reduced the total number of chewing movements (t = 2.53, df = 13, $p < 0.05$), number of single chewing movements (t = 3.27, df = 13, $p < 0.05$), number of bursts (t = 2.45, df = 13, $p < 0.05$), and number of chewing movements occurring in bursts (t = 2.26, df = 13, $p < 0.05$). Figure 2 shows the number of IRTs that occurred within each of the time bins between 0 and 50 ms and 950 and 1000 ms. For rats treated with reserpine plus apomorphine, most of the IRTs were in the range of 150–350 ms, which corresponds to a local frequency of 2.86–6.67 Hz. The peak IRT bin for rats treated with reserpine plus apomorphine was 200–250 ms, which represents the 4–5 Hz frequency range. Because the total number of jaw movements was substantially reduced by coadministration of scopolamine, it is not clear whether scopolamine treatment altered the local freqency of jaw movements. One of the scopolamine-treated rats did show a substantial number of jaw movements within bursts. This rat had a peak IRT in the range of 200–250 ms, which is similar to the local frequency shown by rats treated with reserpine plus apomorphine.

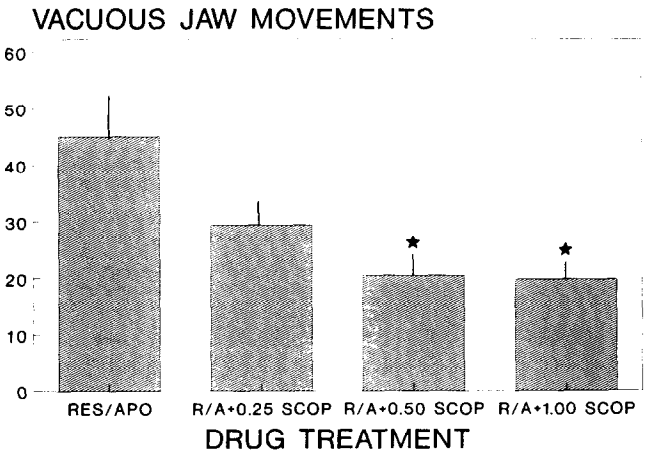

FIG. 1. Results of Experiment 1. Mean (± SEM) vacuous jaw movements after treatment with 5.0 mg/kg reserpine plus 0.1 mg/kg apomorphine and 1.0 ml/kg saline (RES/APO), and reserpine plus apomorphine (R/A) coadministered with 0.25, 0.5, and 1.0 mg/kg scopolamine (SCOP). *Different from reserpine plus apomorphine plus saline, $p < 0.05$)

DISCUSSION

The present experiments indicate that vacuous jaw movements induced by coadministration of 5.0 mg/kg reserpine plus 0.1 mg/kg apomorphine can be reduced by injections of the muscarinic antagonist scopolamine. These results are consistent with the acetylcholine–DA interactions that have been demonstrated in several studies of vacuous jaw move-

TABLE 1

EFFECTS OF DRUG TREATMENTS ON VARIOUS PARAMETERS OF VACUOUS JAW MOVEMENTS OBSERVED IN EXPERIMENT 2

	Reserpine/ Apomorphine [Mean (SEM)]	Reserpine/Apomorphine and 1.0 mg/kg Scopolamine [Mean (SEM)]
Total jaw movements	29.7 (9.7)	5.0 (2.0)*
Single jaw movements	8.0 (1.7)	2.1 (0.5)*
Number of bursts	6.7 (2.2)	1.0 (0.6)*
Movements in bursts	21.7 (8.2)	2.9 (1.8)*

*$p < 0.05$, Student's t-test, different from reserpine plus apomorphine.

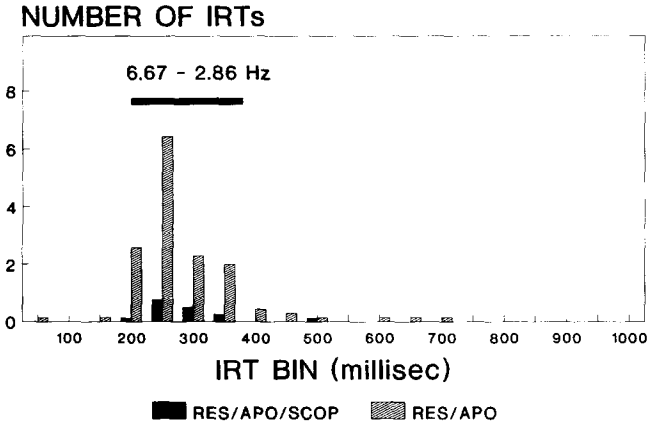

FIG. 2. Mean number of interresponse times (IRTs) within each IRT bin for those vacuous jaw movements that occurred within bursts. Rats were treated either with 5.0 mg/kg reserpine plus 0.1 mg/kg apomorphine and 1.0 mg/kg scopolamine (RES/APO/SCOP), or were treated with reserpine plus apomorphine (RES/APO). Each IRT bin represents a 50-ms time window (0–50, 50–100, and 100–150 ms, up to 950–1000 ms). The number shown on the x-axis is the highest value of the time window for alternate IRT bins. Bar indicates the IRT bins ranging from 150–350 ms, which corresponds to a local frequency of 6.67–2.86 Hz.

ments. Previous work has shown that vacuous jaw movements can be induced by DA antagonists (12,16,24–26,29,30) and cholinomimetics (3,18,24,25,27,28). The vacuous jaw movements induced by chronic administration of haloperidol were suppressed by coadministration of scopolamine or atropine (24). Vacuous jaw movements that were induced by subchronic administration of haloperidol were reduced by repeated injections of scopolamine, and rebound increases in jaw movements were observed upon withdrawal of scopolamine (29). Pilocarpine-induced vacuous jaw movements were reduced by administration of the DA agonist apomorphine (31). Thus, several studies have shown that vacuous jaw movements can be induced by DA hypofunction or muscarinic hyperfunction, and that these effects can be reversed by dopaminergic stimulation or cholinergic blockade (3,4,27–30,31).

The precise neurochemical mechanisms that lead to the generation of vacuous jaw movements are poorly understood. It is unclear whether the rhythmic neuronal activity that underlies vacuous jaw movements is produced directly by interference with striatal DA, or whether DA depletions exert their effects by altering other neurotransmitter systems. One possibility is that DA antagonists or DA depletions lead to an increase in striatal acetylcholine release (2,6), and that this increased cholinergic function generates the conditions that lead to the production of vacuous jaw movements. Such a suggestion is consistent with previous studies indicating that local infusion of cholinomimetic drugs into the ventrolateral neostriatum can produce vacuous jaw movements (18,27), and also is consistent with the ability of muscarinic antagonists to reduce the vacuous jaw movements induced by haloperidol or reserpine [24,29; see also the present results]. Although considerable evidence indicates that DA and acetylcholine are involved in the production of vacuous jaw movements, other studies also have implicated serotonin (19,32).

Experiment 2 demonstrated that reserpine plus apomorphine treatment produced vacuous jaw movements that generally occurred in bursts. Several previous studies have noted that pilocarpine- and haloperidol-induced vacuous jaw movements tend to occur in rapid, repetitive bursts of movement (18,24,25,27–29). The present study extends this work, and offers a detailed description of the temporal characteristics of the vacuous jaw movements induced by reserpine plus low-dose apomorphine treatment. In Experiment 2, the most common interresponse time was in the range of 200–250 ms, which indicates a local frequency of 4–5 Hz. In addition, the vast majority of responses within bursts had a local frequency of 2.86–6.67 Hz. Coadministration of scopolamine affected several parameters of vacuous jaw movements, including the number of jaw movements occurring in bursts, number of bursts, and number of single jaw movements. The scopolamine-treated animals that did show some bursts of vacuous jaw movements tended to have local frequencies similar to those animals that received reserpine plus apomorphine alone.

It has been suggested that perioral movements induced by neuroleptic drugs could serve as a rat model of various movement disorders, including tardive dyskinesia (9) and acute dystonia (26). In addition, it has been observed that vacuous jaw movements share some characteristics with parkinsonian symptoms (3,16,27,29). The present results provide further support for the notion that vacuous jaw movements induced by reserpine plus a low dose of apomorphine could be a useful rat model of parkinsonism. Both vacuous jaw movements and parkinsonian symptoms are produced or exacerbated by DA antagonists, DA depletions, and cholinomimetic drugs (3,4,8, 18,20,21,23–25). Striatal DA depletions have been shown to enhance the vacuous jaw movements induced by haloperidol (14,16), and DA depletions in the ventrolateral neostriatum were shown to induce vacuous jaw movements (16). Evidence indicates that vacuous jaw movements can be reduced by antiparkinsonian drug treatments. Doses of the DA agonist apomorphine that are known to stimulate postsynaptic DA receptors were shown to reduce the vacuous jaw movements induced by pilocarpine (31) and reserpine (4). Muscarinic antagonists have well-documented antiparkinsonian activity (20, 21), and several studies including the present results have indicated that vacuous jaw movements can be reduced by administration of muscarinic antagonists (24,27,29).

The vacuous jaw movements induced by reserpine and low-dose apomorphine treatment could represent a rat model of parkinsonian tremor. According to Findley and Gresty (10), a tremor is defined as a "periodic oscillation of a body member." The local frequency of parkinsonian tremor is typically 3–7 Hz (1), which is the same frequency observed for vacuous jaw movements induced by reserpine plus the low dose of apomorphine (Experiment 2). Although parkinsonian tremor in humans usually involves the hands, there are several reports of parkinsonian tremor including the lip or jaw (1,15,34). Indeed, it has been reported that parkinsonian jaw tremor consists of an "up and down" movement of the jaw (1). Thus, several lines of evidence indicate that vacuous jaw movements in rats share pharmacologic and motor characteristics with human parkinsonian tremor. Perhaps future studies could investigate the feasibility of using vacuous jaw movements in rats as a model for assessing novel drug treatments for idiopathic and neuroleptic-induced parkinsonian tremor.

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