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Effects of Acute Haloperidol and Reserpine Administration on Vacuous Jaw Movements in Three Different Age Groups of Rats

RHEA E. STEINPREIS AND JOHN D. SALAMONE[1]

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

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STEINPREIS, R. E. AND J. D. SALAMONE. *Effects of acute haloperidol and reserpine administration on vacuous jaw movements in three different age groups of rats.* PHARMACOL BIOCHEM BEHAV **46**(2) 405–409, 1993.—In these experiments three different age groups of rats were tested for vacuous jaw movements. The age groups included rats aged 3 months, rats aged 6–9 months, and rats aged 12–15 months. In the first experiment, rats were given a single IP injection of either 0.3% tartaric acid vehicle or 0.4 mg/kg haloperidol. In the second experiment, rats were given injections of vehicle or 5.0 mg/kg reserpine. Haloperidol and reserpine significantly increased vacuous jaw movements. There were significant effects of age on vacuous jaw movements, with rats aged 6–9 months and rats aged 12–15 months showing more jaw movements than 3-month-old rats. In both experiments, the drug × age interaction was not significant, indicating that the combined effects of age and neuroleptic treatment were additive and not synergistic. Haloperidol and reserpine also reduced rearing behavior in all age groups. It is concluded that age is an important variable in studies of vacuous jaw movements.

Dopamine Aging Haloperidol Reserpine Orofacial movements

VACUOUS jaw movements in rats are vertical jaw movements that resemble chewing but are not directed at any particular stimuli (6,17,19). Several conditions are known to be associated with vacuous jaw movements. Studies have shown that vacuous jaw movements are induced by systemic injections of dopamine antagonists or cholinomimetic drugs (3, 4,6,7,14–17,19). Direct intrastriatal injections of the muscarinic agonist pilocarpine have been shown to induce vacuous jaw movements (17). In addition to these observations that a number of pharmacological conditions can induce vacuous jaw movements, some investigators reported that a variety of perioral movements, including vacuous jaw movements, increase with age in untreated control rats (4,7,16,25,26).

Although there is some general agreement about the conditions that lead to the production of vacuous jaw movements, several controversies remain in this field. There is a dispute about whether or not chronic administration of dopamine antagonists is necessary for the induction of vacuous jaw movements (24). Although some studies failed to observe vacuous jaw movements after acute neuroleptic administration (2,4), several other reports indicate that neuroleptic-induced vacuous jaw movements can occur after acute or subchronic administration of dopamine antagonists (1,3,6,14,15,19). Typically, the behavioral effects of acute administration of dopamine antagonists would be interpreted as resulting from interference with dopaminergic activity. However, if chronic administration of dopamine antagonists is necessary for vacuous jaw movements to occur then it is possible that these movements are mediated by increases in dopaminergic transmission, such as those produced by receptor supersensitivity after chronic receptor antagonism [for review, see (24)]. There also is some dispute about the relation between aging and vacuous jaw movements. Some studies reported that perioral movements increase with age (4,7,16,25,26), while others have not found such a relation (5,8).

The present experiments were undertaken to study the effects of acute administration of haloperidol (HP) and reserpine (RES) on vacuous jaw movements in three different age groups of rats. RES was used because this drug acts to deplete monoamines, and all previous studies of vacuous jaw movements induced by acute neuroleptic administration involved postsynaptic dopamine receptor blockade rather than pharmacological depletion of dopamine. In most previous studies of aging and vacuous jaw movements, rats received chronic drug or control treatments, and therefore control rats were observed repeatedly as they aged. This may have resulted in sensitization of the observer with repeated observation [see (24)]. In the present study, acute drug or control treatments were used and all rats were observed only once so there was no possibility of age-related increases in vacuous jaw movements in control rats being related to sensitization of the observer. As well as recording the presence of vacuous jaw move-

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

ments, the observer also recorded rearing behavior to provide an index of gross motor activity that did not involve perioral movements.

METHOD

Subjects

Subjects were 84 male Sprague-Dawley rats obtained from Harlan Sprague-Dawley. Three different age groups were used. One group of rats was approximately 3 months old and weighed between 225-300 g. The second age group consisted of rats that were 6-9 months old and weighed between 350-450 g. The oldest group of rats were 12-15 months old and weighed between 500-750 g. All rats were housed individually in a colony room maintained at 72°F and a 12 L : 12 D cycle (light on at 0700 h). Standard lab chow and water were available ad lib.

Drugs

HP and RES were obtained from Sigma Chemical Co. (St. Louis, MO). Both drugs were dissolved in 0.3% tartaric acid vehicle (VEH), which also served as the control in this study.

General Procedure

Rats were placed in an elevated Plexiglas case (28 × 28 × 28 cm) for habituation 20 min prior to the 5-min observation period. During the 5-min observation period, rats were observed for vacuous jaw movements and rearing behavior. Vacuous jaw movements were defined as a rapid vertical deflection of the lower jaw that resembled chewing but was not directed at any stimulus. Each individual vertical deflection of the jaw was recorded by the observer. Studies of interrater reliability indicate that greater than 90% agreement between observers is obtained by using these behavioral methods. In addition to recording vacuous jaw movements, the observer also counted each occurrence of rearing behavior during the observation period. A rearing response was defined as the rat lifting the anterior portion of its body while maintaining hindpaw contact with the floor. Pilot data indicated that HP and RES have different time courses. Therefore, rats injected with HP or VEH in Experiment 1 were observed 50-55 min after injection whereas rats injected with RES or VEH in Experiment 2 were observed 90-95 min after injection.

Experiments

In Experiment 1, rats from each age group (n = 14 per age group) received injections of VEH (n = 7) or 0.4 mg/kg HP (n = 7) and were tested 50-55 min after injections. In Experiment 2, rats from each age group (n = 14 per age group) received injections of VEH (n = 7) or 5.0 mg/kg RES (n = 7) and were tested 90-95 min after injection.

Data Analysis

All vacuous jaw movements data were log transformed to reduce variability. These data were subjected to factorial analysis of variance (ANOVA). Planned comparisons [see (8), pp. 106-118] were used to examine differences between the two higher age groups and the youngest age group. Because there was not a significant drug × age interaction in either experiment (see below), these planned comparisons included both neuroleptic- and VEH-treated rats. The Mann-Whitney U-test was used to assess differences in the rearing data because the suppression of rearing induced by HP and RES was so complete that most drug-treated rats had no rearing responses. The Pearson product-moment correlation was used to correlate vacuous jaw movement and rearing data among VEH-treated rats. Correlational analyses were not applied to drug-treated rats because of the low variability in the rearing data from drug-treated rats.

RESULTS

The data for vacuous jaw movements in Experiment 1 are presented in Fig. 1. There was a significant effect of age, $F(2, 36) = 5.11$, $p < 0.01$, and planned comparisons indicated that 3-month-old rats showed significantly fewer vacuous jaw movements than rats aged 6-9 months, $F(1, 36) = 8.01$, $p < 0.01$, and rats aged 12-15 months, $F(1, 36) = 9.65$, $p < 0.01$. The overall effect of HP treatment was significant, $F(1, 36) = 31.93$, $p < 0.01$, demonstrating that HP increased vacuous jaw movements. The drug × age interaction was not significant, $F(2, 36) = 0.86$, n.s.

The mean (± SEM) rearing data for Experiment 1 were as follows: 3-month-old rats, VEH 5.0 (1.6), HP 0.0 (0.0); 6- to 9-month-old rats, VEH 1.57 (0.4), HP 0.0 (0.0); 12- to 15-month-old rats, VEH 6.7 (3.0), HP 0.0 (0.0). The Mann-Whitney U-test indicated that there was a significant suppression of rearing ($p < 0.05$) induced by HP in all three age groups. Among all 21 VEH-treated rats, there was not a significant correlation between vacuous jaw movements and rearing behavior, $r(19) = 0.26$, n.s.

The data for vacuous jaw movements in Experiment 2 are presented in Fig. 2. There was a significant effect of age, $F(2, 36) = 10.6$, $p < 0.01$, and planned comparisons indicated that 3-month-old rats showed significantly fewer vacuous jaw movements than rats aged 6-9 months, $F(1, 36) = 12.99$, $p < 0.01$, and rats aged 12-15 months, $F(1, 36) = 18.5$, $p < 0.01$. The overall effect of RES treatment was significant, $F(1, 36) = 49.4$, $p < 0.001$, demonstrating that RES increased vacuous jaw movements. The drug × age interaction was not significant, $F(2, 36) = 2.52$, n.s.

The mean (± SEM) rearing data for Experiment 2 were as follows: 3-month-old rats, VEH 14.2 (4.5), RES 0.14 (0.13); 6- to 9-month-old rats, VEH 1.14 (0.77), RES 0.0 (0.0); 12- to 15-month-old rats, VEH 1.85 (0.99), RES 1.0 (0.53). The Mann-Whitney U-test indicated that there was a significant suppression of rearing ($p < 0.05$) induced by RES in all three age groups. Among all 21 VEH-treated rats, there was not a significant correlation between vacuous jaw movements and rearing behavior, $r(19) = 0.40$, n.s. Four RES-treated rats showed some rearing behavior, and these four rats had a mean number of vacuous jaw movements (70.5) that was higher than the overall mean number of vacuous jaw movements for RES-treated rats.

DISCUSSION

These data clearly show a significant increase in vacuous jaw movements with increasing age, which is evident in control and neuroleptic-treated rats in both experiments. The present results may reflect changes that are specific to vertical deflections of the jaw, and it is possible that other orofacial movements do not increase with age. Nevertheless, these results are consistent with studies that have shown age-related increases in orofacial movements in rats (4,7,16,25,26). The between-groups design coupled with acute injection eliminated the possibility that the observer might have become more sensitive to rating the vacuous jaw movements with repeated ob-

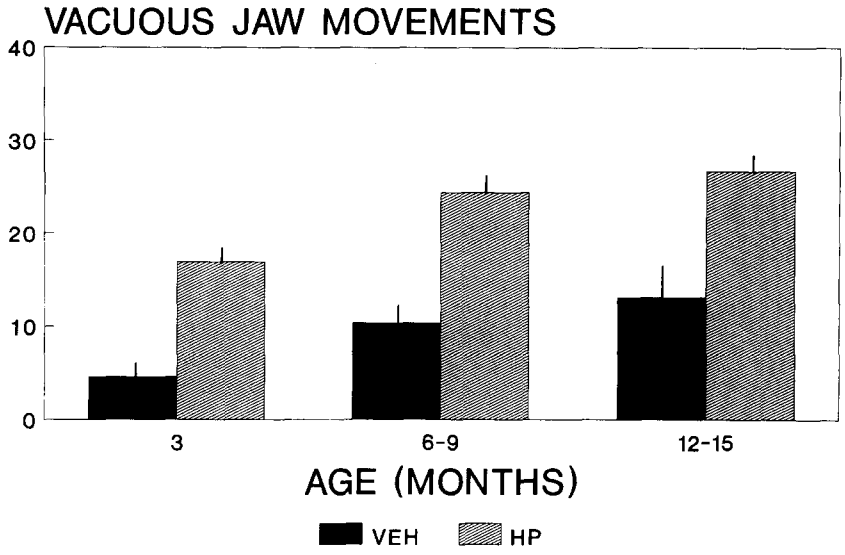

FIG. 1. Mean (± SEM) number of vacuous jaw movements in vehicle (VEH)- and haloperidol (HP)-treated rats from all three age groups.

servations of the same animal [see also (24)]. In the present study, age-related increases in vacuous jaw movements were evident in rats aged 6–9 months, as well as rats aged 12–15 months. These results suggest that age-related increases in vacuous jaw movements in rats do not require that the animal is truly aged (i.e., > 20 months). The lack of a significant age × drug interaction indicates that the combined effects of age and acute injection of 0.4 mg/kg HP or 5.0 mg/kg RES were additive and not synergistic. Of course, this conclusion applies only to the present set of experimental conditions, and it is possible that using other doses, different neuroleptic drugs, or older rats might lead to synergistic effects of neuroleptic treatment and aging.

Results of both experiments indicate that 0.4 mg/kg HP and 5.0 mg/kg RES suppressed rearing behavior in all age groups. Thus, vacuous jaw movements were induced under conditions that also produced other signs of interference with motor activity. Nevertheless, the present results do not provide evidence that vacuous jaw movements are simply an artifact of decreased motor activity (9), nor do they support the notion that low levels of rearing will be closely related to high levels of vacuous jaw movements. Across all age groups, there was not a significant inverse correlation between vacuous jaw movements and rearing behavior in VEH-treated rats in either experiment. Rearing data accounted for only 6–16% of the variance in vacuous jaw movements among VEH-treated rats

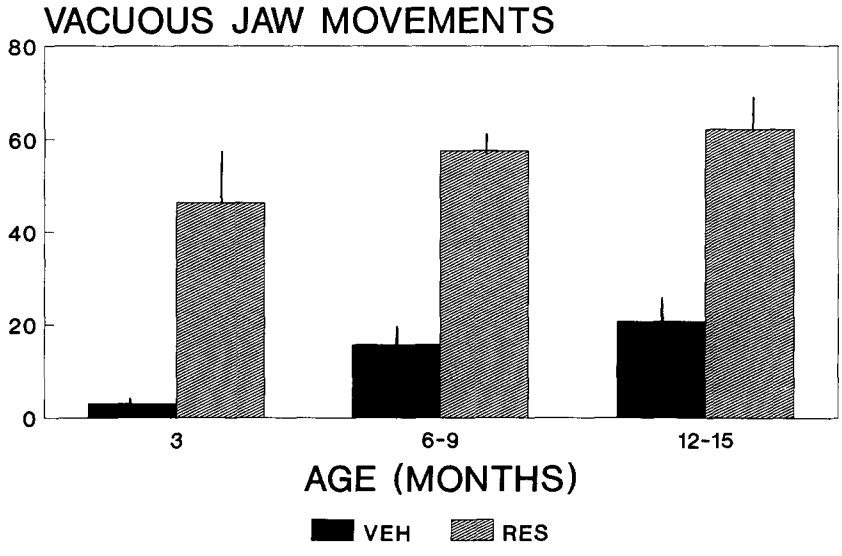

FIG. 2. Mean (± SEM) number of vacuous jaw movements in vehicle (VEH)- and reserpine (RES)-treated rats from all three age groups.

in Experiments 1 and 2. In addition, the four RES-treated rats that showed some rearing had a mean number of vacuous jaw movements that was higher than the overall mean for animals that received injections of RES. These results are consistent with findings from other studies, which indicate that vacuous jaw movements do not show a high negative correlation with rearing in rats with striatal dopamine depletions (6) or rats treated with HP and scopolamine (19).

In the present study, vacuous jaw movements were induced by acute administration of HP and RES. Although some studies failed to observe vacuous jaw movements after acute neuroleptic administration (2,4), the present results are consistent with other studies that reported neuroleptic-induced vacuous jaw movements with acute or subchronic neuroleptic administration (3,6,14,15,19). The present study is the first report that acute RES treatment induces vacuous jaw movements that resemble chewing in rats. It has been observed that repeated administration of 1.0 mg/kg RES induces perioral movements (11) in rats. Although the perioral movements induced by chronic reserpine can include several components, previous studies focused upon tongue protrusion (11). In the present study, few tongue protrusions were noted by the observer after acute RES treatment. RES acts by blocking storage of monoamines and thus depleting brain levels of dopamine, noradrenaline, and serotonin. Because RES has actions on multiple neurotransmitters, there is some ambiguity about the specific mechanism through which RES induces vacuous jaw movements. Several drugs that affect noradrenergic receptors have been shown to have no effect on vacuous jaw movements (14). Depleting central stores of serotonin by administration of parachlorophenylalanine decreased vacuous jaw movements induced by pilocarpine (21). Serotonin agonists *m*-chlorophenlypiperazine, trifluoromethylphenylpiperazine, and quipazine all increased vacuous jaw movements (20). Thus, there is no evidence indicating that depletion of noradrenaline or serotonin would increase vacuous jaw movements. Because most of the motor effects of neuroleptic drugs are related to actions on brain dopamine systems, and because several dopamine antagonists have been shown to induce vacuous jaw movements, it is reasonable to suggest that RES increases vacuous jaw movements largely because it depletes striatal dopamine. This suggestion is consistent with a previous study showing that depletion of striatal dopamine with 6-hydroxydopamine increased vacuous jaw movements (6). Acute administration of HP to rats with striatal dopamine depletions induced a further increase in vacuous jaw movements (6). Recent work from our laboratory indicated that RES-induced vacuous jaw movements were decreased by administration of 0.5–1.0 mg/kg of the dopamine agonist apomorphine (1). Together, these results indicate that vacuous jaw movements can be induced by a variety of conditions that interfere with the functional activity of striatal dopamine.

Several studies demonstrated that brain dopamine systems undergo age-related declines in some indices of presynaptic (13,23) and postsynaptic (12,18) function. Behavioral effects of dopaminergic drugs have been shown to change as a result of aging (22). Thus, it is possible that the increases in vacuous jaw movements that were associated with aging in the present study are related to age-related deficits in dopaminergic function. It has been suggested that vacuous jaw movements in rats may be related to some human movement disorders such as tardive dyskinesia (2,3), dystonia (15), or parkinsonism (6,17,19). Studies of age-related increases in vacuous jaw movements in rats could be a useful avenue of research for studying the role of aging in various motor syndromes.

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