Psychopharmacology (1993) 111:99–105

Psychopharmacology

Vacuous jaw movements induced by sub-chronic administration of haloperidol: interactions with scopolamine

Rhea E. Steinpreis, Patricia Baskin, and John D. Salamone

Department of Psychology, University of Connecticut, Storrs, CT 06269-1020, USA

Received October 9, 1991 / Final version October 7, 1992

Abstract. The present series of experiments was conducted to investigate the vacuous jaw movements induced by sub-chronic administration of haloperidol (HP). In the first experiment, daily injection of 0.4 mg/kg HP for 10 days increased vacuous jaw movements and decreased rearing behavior. The second and third experiments investigated the interaction between the effects of HP and the anticholinergic drug scopolamine. Co-administration of 0.5 mg/kg scopolamine with 0.4 mg/kg HP for 9 days reduced vacuous jaw movements and increased rearing responses relative to rats that received HP alone. Co-administration of HP with 0.25 mg/kg scopolamine for 9 days increased rearing relative to rats that received HP alone, but there was no effect of the lower dose of scopolamine on vacuous jaw movements. Administration of 0.5 mg/kg scopolamine plus 0.4 mg/kg HP on days 11–14 to rats that had received HP alone for 10 days reversed the effect of HP on rearing, but not on vacuous jaw movements. Rats that had received HP plus scopolamine for 10 days showed dramatic increases in vacuous jaw movements when scopolamine was withdrawn. Because vacuous jaw movements are produced within the first few days of administration, reduced by administration of scopolamine, and exacerbated by withdrawal of scopolamine, the pharmacological characteristics of these movements do not appear to bear a close relation to those of tardive dyskinesia in humans. The present results are consistent with the hypothesis that vacuous jaw movements in rats share some characteristics with Parkinsonian symptoms.

Key words: Neuroleptic – Extrapyramidal motor system – Dopamine – Acetylcholine – Haloperidol – Scopolamine – Tardive dyskinesia – Parkinsonism

Administration of DA antagonists or cholinomimetic drugs induces a syndrome of orofacial movements in rats (Iversen et al. 1980; Rupniak et al. 1983, 1985; Salamone et al. 1986, 1990 Ellison et al. 1987). The most frequent movement produced is a rapid chewing-like movement that is not directed at any particular stimulus (Rupniak et al. 1983; Salamone et al. 1986), and which is referred to in the literature as "vacuous" chewing or vacuous jaw movements (Jicha and Salamone 1991). The jaw movements produced by DA antagonists and cholinomimetics typically occur in bursts, with a high frequency of movement within each burst (Rupniak et al. 1983; Salamone et al. 1986, 1990; Kelley et al. 1989). The pharmacology of vacuous jaw movements involves an interaction between DA and acetylcholine (ACh) systems similar to that implicated in other aspects of motor control, including Parkinsonism and other movement disorders (Duvoisin 1967; Arnfred and Randrup 1968; Cools et al. 1975; Rupniak et al. 1986). Vacuous jaw movements induced by chronic administration of DA antagonists were attenuated by anticholinergic drugs and exacerbated by cholinomimetic drugs (Rupniak et al. 1983, 1985).

Most studies of neuroleptic-induced oral movements or vacuous chewing have involved the use of chronic neuroleptic treatment (Iversen et al. 1980; Rupniak et al. 1983; Waddington et al. 1983; Johansson et al. 1986; Ellison et al. 1987; Waddington and Molloy 1987; See et al. 1988; Ellison and See 1989; Stoessl et al. 1989). Nobrega et al. (1989) suggested that neuroleptic-induced changes in oral behavior are usually only seen with chronic administration. Ellison et al. (1987) used a video system to study vertical jaw movements in rats, and reported that acute administration of haloperidol (HP) did not induce jaw movements. Gunne et al. (1986) observed that several antipsychotic drugs failed to produce spontaneous chewing movements in the first few hours after acute administration. However, in some studies vacuous jaw movements have been reported to occur after acute or sub-chronic administration of neuroleptics (Glassman and Glassman 1980; Rosengarten et al. 1983; Rupniak et al. 1985, 1986). In discussing the possible relation between vacuous chewing and tardive dyskinesia, Waddington (1990, p 439) has noted that "the greatest problems of interpretation are provided by those studies

Correspondence to: J.D. Salamone

which have reported the emergence of orofacial movements very early in the course of neuroleptic treatment".

The present studies were undertaken to investigate further the effects of acute and sub-chronic administration of HP on vacuous jaw movements (see below for description of movements). The first experiment examined the emergence of HP-induced jaw movements within the first 10 days of repeated administration. In the second experiment, the interaction between acute HP and the muscarinic antagonist scopolamine was studied in order to determine if repeated administration of scopolamine could reverse the effects of HP on vacuous jaw movements produced by sub-chronic HP. The third experiment investigated the effects of withdrawal of scopolamine from rats that had received HP and scopolamine. The fourth and fifth experiments examined the effects of scopolamine alone and withdrawal from repeated scopolamine injection. There are several types of orofacial movement in rats that can occur with administration of DA antagonists or cholinomimetics (Rupniak et al. 1983; Salamone et al. 1986, 1990; see review by Waddington 1990). In the present study we restricted ourselves to vertical deflection of the lower jaw.

Materials and methods

Subjects. A total of 88 male Sprague-Dawley rats weighing between 350 and 450 gm at the start of each experiment were obtained from Harlan Sprague Dawley. All rats were housed individually in a colony room with a constant temperature of 72°F and a 12-h light/dark cycle (lights on at 0700 hours).

Drugs. All drugs used in these experiments were obtained from Sigma Chemical Company, and were dissolved in a 0.3% tartaric acid solution.

Behavioral observations. These experiments used a Plexiglas observation chamber (12″ × 12″ × 12″). The observation chambers were elevated 10 inches from the observation table to allow for a view from underneath as well as from the sides. For all experiments electromechanical counters were used to record the frequency of vacuous jaw movements and rearing. Vacuous jaw movements were defined as a rapid vertical movement of the lower jaw that resembles chewing, but was not directed at any stimulus (measured as each individual vertical deflection of the jaw). This movement is different from "gaping", which is slower and involves a much wider opening of the mouth (Rupniak et al. 1983; Salamone et al. 1986, 1990). There is no general agreement about the definition of all neuroleptic-induced orofacial movements in rats, and several types of movements have been reported (see Waddington 1990). The present studies were restricted to vertical jaw movements because these movements were readily observable, and inter-rater reliability greater than 90% could be achieved in observations of these movements. Several other studies have employed similar definitions of "vacuous chewing" movements in rats (Salamone et al. 1986, 1990). Rearing was defined as the rat elevating the front part of its body, yet not being engaged in grooming behavior (measured as each individual rear). For experiments 2 and 3 the counters were connected to an event recorder, which produced a record of the temporal sequence of the behaviors.

General procedure and experiments. Prior to the start of each experiment, all rats received 2 days of habituation in the observation chamber for 30 min. All injections were intraperitoneal (IP), and were made between 1300 hours and 1700 hours. For all experiments, rats were observed in 10-min sessions 50–60 min after injection. The observer was unaware of the particular experimental condition of the rat being observed.

In experiment 1, rats received daily injections over a 10-day period of either 0.4 mg/kg HP ($n = 8$) or 0.1 mg/kg 0.3% tartaric acid vehicle solution ($n = 8$). During the 10-min observation period, an observer blind to the experimental conditions observed and recorded vacuous jaw movements and rearing. In experiment 2, rats received daily injections over a 9-day period of 0.4 mg/kg HP (group HP; $n = 16$), 0.4 mg/kg HP with 0.25 mg/kg scopolamine (group LOWSCOP; $n = 16$), or 0.4 mg/kg HP with 0.5 mg/kg scopolamine (group HIGHSCOP; $n = 16$). Behaviors were recorded as described above, with the inclusion of an event recording. All rats received their respective drug treatments on day 10, but no observations were conducted. Then these same rats were used for experiment 3, which represents a continuation of various drug treatments into the period 11–14 days after initial treatment. There were six treatment groups in experiment 3 ($n = 8$ per group), in which each of the three groups from experiment 2 were split into two groups (see Table 1). Group HP received 14 consecutive days of 0.4 mg/kg HP. Group LATESCOP received 0.4 haloperidol for days 1–10, with coadministration of 0.5 mg/kg scopolamine with HP on days 11–14. Group LOWSCOP received 14 consecutive days of coadministration of 0.4 mg/kg haloperidol with 0.25 mg/kg scopolamine. Rats in group LOWOFF ($n = 8$) were co-administered 0.4 mg/kg HP with 0.25 mg/kg scopolamine for days 1–10, but on days 11–14 received 0.4 mg/kg HP alone. Group HIGHSCOP received 14 straight days of coadministration of 0.4 mg/kg haloperidol with 0.5 mg/kg scopolamine. Rats in group HIGHOFF ($n = 8$) were co-administered 0.4 mg/kg HP with 0.5 mg/kg scopolamine for days 1–10, but on days 11–14 received 0.4 mg/kg HP alone. In experiment 4, rats received daily injections over a 9-day period of either vehicle ($n = 8$) or 0.5 mg/kg scopolamine ($n = 16$). All rats received their respective drug treatments on day 10, but no observations were conducted. Then these same rats were used for experiment 5, which represents a continuation of various drug treatments into the period 11–14 days after initial treatment. There were three treatment groups in experiment 5 ($n = 8$ per group). The vehicle group continued to receive vehicle, but the scopolamine group from experiment 4 was split into two groups, one of which continued on scopolamine while the other was switched to vehicle.

Data analyses. All data from these studies were log transformed and analyzed using analysis of variance (ANOVA). Experiment 1 was analyzed using factorial ANOVA with repeated measures on the days variable. In experiments 2 and 4, total number of vacuous jaw

Table 1. Drug treatments used in experiment 3

Group	Treatment days 1–10	Treatment days 11–14
HP	0.4 mg/kg HP	0.4 mg/kg HP
LATESCOP	0.4 mg/kg HP	HP plus 0.5 mg/kg scop
LOWSCOP	HP plus 0.25 mg/kg scop	HP plus 0.25 mg/kg scop
LOWOFF	HP plus 0.25 mg/kg scop	0.4 mg/kg HP
HIGHSCOP	HP plus 0.5 mg/kg scop	HP plus 0.5 mg/kg scop
HIGHOFF	HP plus 0.5 mg/kg scop	0.4 mg/kg HP

movements and total number of rears were collapsed into three 3-day blocks, and analyzed with factorial ANOVA with repeated measures on the days variable. Planned comparisons (Keppel 1982, pp 106–124) were conducted between each group that received scopolamine and the rats that received HP alone, using the error term from the overall ANOVA. In experiments 3 and 5, total jaw movements and total rears from the 11–14 day period were collapsed into one 4-day block and analyzed with simple ANOVA. In experiment 3 five planned comparisons were conducted (HP versus LATESCOP, LOWSCOP versus LOWOFF, HIGHSCOP versus HIGHOFF, HP versus LOWOFF, and HP versus HIGHOFF). In all experiments, the number of planned comparisons was restricted to the number of groups minus one (see Keppel 1982).

For experiments 2 and 3, four additional measures of vacuous jaw movement (other than total number) were obtained by examination of the event records: 1) the number of single jaw movements that were not within 2 s of another jaw movement; 2) the total number of bursts of vacuous jaw movements, with a "burst" being defined as a period of successive jaw movements that were within 2 s of each other; 3) the average burst size of the jaw movements, which was calculated by dividing the total number of vacuous jaw movements within bursts by the number of bursts. Data for these parameters were calculated for the whole 1–9-day period in experiment 2, and the whole 11–14-day period for experiment 3, and simple ANOVA was performed on each of these data sets.

Results

Experiment 1: effects of sub-chronic haloperidol on vacuous jaw movements

The effect of HP on vacuous jaw movements are presented in Fig. 1. ANOVA revealed a significant effect for drug treatment on vacuous jaw movements [$F(1, 14) = 110.9$, $P < 0.001$]. There was no significant effect for days [$F(9, 126) = 1.15$, $P > 0.05$] and there was no significant interaction [$F(9, 126) = 1.7$, $P > 0.05$]. HP produced a significant decrease in rearing [$F(1, 14) = 74.6$, $P < 0.001$]. The effect of HP on rearing is presented in Fig. 2. There was a significant effect of rearing across days [$F(9, 126) = 2.33$, $P < 0.05$], but the day X drug treatment interaction was not significant [$F(9, 126) = 1.83$, $P < 0.05$].

Experiment 2: effects of co-administration of scopolamine on haloperidol-induced vacuous jaw movements

The raw data for the effects of drug on the total number of chews combined in 3-day intervals is presented in Fig. 3. ANOVA revealed a significant effect for drug treatment [$F(2, 45) = 4.53$, $P < 0.05$] and a significant effect for days [$F(2, 90) = 6.96$, $P < 0.01$]. The interaction was not significant [$F(4, 90) = 1.45$, $P > 0.1$]. Planned comparisons indicated that the high dose of scopolamine significantly reduced vacuous jaw movements [$F(1, 45 = 8.28$, $P < 0.01$] but that the low dose did not [$F(1, 45 = 0.45$, n.s.]. In addition, planned comparisons revealed that the overall number of jaw movements across all groups was significantly lower in the 1–3-day period than it was in the 4–6-day period [$F(1, 90) = 9.8$, $P < 0.05$] and in the 7–9-day period [$F(1, 90) = 11.03$, $P < 0.01$].

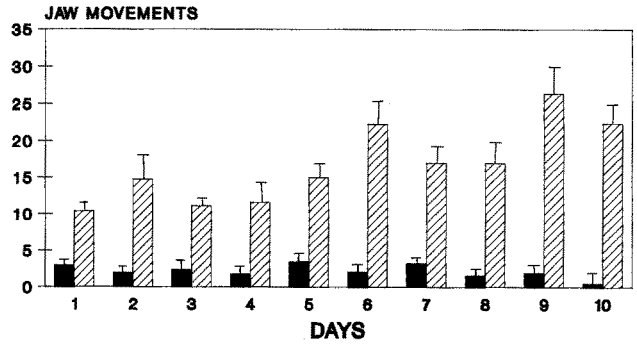

Fig. 1. Mean (± SEM) total number of vacuous jaw movements after injection of 0.4 mg/kg HP or vehicle for 10 days. (■) Saline; (▨) 0.4 HP

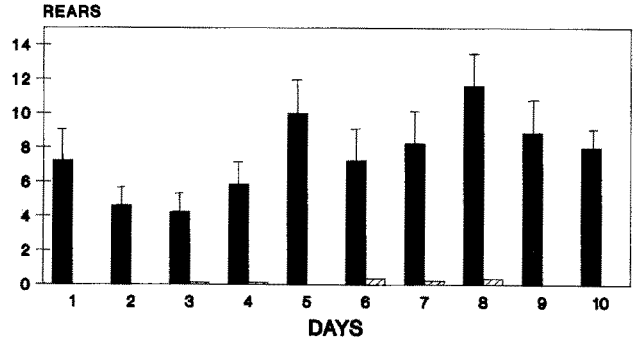

Fig. 2. Mean (± SEM) total number of rearing responses after injection of 0.4 mg/kg HP or vehicle for 10 days. (■) Saline; (▨) 0.4 HP

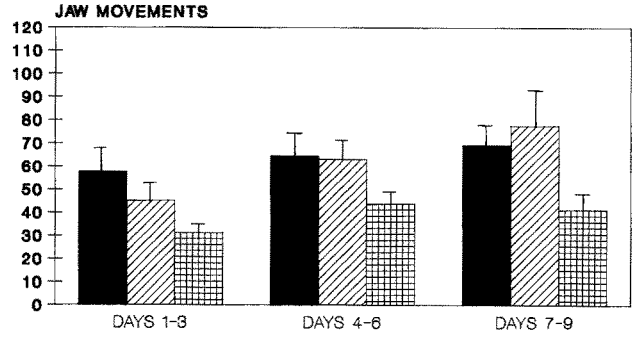

Fig. 3. Mean (± SEM) total number of vacuous jaw movements after injection of 0.4 mg/kg HP, 0.4 mg/kg HP plus 0.25 mg/kg scopolamine, and 0.4 mg/kg HP plus 0.5 mg/kg scopolamine for 9 days (in three 3-day blocks). (■) HP; (▨) LOWSCOP; (▦) HIGHSCOP

The results of analyses of various parameters of vacuous jaw movement are shown in Table 2, which represents data from the entire 9-day period. There was no significant effect of scopolamine on number of single jaw movements [$F(2, 45) = 1.45$, n.s.]. Analyses of data on average burst size indicates that there was an overall treatment effect [$F(2, 45) = 7.4$, $P < 0.05$]. Planned comparisons revealed that the higher dose of scopolamine did not affect average burst size, but rats that received

Table 2. Analysis of the pattern of vacuous jaw movements from the event records in experiment 2

Group	Pattern type			
		Single jaw movements	Average burst size	Number of bursts
HP	Mean	55.9	2.7	49.2
	(SEM)	(6.2)	(0.09)	(6.8)
LOWSCOP	Mean	64.4	4.6	26.0
	(SEM)	(8.1)	(0.54)	(3.4)
HIGHSCOP	Mean	49.4	3.5	18.9
	(SEM)	(3.8)	(0.20)	(2.6)

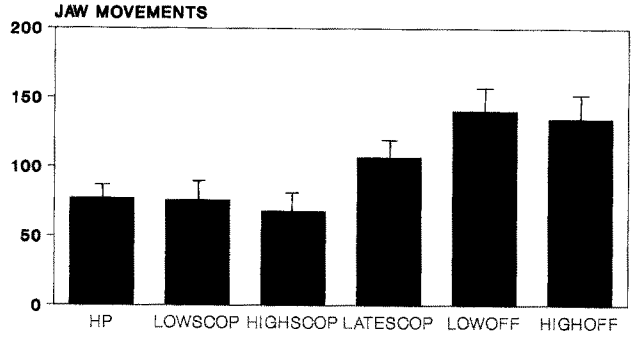

Fig. 5. Mean (± SEM) total number of vacuous jaw movements observed in days 11–14 (experiment 3) for all six groups

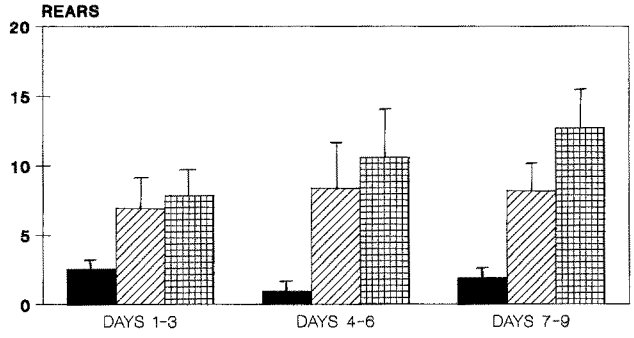

Fig. 4. Mean (± SEM) total number of rearing responses after injection of 0.4 mg/kg HP, 0.4 mg/kg HP plus 0.25 mg/kg scopolamine, and 0.4 mg/kg HP plus 0.5 mg/kg scopolamine for 9 days (in three 3-day blocks). (■) HP; (▨) LOWSCOP; (▦) HIGHSCOP

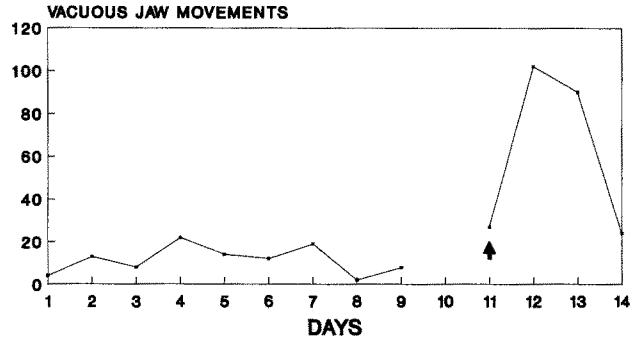

Fig. 6. Vacuous chewing data from an individual rat that received HP plus 0.5 mg/kg scopolamine on days 1–10 (experiment 2), and received HP alone on days 11–14 in experiment 3 (*arrow*). (-●-) Rat 121

0.25 mg/kg scopolamine showed a significant increase in average burst size compared to rats treated with HP alone [$F(1, 45) = 14.58$, $P < 0.01$]. Scopolamine significantly reduced the total number of bursts of jaw movement [$F(2, 45) = 11.8$, $P < 0.01$].

When rears were combined into 3-day blocks (Fig. 4), ANOVA revealed a significant overall difference between drug treatments for rearing [$F(2, 45) = 12.93$, $P < 0.01$], but not across days [$F(2, 90) = 1.34$, $P < 0.01$], and no significant interaction. Planned comparisons revealed that there was a significant difference between the HP and HIGHSCOP groups [$F(1, 45) = 23.7$, $P < 0.01$] and a significant difference between the HP and LOWSCOP groups [$F(1, 45 = 13.8$, $P < 0.01$].

Experiment 3: effects of delayed introduction and withdrawal of scopolamine

For all six treatment groups, vacuous jaw movements were collapsed across subjects for days 11 through 14. These data on total number of jaw movements are presented in Fig. 5. ANOVA revealed a significant overall effect for drug treatment [$F(5, 47) = 4.48$, $P < 0.01$]. Planned comparisons indicated that there was no significant difference between the HP group and the LATESCOP group [$F(1, 47) = 1.66$, $P > 0.05$]. There were significant differences between LOWSCOP AND LOWOFF [$F(1, 47) = 7.76$, $P < 0.05$], HIGHSCOP and HIGHOFF [$F(1, 47) = 12.03$, $P < 0.01$], HP and LOWOFF [$F(1, 47 = 7.27$, $P < 0.05$] and HP and HIGHOFF [$F(1, 47) = 6.32$, $P < 0.01$]. These results demonstrate that withdrawal of scopolamine increased vacuous jaw movements in HP-treated rats. Figure 6 depicts data from an individual rat that received HP plus 0.5 mg/kg scopolamine on days 1–10, and received HP alone on days 11–14. The results of analyses of various parameters of vacuous jaw movement in experiment 3 are shown in Table 3, which represents data from the entire 11–14 day period. There was no significant effect of drug treatment on number of single jaw movements [$F(5, 42) = 1.04$, n.s.]. Analyses of data on average burst size indicates that there was also no treatment effect [$F(5, 42) = 1.6$, n.s.]. However, there was a significant effect of treatment on number of bursts of jaw movement [$F(5, 42 = 5.92$, $P < 0.01$]. Planned comparisons demonstrated that there were significant increases in number of bursts of jaw movements compared to the effects of HP alone in the groups that were withdrawn from the low dose of scopolamine [$F(1, 42) = 7.44$, $P < 0.01$], and withdrawal from the high dose of scopolamine [$F(1, 42) = 6.23$, $P < 0.01$].

The data for rearing was collapsed across days 11 through 14 (Fig. 7). ANOVA revealed a significant effect for drug treatment on rearing [$F(5, 47) = 4.64$, $P < 0.01$]. A planned comparison indicated that the LATESCOP group had significantly more rears than the HP group

Table 3. Analysis of the pattern of vacuous jaw movements from the event records in experiment 3

Group	Pattern type			
Group		Single jaw movements	Average burst size	Number of bursts
HP	Mean	32.3	2.5	17.6
	(SEM)	(6.6)	(0.09)	(2.7)
LOWSCOP	Mean	32.3	3.0	14.0
	(SEM)	(3.1)	(0.27)	(1.6)
HIGHSCOP	Mean	25.4	3.3	12.1
	(SEM)	(3.5)	(0.45)	(2.1)
LOWOFF	Mean	39.9	3.3	29.4
	(SEM)	(6.9)	(0.27)	(3.6)
HIGHOFF	Mean	38.2	3.4	28.4
	(SEM)	(3.6)	(0.32)	(4.6)
LATESCOP	Mean	36.2	4.0	16.2
	(SEM)	(5.5)	((0.64)	(2.6)

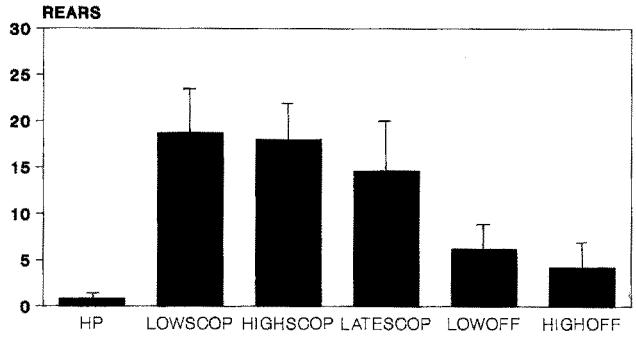

Fig. 7. Mean (± SEM) total number of rearing responses observed in days 11–14 (experiment 3) for all six groups

$[F(1, 47) = 9.4, P < 0.01]$. Planned comparisons also revealed a significant difference in rearing between the HIGHSCOP group and the HIGHOFF group $[F(1, 47) = 8.36, P < 0.01]$, but no significant difference between the LOWSCOP group and the LOWOFF group $[F(2.57, P > 0.05]$, indicating that only removal of the higher dose of scopolamine causes a decrease in rearing. Planned comparisons indicated that there was no difference between the HP group and either the LOWOFF group $[F(1, 47) = 3.51, P > 0.05]$ or the HIGHOFF group $[F(1, 47) = 0.99, P > 0.05]$, indicating that removal of either dose of scopolamine did not produce a greater decrease in rearing than HP alone. In experiment 3, there was no significant correlation between rearing and vacuous jaw movements ($r = -0.16$, $df = 46$, n.s.).

Experiments 4 and 5: effects of repeated scopolamine and withdrawal from scopolamine

The mean (± SEM) number of vacuous jaw movements in experiment 4 were as follows: days 1– 3, vehicle 4.3 (± 1.3), 0.5 mg/kg scopolamine 14.4 (± 2.8); days 4–6, vehicle 7.3 (± 3.3), 0.5 mg/kg scopolamine 14.6 (± 2.6); days 7–9, vehicle 11.1 (± 2.4), 0.5 mg/kg scopolamine 11.7 (± 2.4). There was no significant effect of drug treatment on vacuous jaw movements $[F(1, 22) = 3.01$, n.s.], no significant effect of days $[F(2, 44) = 0.43$, n.s.] and no significant drug × day interaction $[F(2, 44) = 2.3$, n.s.]. The mean (± SEM) number of vacuous jaw movements for days 11–14 in experiment 5 were as follows: vehicle 15.75 (± 2.9), 0.5 mg/kg scopolamine 16.6 (± 3.2), scopolamine withdrawn 19.6 (± 4.4). There was no significant effect of drug treatment on vacuous jaw movements $[F(2, 21) = 0.32$, n.s.]. In addition, there was no significant difference between groups if the analysis was restricted to day 11, which was the day of transition from scopolamine to vehicle. The mean (± SEM) number of vacuous jaw movements for day 11 were as follows: vehicle 2.6 (± 1.0), 0.5 mg/kg scopolamine 2.0 (± 0.7), scopolamine withdrawn 3.6 (± 0.9) $[F(2, 21) = 0.9$, n.s.]. Throughout experiments 4 and 5, scopolamine increased rearing behavior (data not shown).

Discussion

HP produced vacuous jaw movements within the first few days of administration. In most rats, these vacuous jaw movements were evident with the first administration of HP. These results are consistent with other reports showing that acute or sub-chronic administration of a neuroleptic can increase vacuous jaw movements (Glassman and Glassman 1980; Rosengarten et al. 1983; Rupniak et al. 1985, 1986; Jicha and Salamone 1991). However, the present findings remain controversial in view of the fact that some studies have failed to observe vacuous jaw movements in the first few hours after acute neuroleptic injection (Gunne et al. 1986; Ellison et al. 1987). Gunne et al. (1986) reported that daily injections of 1.0 mg/kg HP for 3 days actually decreased vacuous jaw movements in the first few hours after injection. The reasons for these apparent discrepancies in the literature remain unclear, and it has been suggested that the test apparatus is an important variable in these studies (Ellison 1991; Levy et al. 1987).

Experiment 2 demonstrated that repeated administration of 0.5 mg/kg scopolamine reduced the vacuous jaw movements induced by HP within the first few days of administration, which is consistent with previous reports that scopolamine reduced the oral movements induced by chronic administration of HP (Rupniak et al. 1983). In the present study, it was observed that scopolamine reduced vacuous jaw movements by decreasing the number of bursts of jaw movements, rather than affecting single movements or decreasing the average number of movements per burst. In addition, experiment 3 demonstrated that withdrawal from repeated administration of scopolamine produced a "rebound" effect, with these rats manifesting the highest levels of vacuous jaw movements in the entire study. The shift from HP plus scopolamine to HP alone was characterized by an increase in the number of bursts of jaw movements. It is possible that repeated administration of scopolamine led to cholinergic receptor supersensitivity, which facilitated jaw movements when the scopolamine was withdrawn. The results of experiment 5 indicate that withdrawal from repeated scopolamine in the absence of HP did not induce vacuous jaw

movements, which suggests that the major effect of withdrawal from repeated injection of scopolamine may be to facilitate the actions of other conditions that produce vacuous jaw movements.

The results of the third experiment indicated that daily injections of 0.5 mg/kg scopolamine after 10 days of HP administration did not reduce HP-induced vacuous jaw movements. These results indicate that scopolamine was more effective when administered at the start of neuroleptic administration, than if administered once the vacuous jaw movements had already emerged. Possibly, HP produces greater effects with repeated administration (Grace and Bunney 1986; Ljungberg 1990; see significant effect of days in experiment 2), and a higher dose of scopolamine than 0.5 mg/kg is necessary to reverse the effects of HP after several days of administration of HP. Rupniak et al. (1983) and Stoessl et al. (1989) showed that 0.5 mg/kg scopolamine reduced the vacuous chewing responses induced by chronic neuroleptics. However, in those studies HP was administered gradually via drinking water or depot injection, whereas in the present study HP was given in a single injection at the same time as the scopolamine. Possibly, the effects of HP are more difficult to reverse shortly after a large IP injection.

Scopolamine was able to increase rearing behavior in HP-treated rats, regardless of the dose used or time course of its administration. The effects of scopolamine on rearing showed a somewhat different pattern from the effects of scopolamine on vacuous jaw movements. For example, in experiment 2 the lower dose of scopolamine did not attenuate vacuous jaw movements but was successful in increasing rearing behavior. In experiment 3, even though adding the higher dose of scopolamine after 10 days of HP administration did not reduce vacuous jaw movements, it was effective in increasing rearing. In addition, rearing and vacuous jaw movements were not significantly correlated with each other in experiment 3. Other work from our laboratory has demonstrated that DA depletion in the ventrolateral striatum increases vacuous jaw movements but does not produce akinesia or reduce rearing, while DA depletions in dorsolateral striatum reduce rearing but do not produce vacuous jaw movements (Jicha and Salamone 1991). These results indicate that the effects of interference with DA systems on rearing and vacuous jaw movements are dissociable from each other, and that vacuous jaw movements are not merely an artifact of reduced motor activity (Levy et al. 1987).

Vacuous jaw movements induced by chronic neuroleptic treatment have been offered as a possible model of tardive dyskinesia (Ellison et al. 1987; Stoessl et al. 1989). There are several lines of evidence suggesting that the particular movements observed in the present study (early-onset vertical deflections of the lower jaw) do not closely resemble tardive dyskinesia. Tardive dyskinesia takes months or years to develop, whereas in experiments 1 and 2, vacuous jaw movements were present in the first few days of HP administration. In experiment 2, the higher dose of scopolamine was effective in attenuating the HP-induced vacuous jaw movements. Anticholinergic drugs have been shown to exacerbate tardive dyskinesia (Crane 1968; Klawans 1973; Burnett et al. 1980). In experiment 3 it was observed that removal of scopolamine after day 10 produced dramatic increases in vacuous jaw movements. In contrast, removal of anticholinergic drugs in humans with tardive dyskinesia actually reduces dyskinesic symptoms (Burnett et al. 1980). Yet despite the results of the present studies, it remains possible that other types of orofacial movements in rats (e.g. late onset movements, or movements shown during neuroleptic withdrawal) do have characteristics resembling tardive dyskinesia.

It has been suggested that vacuous jaw movements in rats that are induced by HP, cholinomimetics, and DA depletion share some characteristics with Parkinsonian symptoms (Salamone et al. 1990; Jicha and Salamone 1991). Parkinsonian symptoms and vacuous jaw movements are produced by DA antagonists, exacerbated by cholinomimetics, and reduced by anticholinergic drugs (Duvoisin 1967; Marsden et al. 1975; McEvoy 1983; Rupniak et al. 1983, 1985; Noring et al. 1984; Salamone et al. 1986, 1990). Pilocarpine-induced vacuous jaw movements in rats were reduced by the DA agonist apomorphine (Stewart et al. 1988). Striatal DA depletion was shown to facilitate vacuous chewing induced by HP (Gunne et al. 1982) and vacuous jaw movements were produced by depletion of DA in ventrolateral striatum (Jicha and Salamone 1991).

The neurochemical mechanisms that lead to the generation of vacuous jaw movements remain uncertain. Local injections of cholinomimetic drugs into the ventrolateral striatum induce vacuous jaw movements (Kelley et al. 1989; Salamone et al. 1990). It is possible that vacuous jaw movements can be produced by increasing cholinergic tone in the ventrolateral striatum, and that DA antagonists and DA depletion cause vacuous jaw movements because they indirectly increase ACh release (Agid et al. 1975; Guyenet et al. 1975). This suggestion is consistent with the pattern of the DA/ACh interactions shown in studies of vacuous jaw movements.

Acknowledgements. This work was supported by a grant from the University of Connecticut Research Foundation.

References

Agid Y, Guyenet P, Glowinski J, Beaujouan JC, Javoy F (1975) Inhibitory influence of the nigrostriatal dopamine system on the striatal cholinergic neurons in the rat. Brain Res 86:488–492

Arnfred T, Randrup A (1968) Cholinergic mechanism in brain inhibiting amphetamine-induced stereotyped behavior. Acta Pharmacol Toxicol 26:384–388

Burnett GB, Prange AJ, Wilson IC, Jolliff LA, Creese IC, Snyder SH (1980) Adverse effects of anticholinergic antiparkinsonian drugs in tardive dyskinesia. Neuropsychobiology 6:109–120

Cools AR, Hendriks G, Korten J (1975) The acetylcholine-dopamine balance in the basal ganglia of Rhesus monkeys and its role in dynamic, dystonic, dyskinetic epileptoid motor activities. J Nerv Trans 36:91–105

Crane GE (1968) Tardive dyskinesia in patients treated with major neuroleptics: a review of the literature. Am J Psychiatry 124:40–48

Duvoisin RC (1967) Cholinergic-anticholinergic antagonism in parkinsonism. Arch Neurol 17:124–136

Ellison G (1991) Spontaneous orofacial movements in rodents induced by long-term neuroleptic administration: a second opinion. Psychopharmacology 104:404–408

Ellison G, See RE (1989) Rats administered chronic neuroleptics develop oral movements which are similar in form to those in humans with tardive dyskinesia. Psychopharmacology 98:564–566

Ellison G, See R, Levin E, Kinney J (1987) Tremorous mouth movements in rats administered chronic neuroleptics. Psychopharmacology 92:122–126

Glassman RB, Glassman HN (1980) Oral dyskinesia in brain-damaged rats withdrawn from neuroleptic: implication for models of tardive dyskinesia. Psychopharmacology 69:19–25

Grace AA, Bunney BS (1986) Induction of depolarization block in midbrain dopamine neurons by repeated administration of haloperidol: analysis using in vivo intracellular recording. J Pharmacol Exp Ther 238:1092–1100

Gunne LM, Growden J, Glaeser B (1982) Oral dyskinesia in rats following brain lesions and neuroleptic administration. Psychopharmacology 77:134–139

Gunne LM, Andersson U, Bondesson U, Johansson P (1986) Spontaneous chewing movements in rats during acute and chronic antipsychotic drug administration. Pharmacol Biochem Behav 25:897–901

Guyenet PG, Jovoy F, Agid Y (1975) Effects of dopaminergic agonists and antagonists on the activity of the neo-striatal cholinergic system. Brain Res 84:227–244

Iversen SD, Howells RB, Hughs RP (1980) Behavioral consequences of long-term treatment with neuroleptic drugs. Adv Biochem Psychopharmacol 24:305–313

Jicha G, Salamone JD (1991) Vacuous jaw movements and feeding deficits in rats with ventrolateral striatal dopamine depletions: possible relation to Parkinsonian symptoms. J Neurosci 11:3822–3829

Johansson P, Casey DE, Gunne LM (1986) Dose-dependent increases in rat spontaneous chewing rates during long-term administration of haloperidol but not clozapine. Psychopharmacol Bull 22:1017–1019

Kelley AE, Bakshi VP, Delfs JM, Lang CG (1989) Cholinergic stimulation of the ventrolateral striatum elicits mouth movements in rats: pharmacological and regional specificity. Psychopharmacology 99:542–549

Keppel G (1982) Design and analysis: a researcher's handbook. Prentice-Hall, Englewood Cliffs, NJ

Klawans HL (1973) The pharmacology of tardive dyskinesia. Am J Psychiatry 130:82–86

Levy AD, See RE, Levin ED, Ellison GD (1987) Neuroleptic-induced oral movements in rats: methodological issues. Life Sci 41:1499–1506

Ljungberg T (1990) Differential attenuation of water intake and water-rewarded operant responding by repeated administration of haloperidol and SCH 23390 in the rat. Pharmacol Biochem Behav 35:111–115

Marsden CD, Tarsy D, Baldessarini RJ (1975) Spontaneous and drug-induced movement disorders in psychotic patients. In: Bendon DF, Blumer D (eds) Psychiatric aspects of neurological disease. Grune & Stratten, New York, pp 219–266

McEvoy JP (1983) The clinical use of anticholinergic drugs as treatment for extrapyramidal side effects of neuroleptic drugs. J Clin Psychopharmacol 3:288–301

Nobrega JN, Dixon LM, Troncone LRP, Barros HT (1989) Effects of chronic haloperidol on stress-induced oral behavior in rats. Psychopharmacology 98:476–482

Noring U, Povlesen UJ, Casey DE, Gerlach J (1984) Effect of a cholinomimetic drug (RS 86) in tardive dyskinesia and drug-related parkinsonism. Psychopharmacology 84:569–571

Rosengarten H, Schweitzer JW, Freidhof AJ (1983) Induction of oral dyskinesias in naive rats by D1 stimulation. Life Sci 33:2479–2482

Rupniak NMJ, Jenner P, Marsden CD (1983) Cholinergic modulation of perioral behavior induced by chronic neuroleptic administration to rats. Psychopharmacology 79:226–230

Rupniak NMJ, Jenner P, Marsden CD (1985) Pharmacological characterization of spontaneous or drug-induced purposeless chewing movements in rats. Psychopharmacology 85:71–79

Rupniak NMJ, Jenner P, Marsden CD (1986) Acute dystonia induced by neuroleptic drugs. Psychopharmacology 88:403–419

Salamone JD, Lalies MD, Channell SL, Iversen SD (1986) Behavioral and pharmacological characterization of the mouth movements induced by muscarinic agonists in the rat. Psychopharmacology 88:467–471

Salamone JD, Johnson CJ, McCullough LD, Steinpreis RE (1990) Lateral striatal cholinergic mechanisms involved in oral motor activities in the rat. Psychopharmacology 102:529–534

See RE, Levin ED, Ellison GD (1988) Characteristics of oral movements in rats during and after chronic haloperidol and fluphenazine administration. Psychopharmacology 94:421–427

Stewart BR, Jenner P, Marsden CD (1988) Pharmacological characterization of pilocarpine-induced chewing in the rat. Psychopharmacology 96:55–62

Stoessl AJ, Dourish CT, Iversen SD (1989) Chronic neuroleptic-induced mouth movements in rats: suppression by CCK and selective dopamine D1 and D2 receptor antagonists. Psychopharmacology 98:372–379

Waddington JL (1990) Spontaneous orofacial movements induced in rodents by very long-term neuroleptic drug administration: phenomenology, pathophysiology and putative relationship to tardive dyskinesia. Psychopharmacology 101:431–447

Waddington JL, Molloy AG (1987) The status of late-onset vacuous chewing /perioral movements during long-term neuroleptic treatment in rodents: tardive dyskinesia or dystonia. Psychopharmacology 91:136–137

Waddington JL, Cross AJ, Gamble SJ, Bourne RC (1983) Spontaneous orofacial dyskinesia and dopaminergic function after 6 months of neuroleptic treatment. Science 220:530–532