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Emergence of Oral and Locomotor Activity in Chronic Haloperidol-Treated Rats Following Cortical *N*-Methyl-D-Aspartate Stimulation

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GRIMM, J. W., P. J. KRUZICH AND R. E. SEE. *Emergence of oral and locomotor activity in chronic haloperidol-treated rats following cortical* N-*methyl*-D-*aspartate stimulation.* PHARMACOL BIOCHEM BEHAV **60**(1) 167–173, 1998.—Neuroleptic-induced orofacial movements in rats have been widely utilized as an animal model of tardive dyskinesia (TD). The present study investigated the role of the oral motor cortex in these movements by applying direct cortical stimulation in rats exposed to chronic haloperidol. Rats received depot IM injections of haloperidol decanoate or sesame oil vehicle every 3 weeks (10 rats per group). After 24 weeks of injections and a 3-week withdrawal period, bilateral guide cannulae were implanted into the primary oral motor cortex. After a 1-week recovery, bilateral microinfusions of saline vehicle followed by 1, 3, and 10 mM N-methyl-D-aspartate (NMDA) were given and observations of oral activity, locomotion, rearing, and grooming were recorded. Haloperidol-treated rats displayed a significant emergence of NMDA stimulated oral activity (nondirected oral movements, oral tremor, audible teeth grinding, and directed oral movements). In addition, rearing and locomotion were significantly elevated in these animals. In contrast to haloperidol-treated rats, sesame oil-treated rats showed no significant emergence of any motor activity. These results suggest that chronic haloperidol administration alters primary motor cortex efferents, and that this effect may be a factor in the manifestation of chronic neuroleptic induced motor side effects, such as TD. © 1998 Elsevier Science Inc.

Oral movements NMDA Tardive dyskinesia Haloperidol Motor cortex Glutamate

EXTRAPYRAMIDAL side effects (EPS) often develop following treatment with neuroleptic drugs, particularly those drugs classified as "typical" according to behavioral and pharmacological profiles (9). A form of late-onset EPS, tardive dyskinesia (TD), is characterized by persisting choreoathetoid movements, primarily of the orofacial region. TD has been extensively modeled in rats administered chronic neuroleptics, with most evidence showing a neuroleptic-induced increase in the total number of oral movements observed over time (12,17,25,43) and late-onset changes in the form of oral movement activity (41,44).

The primary pathophysiology underlying the abnormal movements of TD is most commonly thought to reside in the corpus striatum. Oral activity can be readily elicited by direct stimulation of subregions of the striatum (particularly the ventrolateral striatum) using a number of pharmacological agents (3,8,22,23,36,40). A large body of evidence has also shown a variety of neuroleptic-induced changes in striatal neurochemistry and physiology, ranging from dopamine (DA) receptor upregulation to loss of striatal neurons [(45) for review]. More recently, corticostriatal glutamatergic input has received increasing attention in regards to TD pathophysiology (24). Chronic neuroleptic exposure has been shown to selectively increase basal and potassium stimulated levels of extracellular glutamate in the striatum (44,48,49,56). In addition, chronic haloperidol increased the number of perforated synapses in the striatum (46). These synapses have recently been identified as glutamatergic, with origins in the motor cortex (28,29).

Previous work has characterized the production of oral activity, including non-directed oral movements, following electrical stimulation of the primary jaw area of the motor cortex (31,38,39). In addition, cortical lesions induce orofacial move-

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ments including aberrant tongue protrusions, biting, and chewing (5). The effects of cortical lesions on oral movements are exacerbated by repeated neuroleptic exposure (11,16). It is possible that descending pathways of the motor cortex, such as the corticostriatal glutamate projection, are altered in animals treated with chronic neuroleptics. The present study investigated this possibility by examining the behavioral effects of direct chemical stimulation of the oral motor cortex in rats following 6 months of chronic haloperidol administration. It was predicted that haloperidol treated rats would demonstrate an enhanced oral behavioral response to cortical stimulation.

METHOD

Subjects and Drug Administration

Female Sprague–Dawley rats (3 months old; 250–275 g) were separated into two groups ($n = 10$ per group). The haloperidol group (HAL) received IM injections of haloperidol decanoate (21 mg/kg) in sesame oil vehicle every 3 weeks over the course of 24 weeks. Injections (0.5 ml/kg of a 42 mg/ml solution) were divided between both hind legs so as to reduce the bolus size. Control animals (CON) received IM injections of vehicle on the same days and for the same duration as HAL animals. Animals were housed in pairs, each consisting of one HAL and one CON animal. Weights were recorded prior to each injection and prior to cortical stimulation. All animals had free access to laboratory rat chow and water. The animals were cared for in compliance with the NIH Guide for the Care and Use of Laboratory Animals and the experimental protocols were approved by an institutional review committee.

Surgery

Two weeks following the final injection of drug or vehicle, rats were prepared for cortical stimulation. Rats were injected with atropine sulfate (0.054 mg in 0.1 ml, IM), anesthetized with equithesin (2.5 ml/kg, IP), placed in a stereotaxic device (Stoelting) with the incisor bar set at −3.4 mm, and bilateral stainless steel guide cannulae (22 gauge, 9 mm) were lowered into holes drilled in the exposed skull and secured with dental cement. Coordinates for cannulae placement were A +3.5, L ±3.5, and V −1.6 from bregma as identified on the surface of the skull (34). These coordinates were selected based on previous studies that demonstrated that direct electrical stimulation of this area of the cortex produces jaw, lip, and tongue movements (31,38). In addition, a large percentage of corticostriatal cell bodies have been localized to this region that includes cortical layers 3–5 (1,27). Stainless steel obturators (28 gauge) were placed into the cannulae following surgery and rats were given penicillin G (32,000 U in 0.05 ml, IM).

Behavioral Assessment

Following a 1-week recovery, single rats were placed into Plexiglas observation boxes (28 × 28 × 25 cm). Boxes contained a mirror on the back wall to aid in the observation of motor behaviors. Incandescent lighting was placed above the boxes and general room lighting was reduced to highlight the observation chambers. Observations were 3 min in duration and occurred two times every hour (5 min and 20 min after the hour) for 4 h, with a final observation occurring at the fifth hour. Microinfusions occurred at the beginning of each hour, except for the first hour, which had no infusion. Rats were habituated to the boxes for 30 min prior to the first hour. All microinfusions were bilateral through 28-gauge, 10 mm infusion cannulae that extended 1 mm beyond the guide cannulae. Infusions were 1 μl per side delivered over 3 min and probes were then left in place for 2 min. The second hour, rats were infused with buffered saline, pH 4, which matched the pH of *N*-methyl-D-aspartate (NMDA) in solution. At the beginning of the next 3 h, infusions progressed through three concentrations (1, 3, and 10 mM) of NMDA dissolved in buffered saline (pH 4). Behaviors were scored using a computer with observations entered on a numeric keypad. Oral activities were scored as durations of non-directed oral movements (vacuous chewing), audible oral movements (grating of upper and lower incisors), orofacial tremor, and directed oral movements (chewing an object such as shavings). Non-oral activities were scored as durations of locomotor activity (ambulatory movement of all limbs), rearing (front paws lifted off of the chamber floor), and grooming.

Histology

Three days following cortical stimulation rats were deeply anesthetized with equithesin. Prior to perfusion, 1 ml of blood was collected from the right ventricle of the heart. This sample was centrifuged and the plasma was collected and stored for high performance liquid chromatographic analysis of haloperidol levels as previously described (47). Immediately following blood collection, rats were transcardially perfused with a 4% formaldehyde fixative. Following perfusion, guide cannulae were removed from the skull by pulling the cranioplastic cap rapidly upwards. Brains were extracted, stored in the fixative, and later sliced on a vibratome in serial 50 μm coronal sections through the frontal cortex. Sections were stained with cresyl violet and examined with a light microscope for verification of cannulae placements.

Statistics

Basal activity scores for each behavior (sum of both 3 min measures taken the first hour) were compared between HAL and CON groups with independent *t*-tests. Data following infusions were analyzed with two-way repeated-measures analyses of variance (two-way RM ANOVAs). Behavioral activity scores following cortical infusions were analyzed separately for each behavior. In addition, scores immediately following infusions and 20 min following infusions were analyzed separately. Following a significant main effect for dose, posthoc comparisons (Student–Newman–Keuls test) were conducted between doses within each group only. Following a significant interaction, post hoc comparisons were conducted between all pairs of data points, both within and between groups. Results are expressed as the mean ± standard error of the mean (SEM).

RESULTS

For haloperidol-treated animals, plasma levels of haloperidol at the time of perfusion were 1.97 ± 0.10 ng/ml. Figure 1 indicates the region of probe placements in the cortex. Histological examination revealed infusion cannulae tip placements in layers 3–5 of the cortex. There was no evidence for obvious necrosis near the infusion sites.

Basal motor activity was calculated as the total score for both measures in the first hour (6 min total). Group means of these scores and results of statistical analyses are presented in Table 1. In general, motor activity was quite low, indicating that the animals were well habituated to the test apparatus. The only behavior that showed a significant difference prior to cortical infusion was non-directed oral movements, with the HAL rats significantly elevated over the CON group.

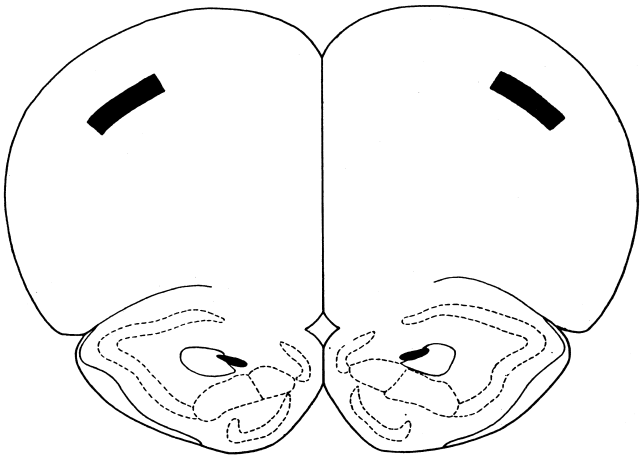

FIG. 1. This figure depicts the location of infusion cannulae tip placements into the oral motor cortex. The drawing is modified from an atlas of the rat brain (34).

F-values for two-way RM ANOVAs for behavioral measures recorded at 5 min following cortical infusion are shown in Table 2. Data for oral behaviors at 5 min after infusion are presented in Figs. 2 and 3. Comparison between HAL and CON rats following vehicle infusion revealed no significant differences. Infusion of 1 mM NMDA produced a robust and significant activation of nondirected oral movements and audible oral movements in the HAL rats. This effect was less apparent after infusion of 3 and 10 mM. The significant interaction found for oral tremor also indicates that HAL rats were more sensitive to the effects of NMDA when compared to CON rats. In contrast to the enhancement of several measures of oral activity at 1 mM NMDA, directed oral movements were significantly activated in HAL rats only after the 10 mM infusion. CON rats failed to show significant activation of any of these oral behaviors across all concentrations of NMDA. Pearson correlations were also calculated between basal and NMDA stimulated oral movements. There were no significant correlations between basal oral activity and NMDA stimulated oral activity.

TABLE 1

BASAL (6 MIN) BEHAVIORAL ACTIVITIES (MEANS ± SEM)

Behavior	HAL	CON	*t*-Value
Non-directed OM	14.87 ± 4.16	1.05 ± 0.32	−3.32*
Audible OM	2.03 ± 1.37	0 ± 0	1.48
Tremor	6.61 ± 4.41	0 ± 0	1.50
Directed OM	0 ± 0	0.31 ± 0.31	−1.0
Locomotion	0.19 ± 0.33	1.05 ± 0.43	−1.96
Rearing	0.09 ± 0.09	0.49 ± 0.35	−1.11
Grooming	0 ± 0	6.42 ± 5.10	−1.26

*Indicates significant difference, $p < 0.05$. All comparisons had 18 degrees of freedom.

Figure 4 illustrates the duration of non-oral motor activity (locomotion, rearing, and grooming). HAL rats showed an overall greater increase in locomotor activity compared with CON rats following cortical stimulation at all three concentrations of NMDA. In addition, HAL rats showed a significant increase in rearing at 1 mM NMDA. Although there was an indication of enhanced grooming behavior in the HAL rats, there were no significant differences.

Analysis of data following cortical infusions revealed no significant effects when comparing behaviors 20 min following infusions and the final measure at 5 h (data not shown). This indicates that for all behaviors measured, the effects of cortical stimulation were limited to 5 min following infusions of NMDA.

DISCUSSION

The current results support the hypothesis that cortically stimulated oral activity is enhanced after chronic haloperidol administration in rats. In addition, the results suggest that locomotion and rearing may be similarly affected. It is noteworthy that the response of HAL rats was drastically different from vehicle-treated animals, with the CON animals showing no significant increases in motor activity at any concentration of NMDA. This fact suggests that the neuroleptic induced effect was emergent, because significant oral and locomotor ac-

TABLE 2

F-VALUES FROM TWO-WAY RM ANOVAS FOR BEHAVIORS 5 MIN FOLLOWING CORTICAL INFUSIONS OF NMDA

Behavior	Main Effect for Group (HAL vs. CON)	Main Effect for Dose (NMDA)	Interaction (Group × Dose)	Significant Post Hoc(s)
Non-directed OM	6.91*	5.17†	2.92*	yes
Audible OM	9.65†	2.06	3.07*	yes
Tremor	1.17	1.69	2.85*	no
Directed OM	2.94	2.84*	3.02*	yes
Locomotion	10.81†	4.43†	2.03	yes‡
Rearing	15.54†	4.27†	4.36†	yes
Grooming	0.85	1.92	0.84	no

Significant effects, *$p < 0.05$ and †$p < 0.01$. Degrees of freedom were as follows: group (1,18), dose (3,54), and interaction (3,54). "Yes" in far right column indicates significant post hoc comparison(s) (Student–Newman–Keuls); see Figs. 2–4 for graphical depictions of comparisons.

‡Indicates that only overall group means were compared, with HAL > CON, $p < 0.05$, and that overall concentration effects were compared with 1 mM vs. veh, 3 mM vs. veh, and 10 mM vs. veh, all significantly different, $p < 0.05$.

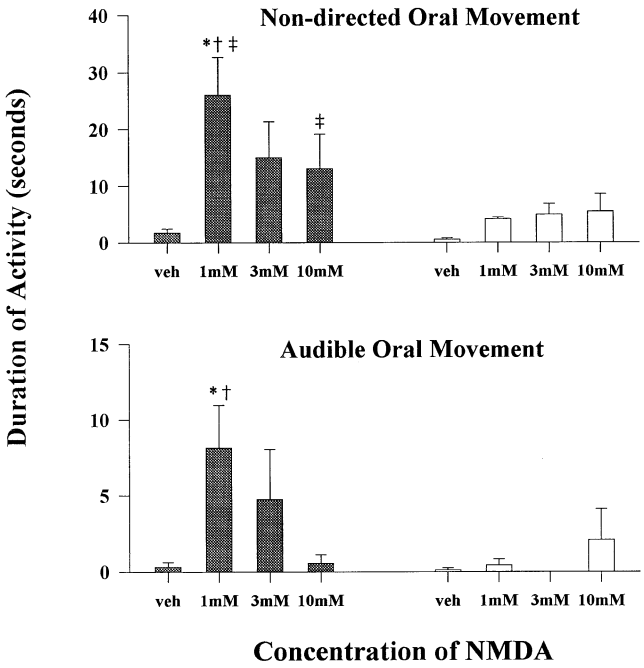

FIG. 2. Duration of NMDA-stimulated non-directed oral movement and audible oral activity in HAL rats (shaded bars) and CON rats (open bars), over a range of three concentrations. * Indicates a significant difference from vehicle and all concentrations in the CON group ($p < 0.05$), † indicates a significant difference from vehicle infusion in the HAL group ($p < 0.05$), and bars with ‡ are significantly different from one another ($p < 0.05$), indicating a within-treatment group difference.

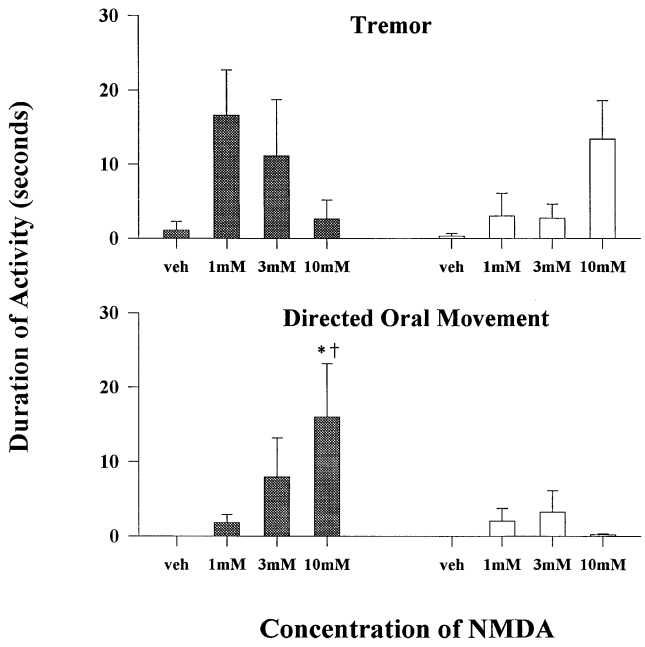

FIG. 3. Duration of NMDA stimulated tremor and directed oral movement in HAL rats (shaded bars) and CON rats (open bars), over a range of three concentrations. * Indicates a significant difference from vehicle and all concentrations in the CON group ($p < 0.05$) and † indicates a significant difference from vehicle infusion in the HAL group ($p < 0.05$).

tivation only occurred in neuroleptic-treated rats. A number of studies have shown enhancement of motor responses in neuroleptic treated rats, including oral movements and locomotion following systemic administration of drugs such as DA agonists (10,53). To our knowledge, this is the first report of enhanced oral movements and locomotor activity in chronic neuroleptic-treated rats via direct cortical stimulation.

The NMDA-mediated cortical stimulation presumably resulted in activation of corticostriatal projections, because NMDA applied to the frontal cortex has been shown to increase glutamate levels in the striatum (32). NMDA receptors have been localized throughout the layers of the cortex, and it has been suggested that NMDA interacts in all afferent and efferent systems of the cortex (7). Motor-related thalamic afferents to the cortex have been identified (6) that produce a glutamate-mediated excitatory effect on cortical neurons (33). NMDA exerts an excitatory influence on cortical cells (51), and recent evidence suggests that presynaptic autoreceptive NMDA receptors exert a facilitatory influence over glutamate release (2,20). Excitation of corticostriatal projections could, therefore, have been mediated via direct activation of these cells or by presynaptic local excitatory circuits (51).

The emergence of motor behaviors in the HAL rats was related to the concentration of NMDA infused into the cortex. The most robust oral behavioral response occurred with the 1 mM concentration of NMDA. This low concentration may have affected the behavioral response at subsequent higher concentrations, perhaps by decreasing available glutamate from corticostriatal terminals or via some form of inhibitory feedback response. This explanation does not fully account for the finding that the greatest amount of non-directed oral activity was seen in the HAL animals following 10 mM NMDA. It is possible that response competition between non-directed and directed oral movements resulted in a shift of expression at the different concentrations, although the total duration of directed oral movements was considerably less than the sum of non-directed oral movements, tremor, and audible oral activity. Although the behavioral observations following second and third infusions of NMDA are confounded by exposure history, they do contribute to an understanding of oral behavior following chronic haloperidol. As noted above, non-directed oral activity was most apparent following the third and highest concentration of NMDA. In addition, no significant exposure effects were observed in the control (oil-treated) rats. The behaviors occurring following the later infusions of NMDA were, therefore, relevant to chronic haloperidol treatment.

These emergent motor effects were likely mediated by chronic haloperidol-induced changes in the function of glutamatergic cortical efferents. Cortical stimulation has been shown to increase glutamate in the striatum (15,35) and changes in dopaminergic tone modulate striatal glutamate activity (4,26, 57). As mentioned above, chronic DA receptor blockade by haloperidol leads to increased basal levels of striatal glutamate (44,48,49,56). Chronic haloperidol increased glutamatergic perforated synapses in the striatum (29,46), an effect simulated by direct activation of the corticostriatal pathway (28). Furthermore, NMDA and non-NMDA receptor antagonists have been reported to block oral movements induced by striatal microinfusions of amphetamine (22). A role of the corticostriatal projection in the exaggerated oral and locomotor activity seen in the chronic haloperidol-treated rats is, therefore, quite

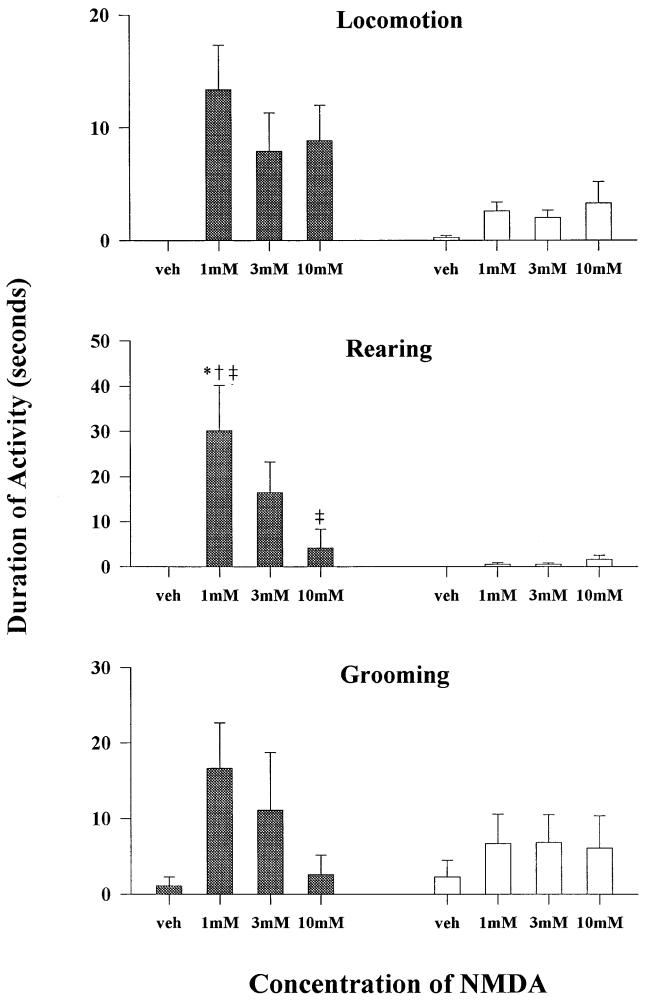

FIG. 4. This figure compares non-oral NMDA-stimulated behaviors in HAL rats (shaded bars) and CON rats (open bars) over a range of three concentrations. * Indicates a significant difference from vehicle and all concentrations in the CON group ($p < 0.05$), † indicates a significant difference from vehicle infusion in the HAL group ($p < 0.05$), and bars with ‡ are significantly different from one another ($p < 0.05$), indicating a within-treatment group difference.

tenable. The enhanced motor response in the HAL rats may be due to heightened release of glutamate in the striatum. The fact that the CON rats did not show such a behavioral response suggests that glutamate release may be tightly regulated in normal animals, but that pathologic changes induced by neuroleptics may disrupt such regulation.

Other possible glutamatergic mechanisms that may have produced the motor behaviors seen only in the HAL rats include a sensitization of glutamate receptors in the cortex, as antipsychotic drugs have been shown to increase NMDA receptor binding in cortical areas (54). Alternatively, NMDA receptors could be altered within the striatum, as it was found that the noncompetitive NMDA antagonist, MK-801, blocked the expression of perforated synapses by subchronic haloperidol (29). It is also possible that excessive activity of glutamatergic innervation in this area could lead to impairment or loss of striatal neurons due to excitotoxic damage (24), perhaps directly or indirectly releasing inhibitory output pathways.

A more direct dopaminergic mechanism underlying the observed emergent behaviors is also possible. Enhanced glutamate mediated DA release and/or increased DA receptor sensitivity in the striatum in the HAL rats could have contributed to the emergent behavioral response to cortical stimulation. Cortical stimulation has been reported to increase striatal DA release (52), and glutamate can stimulate DA release at nigrostriatal terminals (14,37). Striatal DA receptor supersensitivity has been hypothesized to mediate the behavioral sensitization and elevated oral movements found in chronic haloperidol treated rats [for review, (13,30,45)]. However, several studies assessing spontaneous oral behaviors and receptor binding in the same animals administered chronic neuroleptics have reported a lack of correlation between oral movement increases and changes in DA receptors (25,42, 50,55). Thus, it is unlikely that striatal DA receptor upregulation is the primary substrate of the emergent behaviors seen in the HAL rats. If DA receptor activation was a component of the observed effects, it is important to note that elicited behaviors were observed despite persisting levels of available haloperidol. It is possible that at a later withdrawal point, a more dramatic emergence of cortically stimulated behaviors would have been apparent.

A final possible explanation of the emergence of cortically stimulated movements in the present study is seizure activity. Chronic neuroleptic induced oral movements have been previously described as resembling masticatory movements during grade I seizures in electrical kindling experiments (13). In addition, there is some evidence that behavioral sensitization to DA agonists not only occurs in rats pharmacologically sensitized, but also in rats exposed to electrical kindling of the ventral tegmental area (12). If seizure mechanisms were involved at some level in the behaviors observed in the present study, these findings would suggest a novel substrate of neuroleptic-induced kindling of oral and locomotor activity through the oral motor cortex. However, seizure-like movements were not apparent in either HAL or CON rats in the present study. In addition, if seizure-like effects played a role in causing the noted effects, higher concentrations of NMDA should have lead to an even greater increase in oral and locomotor behaviors.

Emergence of non-oral motor behaviors, as with oral behaviors, markedly distinguished HAL from CON rats. The reason for the NMDA activation of non-oral behaviors is not clear, because the infusion sites were located in an area of the motor cortex previously well characterized as an orofacial region (18,38). It is possible that the microinfusion technique utilized in the present study allowed for diffusion of NMDA from the cannulae sites, which could have affected nearby cortical regions leading to increased locomotor and rearing activity. This is unlikely, considering that the oral motor regions are relatively distant from areas involving forelimb and hindlimb control (18,38). In addition, the appearance of behaviors observed in the present study was limited to the first few minutes after infusions. Another explanation is that activation of the target area of motor cortex indirectly affected other cortical and striatal regions beyond those involved in oral activities. For example, pharmacological stimulation of subregions of the ventral striatum increases locomotor activity (21), and such effects are potentiated in haloperidol-treated rats (19). The enhanced locomotor activity seen in the haloperidol-treated rats may even represent a form of akathisia-like behavior, in contrast to the oral movement increases, which may be more of a TD analogue. Regardless, the fact that the greatest behavioral effects, both oral and non-oral,

occurred at similar doses of NMDA suggests a common underlying factor, perhaps corticostriatal activation.

The results of the present study indicate that alterations in descending projections of the oral motor cortex are involved in the production of aberrant movements in rats chronically exposed to haloperidol. Although several mechanisms can be hypothesized as having mediated the observed effects, the results from direct cortical stimulation implicate an important role of cortical projections and further support the theory that glutamatergic dysfunction may contribute to TD. Continued assessment of corticostriatal function should provide a clearer understanding of the exact role of these pathways in TD and other chronic neuroleptic-induced motor side effects.

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