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Vacuous Jaw Movements in Rats Induced by Acute Reserpine Administration: Interactions With Different Doses of Apomorphine

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BASKIN, P. AND J. SALAMONE. *Vacuous jaw movements in rats induced by acute reserpine administration: Interactions with different doses of apomorphine.* PHARMACOL BIOCHEM BEHAV 46(4) 793–797, 1993.—Two experiments were conducted to study the vacuous jaw movements induced in rats by acute administration of the monoamine-depleting agent reserpine. In the first experiment, different doses of reserpine (1.25, 2.5, and 5.0 mg/kg) were assessed for their ability to induce vacuous jaw movements. Acute administration of reserpine induced a dose-related increase in vacuous jaw movements, with the two highest doses being significantly different from the vehicle control. In the second experiment, interactions between 5.0 mg/kg reserpine and the dopamine agonist apomorphine were investigated. Coadministration of reserpine with the lowest dose of apomorphine (0.1 mg/kg) significantly increased vacuous jaw movements relative to reserpine alone. The two higher doses of apomorphine (0.5 and 1.0 mg/kg) significantly decreased vacuous jaw movements in reserpine-treated rats. These results demonstrate that vacuous jaw movements are induced by acute reserpine treatment in a dose-related manner. In addition, the interactions with apomorphine suggest that vacuous jaw movements are stimulated by decreases in dopamine release produced by low doses of apomorphine that are thought to have mainly presynaptic actions, but that these movements are decreased by higher doses of apomorphine that are known to act postsynaptically.

Dopamine Motor control Vacuous jaw movements Extrapyramidal movement disorders

ADMINISTRATION of dopamine antagonists has been reported to result in perioral movements in rats (3,5–9,11–13,17,18,22,23). Although a wide variety of different drug-induced perioral movements have been observed in rats (23), one of the most common is referred to as "purposeless chewing" (13) or "vacuous jaw movements" (8,17,18). These movements involve rapid vertical deflections of the lower jaw that resemble chewing, but are not directed at any particular stimulus [see (15–18)]. Considerable evidence indicates that vacuous jaw movements are induced by administration of dopamine antagonists and cholinomimetics (12,13,15,16). Depletions of striatal dopamine were shown to exacerbate neuroleptic-induced vacuous jaw movements (6). In addition, local depletions of dopamine in the ventrolateral striatum produced vacuous jaw movements and accentuated those induced by haloperidol (8). The magnitude of the reductions of dopamine levels in the ventrolateral striatum that were induced by injections of 6-hydroxydopamine were highly correlated with the production of vacuous jaw movements (8).

There is some dispute about whether or not chronic administration of dopamine antagonists is required to produce vacuous jaw movements. Some studies have specifically looked for chewing movements after acute administration of dopamine antagonists, but reported that these movements did not occur (3,7). Nevertheless, a large number of studies, conducted in different laboratories and using different neuroleptics, have reported that acute or subchronic administration of dopamine antagonists can produce vacuous jaw movements (5,8,13, 14,17,18). Recently, it was reported that acute administration of 0.4 mg/kg haloperidol or 5.0 mg/kg reserpine could induce vacuous jaw movements in three different age groups of rats (18). Thus, it has been observed that acute administration of dopamine receptor antagonists as well as acute administration of the monoamine-depleting agent reserpine can induce vacuous jaw movements in rats.

The present studies were designed to investigate the vacuous jaw movements induced by acute reserpine administration. In the first experiment, different doses of reserpine (1.25, 2.5, and 5.0 mg/kg) were assessed for their ability to induce vacuous jaw movements. The second experiment was designed to investigate interactions between acute reserpine and apomorphine in the production of vacuous jaw movements. Apomorphine is a nonselective dopamine agonist, which has been shown to reduce pilocarpine-induced vacuous jaw movements (21). Two moderate-to-high doses of apomorphine (0.5 and 1.0 mg/kg) were administered in combination with 5.0 mg/

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kg reserpine to assess the effects of postsynaptic dopamine receptor stimulation on reserpine-induced vacuous jaw movements. In addition, a low dose of apomorphine (0.1 mg/kg) was coadministered with reserpine to determine if a low dose of apomorphine, which is hypothesized to have mostly presynaptic actions on dopamine terminals that decrease dopamine release (1,2,4), could act to facilitate reserpine-induced vacuous jaw movements.

METHOD

Subjects

The subjects were 64 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 12L : 12D cycle (lights off at 0900 h). Standard lab chow and water were available ad lib. Animals were maintained in the colony room until 6–9 months of age, so that average weights at the start of the experiment were 450–600 g. Rats of this age were used for the present study because previous work has shown that vacuous jaw movements are higher in rats at this age than they are when the rats are younger [e.g., 3 months; see (18)].

Drugs

All drugs used in these experiments were obtained from Sigma Chemical Company. Reserpine (RES) was dissolved in a warmed 0.3% tartaric acid vehicle solution. For all experiments, the IP injection volumes for RES were 2.0 ml/kg. Apomorphine was dissolved in a 0.1% ascorbate solution, and IP injections of apomorphine were in a volume of 1.0 ml/kg.

General Procedure

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 1230 and 1600 h, which was 3.5–7 h after the lights went off. Rats were observed in the dark portion of their light/dark cycle to minimize the possiblity that rats would fall asleep after RES treatment. In both experiments, mechanical counters were used to record the frequency of vacuous jaw movements and rearing during a 5-min observation period conducted 90–95 min postinjection of either RES or VEH. Vacuous jaw movements were defined as rapid vertical deflections of the lower jaw that resembled chewing but were not directed at any particular stimulus. The observer counted each individual vertical deflection of the jaw as one vacuous jaw movement response, and recorded 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. The observer also counted the number of rearing responses that occurred during the behavioral observation period.

Experiments

In Experiment 1, rats were randomly assigned to receive IP injections of either 2.0 ml/kg tartaric acid vehicle, 1.25 mg/kg RES, 2.5 mg/kg RES, or 5.0 mg/kg RES (n = 7 for all groups). Seventy minutes postinjection individual animals were placed in the observation chamber for a 20-min habituation period prior to behavioral observation, and the rats were observed 90–95 min after drug treatment. In Experiment 2, all animals first received an IP injection of RES (5.0 mg/kg) 90 min prior to the time at which behavioral observations began. Ten minutes before behavioral observations began, rats received IP injections of either 0.1 % ascorbic acid vehicle, 0.1 mg/kg apomorphine, 0.5 mg/kg apomorphine, or 1.0 mg/kg apomorphine (n = 9 for all groups). Animals were placed in the apparatus for a 5-min habituation prior to observation from 90–95 min after RES injection. In addition to the measurement of vacuous jaw movements and rearing behavior described above, the presence or absence of locomotion, sniffing, or other behavioral responses was noted for each rat in Experiment 2.

Data Analysis

A simple one-way analysis of variance (ANOVA) was utilized to assess the effects of drug treatments on vacuous jaw movements and rearing behavior (10) for Experiments 1 and 2. Significant omnibus analyses were subjected to post hoc comparisons using the Newman-Keuls multiple comparisons test (alpha = 0.05).

RESULTS

Experiment 1

A dose-response curve depicting the effects of acute treatment with reserpine on vacuous jaw movements is presented in Fig. 1. There was a significant overall effect of drug treatment on vacuous jaw movements, $F(3, 24) = 20.34$, $p < 0.001$. Post hoc analysis of these data revealed that treatment with either 2.5 or 5.0 mg/kg RES significantly increased vacuous jaw movements relative to control rats. No significant effects were observed for 1.25 mg/kg RES treatment compared to controls. Rats administered 2.5 or 5.0 mg/kg RES also showed significantly more vacuous jaw movements than rats treated with 1.25 mg/kg RES. However, no significant differences in the mean number of vacuous jaw movements were observed when comparing animals injected with 2.5 mg/kg RES to those receiving 5.0 mg/kg. Rearing was significantly decreased by RES treatment, $F(3, 24) = 4.98$, $p < 0.01$ (see Fig. 2). A post hoc comparison of treatment means

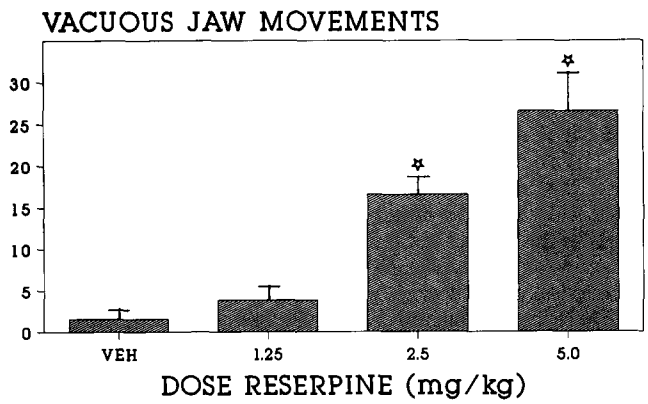

FIG. 1. Mean ± SEM vacuous jaw movements after treatment with tartaric acid vehicle (VEH), 1.25, 2.5, or 5.0 mg/kg RES in Experiment 1. *Different from vehicle, $p < 0.05$.

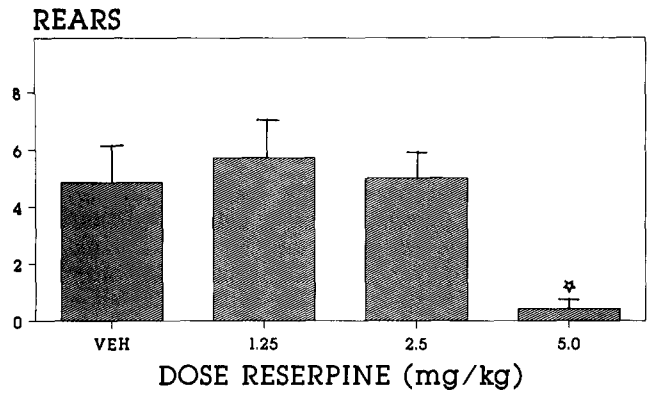

FIG. 2. Mean ± SEM number of rearing responses after treatment with vehicle, 1.25, 2.5, or 5.0 mg/kg RES in Experiment 1. *Different from vehicle, $p < 0.05$.

demonstrated that the 5.0 mg/kg dose of RES significantly lowered rearing behavior relative to vehicle injection. The 1.25 mg/kg RES group and the 2.5 mg/kg RES group did not significantly differ from the vehicle injection group.

Experiment 2

The effects of combined treatments with RES and apomorphine on vacuous jaw movements are shown in Fig. 3. There was a significant overall effect of drug treatment on vacuous jaw movements, $F(3, 32) = 23.35, p < 0.01$. Post hoc analyses demonstrated that the effects of coadministration of apomorphine with 5.0 mg/kg RES on vacuous jaw movements differed markedly depending upon the dose of apomorphine. Administration of 0.1 mg/kg apomorphine with 5.0 mg/kg RES significantly increased vacuous jaw movements relative to RES alone. In contrast, coadministration of 0.5 and 1.0 mg/kg apomorphine with 5.0 mg/kg RES significantly reduced vacuous jaw movements relative to the effects of RES alone. The groups that received 0.5 mg/kg apomorphine plus RES and 1.0 mg/kg apomorphine plus RES did not differ from each other, but both of these groups had significantly lower levels of vacuous jaw movements compared to 0.1 mg/kg apomorphine plus RES.

There was not a significant treatment effect for rearing behavior in Experiment 2 (Fig. 4). Observation of other behaviors indicated that four of the rats that received 5.0 mg/kg RES and five of the rats that received 5.0 mg/kg RES plus 0.1 mg/kg apomorphine were rated as being awake but immobile. Five of the rats that received 5.0 mg/kg RES and four of the rats that received 5.0 mg/kg RES plus 0.1 mg/kg apomorphine were rated as having only periodic movement. In contrast, all 18 of the rats that received either RES plus 0.5 mg/kg apomorphine or RES plus 1.0 mg/kg apomorphine were observed to have continuous sniffing, head and body movements. None of the rats in any group showed apomorphine-induced gnawing behavior.

DISCUSSION

The present study demonstrated that acute administration of the monoamine-depleting agent RES produced a dose-related increase in vacuous jaw movements in rats. Significant effects relative to control treatments were apparent after injections of 2.5 and 5.0 mg/kg RES. In the present study, vacuous jaw movements were defined as vertical deflections of the lower jaw. Previous work has shown that repeated administration of 1.0 mg/kg RES induced perioral movements in rats (11). However, these authors focussed upon tongue protrusions as the major behavioral index of perioral movements (11). Very few tongue protrusions were observed in the present experiments, and it is possible that some perioral movements will not be present unless repeated or chronic RES administration is used. Nevertheless, the results of Experiments 1 and 2 outlined above demonstrate that vertical jaw movements resembling chewing do occur after acute RES administration. These results are consistent with a previous study showing that acute administration of 5.0 mg/kg RES significantly increased vacuous jaw movements in three different age groups of rats (18). In addition, the present results are consistent with previous investigations showing that acute administration of neuroleptic drugs can induce vacuous jaw movements or "purposeless chewing" in rats (5,8,13,14,17,18).

As well as inducing vacuous jaw movements, RES also decreased rearing behavior. In general, conditions that decreased rearing (i.e., high dose of RES, and RES plus 0.1 mg/kg apomorphine) tended to increase vacuous jaw movements. It is possible that decreases in the activity of axial musculature

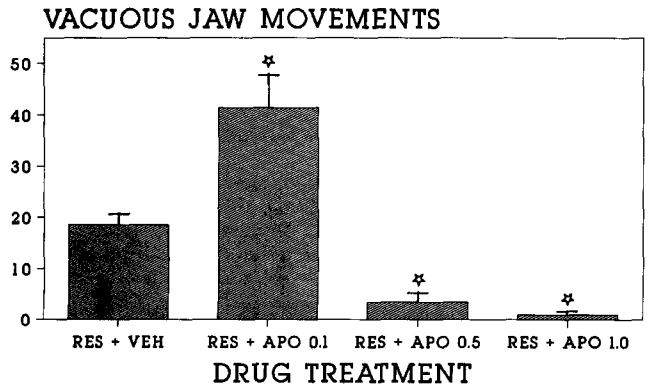

FIG. 3. Mean ± SEM vacuous jaw movements after various drug treatments in Experiment 2 (RES, 5.0 mg/kg reserpine; VEH, ascorbate vehicle; APO, apomorphine; doses of apomorphine are in mg/kg). *Different from 5.0 mg/kg reserpine plus vehicle, $p < 0.05$.

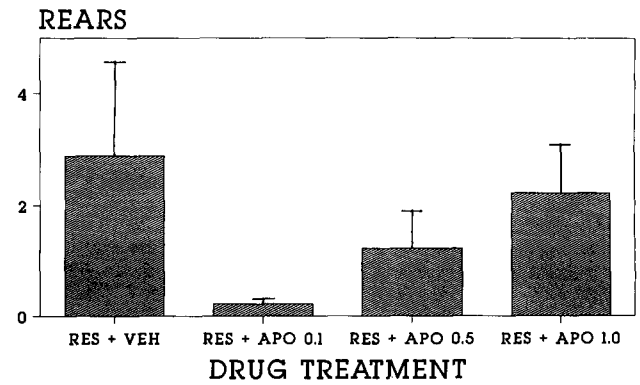

FIG. 4. Mean ± SEM number of rearing responses after various drug treatments in Experiment 2.

involved in behaviors such as rearing are somewhat related to increases in movements involving distal musculature such as those seen in vacuous jaw movements. However, it is important to emphasize that the dose-response curves were different for the effects of RES on rearing and vacuous jaw movements (see Figs. 1 and 2). The only dose of RES that significantly reduced rearing was 5.0 mg/kg, and it was observed that rats receiving 2.5 mg/kg RES showed significant increases in vacuous jaw movements, although they did not demonstrate a significant suppression of rearing. These data suggest that the induction of vacuous jaw movements is not necessarily tied to decreases in rearing under all circumstances, and also demonstrate that vacuous jaw movements are not merely an artifact of decreased motor activity. It has been reported that there was not a significant negative correlation between vacuous jaw movements and rearing behavior in rats treated with haloperidol and scopolamine (17), nor in aged rats (18). Previous work has shown that increases in vacuous jaw movements were dissociable from effects on rearing behavior or locomotion in rats with striatal dopamine depletions (8). Thus, increases in vacuous jaw movements and decreases in rearing or locomotion may be loosely associated with each other because both of these effects may be generally related to interference with brain dopamine systems (see discussion below). Nevertheless, induction of vacuous jaw movements and suppression of motor activity may be somewhat dissociable from each other because different brain mechanisms mediate each effect (8).

The actions of apomorphine on reserpine-induced vacuous jaw movements were quite complex, and varied markedly depending upon the particular dose of apomorphine. The higher doses of apomorphine (0.5 and 1.0 mg/kg) significantly reversed the effects of reserpine on vacuous jaw movements. Coadministration of these doses of apomorphine with RES was accompanied by obvious indices of postsynaptic dopamine receptor stimulation, such as sniffing and head movements. These results are consistent with previous reports showing that 1.0 mg/kg apomorphine significantly reduced the vacuous jaw movements induced by the muscarinic agonist pilocarpine (21). In contrast, coadministration of 0.1 mg/kg apomorphine with RES significantly enhanced vacuous jaw movements relative to RES alone. The magnitude of this increase was very large (see Fig. 3), and most rats that received 0.1 mg/kg apomorphine plus RES showed levels of vacuous jaw movements that were outside the range of rats that received RES alone.

The present results are generally consistent with the notion that vacuous jaw movements can be induced by interference with dopaminergic transmission. RES blocks monoamine storage, leading to a depletion of dopamine, norepinephrine, and serotonin. Norepinephrine and serotonin antagonists or depleting agents have not been shown to induce vacuous jaw movements (13,19,20), and inhibition of serotonin synthesis by administration of parachlorophenylalanine actually was shown to reduce pilocarpine-induced vacuous jaw movements (19). In contrast, a variety of dopamine antagonists have been shown to induce vacuous jaw movements following acute or subchronic administration (5,13,14,17,18). Depletions of striatal dopamine by injections of 6-hydroxydopamine have been shown to induce vacuous jaw movements, and the vacuous jaw movements induced by dopamine depletion were exacerbated by administration of the dopamine antagonist haloperidol (8). In the present study, adminstration of 0.5–1.0 mg/kg of the dopamine agonist apomorphine decreased RES-induced vacuous jaw movements. This demonstrated that RES-induced vacuous jaw movements can be reduced by stimulating postsynaptic dopamine receptors. A reasonable explanation for the ability of 0.1 mg/kg apomorphine to exacerbate the vacuous jaw movements induced by RES is that this low dose of apomorphine acted presynaptically to decrease dopamine release. Considerable evidence indicates that low doses of apomorphine can decrease dopaminergic transmission through relatively selective actions on dopamine autoreceptors (1,2,4). Thus, it is possible that depletion of dopamine with RES treatment, combined with decreases in dopamine release produced by injection of 0.1 mg/kg apomorphine, served to produce substantial decreases in dopamine release that led to dramatic increases in vacuous jaw movements.

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