Quantifying Operant Behavior Deficits in Rats with Bilateral 6-Hydroxydopamine Lesions of the Ventrolateral Striatum

Ruey-Ming Liao[1], Stephen C. Fowler[2] and Mary J. Kallman[3]

Department of Psychology[1]
National Cheng-Chi University
Taipei, Taiwan, ROC
Department of Human Development[2]
University of Kansas
Lawrence, Kansas, USA
and
Eli Lilly and Company[3]
Greenfield Laboratories
Greenfield, Indiana, USA

Abstract

The present study examined the effects of bilateral 6-hydroxydopamine lesions in the ventrolateral striatum on the operant behavior of rats. Use of the specially modified operant chambers allowed the measurement of forelimb response force and duration as well as the time intervals between selected behavior in the press-consume-press sequence. More specifically, four time intervals between separate behavioral events were measured: 1) the time from the end of forelimb response to entry of muzzle into the reinforcement well, 2) the time from muzzle entry to the first tongue lick of the water reinforcer; 3) the time from the last lick to muzzle withdrawal from the reinforcement well, and 4) the time from muzzle withdrawal to the beginning of the next forelimb operant response. As determined by neurochemical (HPLC) analysis, the lesioned group exhibited dopamine levels that were 35 % of the control group. The operant behavioral deficits were most profoundly appeared in the first week of postoperative test. Behaviorally, the lesioned group exhibited longer forelimb response durations (bradykinesia), and decrements were seen in both the number of muzzle entries and the number of recorded licks during reward consumption. Furthermore, the lesion significantly increased the average latency to switch from the forelimb response to the entry of the muzzle into the reward well. The latency from well entry to the first tongue extension to the reward was also increased by the lesion. These data support the view that the rodent neostriatum is important in the control of behavioral sequences for psychomotor function and at the same time demonstrate the utility of new quantitative behavioral methods for investigating such functions.

Key Words: 6-hydroxydopamine, striatum, operant behavior, forelimb, head-entry, lick, rat

Introduction

Bilateral destruction of the striatum in the rats produce deficits in various behavioral tasks characterized as either reflexive or learned, including somatosensory reflexes (8), locomotor activity (24), feeding behavior (15, 21, 22, 23, 28), avoidance behavior (17, 31), spatial learning behavior (30), and appetitive operant behavior (5, 27). Because the rodent striatum contains the major terminal region for the mesotelencephalic dopamine (DA) projection (1), it has been suggested that the striatal DA plays a crucial role in behavioral functions. Evidence to support this idea can be collected from previous

Corresponding author: Ruey-Ming Liao, Ph.D., Department of Psychology, National Cheng-Chi University, Taipei, Taiwan, ROC. Tel: (02) 9387048, Fax: (02) 9390644, E-mail: rmliao@cc.nccu.edu.tw

studies using 6-hydroxydopamine (6-OHDA), a dopaminergic neurotoxin that induces striatal lesions leading to behavioral deficits to various degrees (5, 15, 17, 28). Moreover, behavioral impairments produced by DA receptor blockade consequent to neuroleptic drug treatment are congruent to this hypothesis (review see 7). Due to the relatively gross measures of behavior used in much of the previous work, the specific role of DA in rodent behavior performance remains unclear. This is especially true for the learned or conditioned behavior such as the operant behavior.

Although suppression of operant responding on different schedules of reinforcement has been reported in rats following lesions of various DA-rich loci (25) or following widespread lesions via intraventricularly administered neurotoxin (20), relative little research has been performed to investigate the operant effects of dopaminergic depletions by 6-OHDA lesions in the striatum. One exception is the recent work of Salamone and collegues, who evaluated the putative striatal substrates of food-related instrumental behaviors (5, 27). In comparing three striatal subregions, their results showed that DA depletion in the ventrolateral striatum produced the most profound deficits in lever-pressing and food consumption. Furthermore, they reported that the operant deficits was resulted from the slowness of local response rate for the fixed-ratio 5 (FR5) behavior. It was then suggested that DA in the ventrolateral striatum is particularly necessary for maintaining the operant behavior. These cited data along with the converging evidence indicating that the rodent striatal region is related to oral movement and forelimb control (4, 18, 21, 23, 24), suggest that the modulation of distinctive components of operant behavior by striatal DA activity is somewhat localized. Therefore, the present study aimed to further examine the role of ventrolateral DA involved in the performance of operant behavior. For some time it has been recognized that operant measures have considerable utility in behavioral neuroscience, even though operant data has almost always been limited to response rate (14). By complementing the rate variable, measurements of the biophysical characteristics of operant response, such as duration, force, and force-time waveform, have been shown to provide important information in revealing the operant behavioral mechanisms under DA receptor blockade (11, 12, 16). Likewise, these measurement techniques should be useful and sensitive in analyzing the operant behavior following the 6-OHDA lesions in the ventrolateral subregion of the striatum.

Methods

Subjects

The subjects were 12 male Sprague-Dawley rats (Holtzman Co.), averaging approximately 375 g in body weight at the time of 6-OHDA treatment. Each rat was housed individually with Purina lab chow available ad libitum. By limiting their water access to approximately 3 min per day, the rats were maintained at 85 % of their pre-experiment body weight. The water access was provided 30 min after the daily sessions. Training and/or testing sessions were administered at the same time period during the light portion of the 12-hr light-dark cycle in the vivarium.

Apparatus

Eight, simultaneously operative, conditioning chambers were utilized. The chambers, measuring 23 cm long, 20 cm wide, and 19 cm high, were fitted with a grid floor constructed of stainless steel rods running parallel to the front of the chamber. The chamber front and back panels were fashioned of 1.6 mm aluminum, while the top and sides were 6.3 mm clear plexiglas. Illumination was provided by a 24-volt GE 1819 light bulb mounted on the left side panel 4 cm from the chamber top and 4 cm from the front panel. Mounted on the lower right front panel was a cylindrical recession that permitted access to a solenoid operated dipper with a volume of 0.1 ml. A rectangular opening, 3.0 cm wide and 2.5 cm high, was centered in the front panel 5.5 cm above the grid floor. Each chamber was equipped with a Sensotec isometric force transducer (model 31, Sensotec Inc., Columbus, OH). Attached to the top of each transducer was an 18 mm diameter circular disk. Each transducer was located outside the chamber 2.5 cm from the center of the disk to the outside plane of the chamber wall. Two sets of photosensors (SEP8703-001 and SEP8403-301, Radio Shack) were installed inside the cylindrical recess to measure the head entries into the reward well. A photodetector was also positioned to detect tongue licks on the dipper during reinforcement delivery.

Contingencies were programmed and data were recorded with microcomputers (Z-159, Zenith) equipped with Labtender interface boards manufactured by Scientific Solutions. Detailed descriptions of these measurement techniques were given elsewhere (10). The software, written in Turbo Pascal, directed the A/D converter of each computer to sample the output of the transducer at 100 Hz for two chambers simultaneously. These samples were used to define a response, its duration, and/or its peak force. A forelimb response was defined as any emitted force rising above a threshold of 4 g. A lick or a head entry in the operant chamber was determined by the photobeam interruption. Response force was measured with a precision of 1 g and duration with a

precision of 0.01 sec. The peak force and duration variables were recorded online and in real time.

Procedure

Prior to lesioning, all subjects were trained to perform the forelimb operant response. Training began with a 15-min session of exposure to a variable-time 30-s schedule of 4-s dipper presentation (magazine training). In subsequent 15-min sessions all animals were manually shaped to press the 18 mm disk mounted on the force transducer (which served as the operandum instead of the more conventional movable lever). After shaping, the animals were placed on an continuous reinforcement (CRF) schedule for 21 sessions. Each CRF session of 4 min was conducted in the time period from 8:00 to 10:00 am. The dipper presentation time was 2.5 sec from the beginning of the CRF sessions to the end of experiment. Tap water served as the reinforcer for the operant responding.

In all 11 dependent variables were derived from the force transducer and photobeam recordings (see Figure 1 for a descriptive diagram showing durations and latencies of events; note that force amplitude which was recorded is depicted only as an event in this diagram). The dependent variables were forelimb mean peak force, forelimb duration, number of forelimb responses per 4-min session, average tongue lick duration, number of licks, duration of muzzle for head entries, number of head entries, latency from forelimb response termination to head entry into reinforcement well (FH latency), latency from head entry to the beginning of the first lick (HL latency), latency from the end of the last lick to head exit (LH latency), and head exit to the beginning of the next forelimb response (HF latency).

Following preoperative testing, animals were randomly assigned into the ventrolateral striatum lesion group (N=6) and the sham control group (N=6). Stereotaxic surgery was conducted under anesthesia of 6 mg/kg xylazine and 80 mg/kg ketamine, IM injections for both. In order to reduce neurotoxic damage to noradrenergic terminals, the animals were given 30 mg/kg desipramine (IP) 30 min prior to the 6-OHDA infusions (2,3). As determined from Paxinos and Watson (19) the coordinates for injection of the toxin were as follows; AP=0.9 mm, L=±3.7 mm, and D=-5.7 mm (AP refered to the bregma and D refered to the dura). Once the injector cannula was in position, 6 ug of 6-OHDA hydrochloride (Sigma Co.) dissolved in ice cold 1 ul isotonic ascorbic aci d (0.02%) vehicle was mannually administered with a microsyringe across 5 min. The injector remained in position for another 5 min to enhance diffusion from injection site. Subsequently, the wound was sutured and 0.2 ml

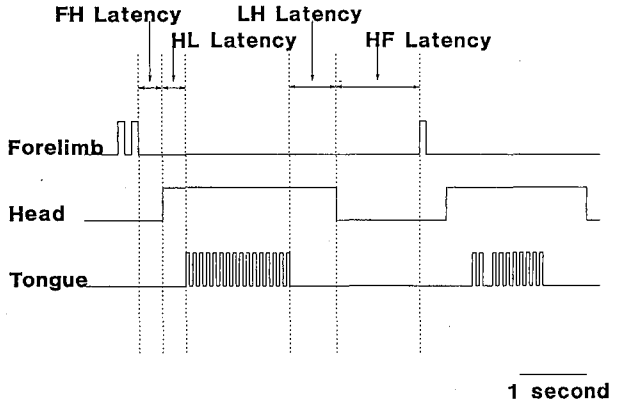

Fig. 1. This diagram, at the microbehavioral level, illustrates the sequential performance of rats in the modified operant chamber. Four latencies in the sequencing of behavior were used as dependent variables as shown. F, H and L abbreviate forelimb, head (muzzle), and lick (tongue), respectively. For example, the FH latency represents the rat's switching from forelimb-press to head-entry into the reinforcement well (see Procedure for more details).

of penicillin (60000 units) was injected (IM) to reduce the likelihood of postoperative infection.

Rats were allowed to recover in their home cages for seven days. Special nutrients of chocolate milk and wet mash (ground lab chow) were provided during the recovery period. After the 7-day recovery, postoperative tests were conducted with daily sessions of 4 min for a month (but only the first week of postoperative data were presented here). Following the completion of behavioral data collection, rats were killed by decapitation. Their brains were rapidly removed and dissected on ice for high performance liquid chromotography (HPLC) analyses. Each brain was sectioned with a scalpel 1.5 mm in front of the optic chiasm and again 0.5 mm behind the chiasm. The striatum was removed from this 2 mm thick block of tissue by peeling off the overlying cortex and sectioning off the surrounding tissue with a metal spatula. This wedge of striatum represented the portion of the striatum located between 1.6 mm anterior to bregma and 0.4 mm posterior to bregma. After dissection, these striatal samples were quickly frozen on dry ice. These samples were weighed and stored in a deep freezer (-70 degrees centigrade) until assayed. The extraction procedure for HPLC analyses was conducted following the method of Gregory et al. (13).

Results

Postoperation Recovery

Inspection of the postoperative data (first day of postoperative data collection was the eighth day after

the lesion) showed that the effects of 6-OHDA lesions were more conspicuous in the first week. Therefore, the results reported here are based on the first postoperative test week. Although varying degrees of akinesia were exhibited by lesioned rats, all subjects started gaining weight on the first day after surgery. By the end of 7 postoperative test days, the means of body weight were back to what both groups had in the preoperative period. In terms of ANOVA for body weight changes across 7 postoperative test days, there was no significant difference between the two groups and no interaction between group and day. However, the body weight significantly increased across the seven home-cage-only days, $F_{(6,60)}=7.585$, $p< 0.001$.

Neurochemical Analyses

Each subject supplied two striatal samples, taken one from each hemisphere for HPLC analyses of the DA level. Since the ANOVA result showed no significant difference between right and left striatal samples, the average of both samples in each rat for DA level was used for data analyses. Rats treated with 6-OHDA had significantly lower dopamine levels than the control rats, $t=10.511$, $df=10$, $p<0.001$. Group means and standard errors of the means (SEM) of the DA concentrations remaining in the assayed tissue for the control and lesioned groups were 1295±67 and 451±43 ng/100 g tissue, respectively. The lesioned group exhibited a 65% DA depletion compared with the control group.

Behavioral Analyses

As shown in Figure 2, the number of forelimb responses for the lesioned group was not significantly different from that of the control one. Both the forelimb response force and the response duration appeared to be higher in 6-OHDA treated rats than in the control ones. However, the statistical difference between groups revealed by the ANOVA results was significant only for the forelimb duration, $F(1,10)=4.24$, $p=0.06$. The $p=0.06$ was considered to be significant because previous work with decreased dopamine function induced by the dopamine receptor blocker haloperidol produced increased response duration (e.g., 16). This expectation makes the result significant as a one-tailed hypothesis test.

Figures 3 and 4 illustrate the results for head-entry into the reward well and tongue lick on the water dipper, respectively. No significant difference between two groups was revealed for the duration measures of the head-entry or for the lick behavior. But, the lesioned rats made significantly fewer of head entries and licks than the control ones did, $F(1,10)=5.426$, $p<0.05$ and $F(1,10)=12.206$, $p<0.001$, respectively.

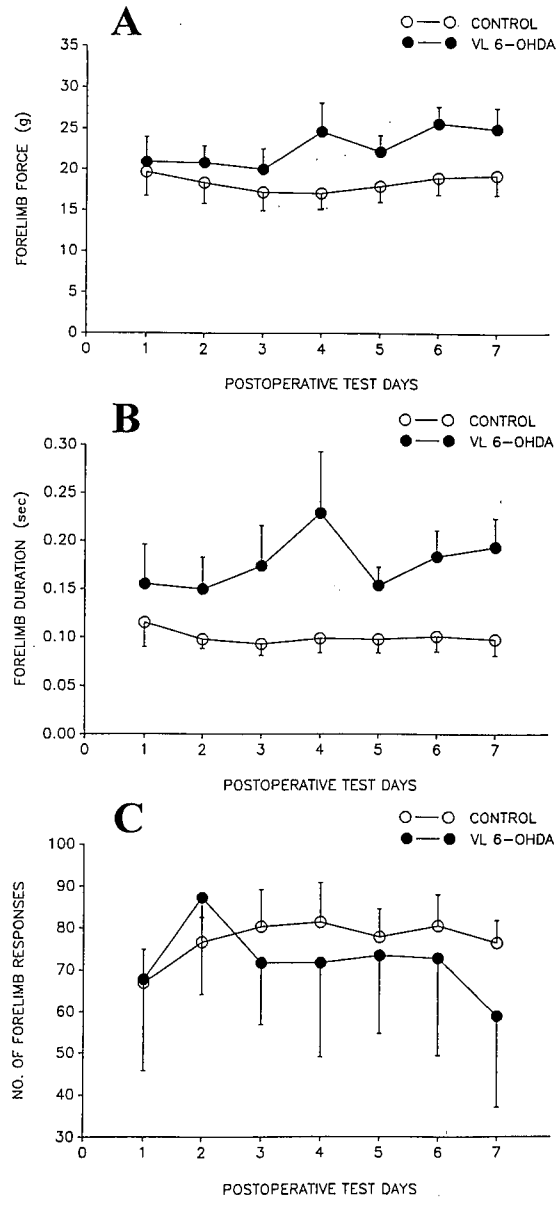

Fig. 2. Group means of the forelimb responding for the sham control and 6-OHDA lesions in the ventrolateral (VL) striatum across 7 days of postoperative testing. Data are presented for the variables of force (panel A), duration (panel B), and number of forelimb responses (panel C) from top to bottom, respectively. Each error bar represents 1 SEM.

Behavioral sequencing of individual acts during the operant performance was quantified by the latency measures (See Fig. 5). The lesioned rats had significant slowing for the FH latency, $F(1,10)=9.92$, $p<0.01$, for the HL latency, $F(1,10)=6.581$, $p<0.0\,5$, and for the LH latency, $F(1,10)=7.373$, $p<0.05$. However, the increase in the HF latency was not significant possibly owing to the large variability in this measures for two of the days.

In summary, the foregoing behavioral data

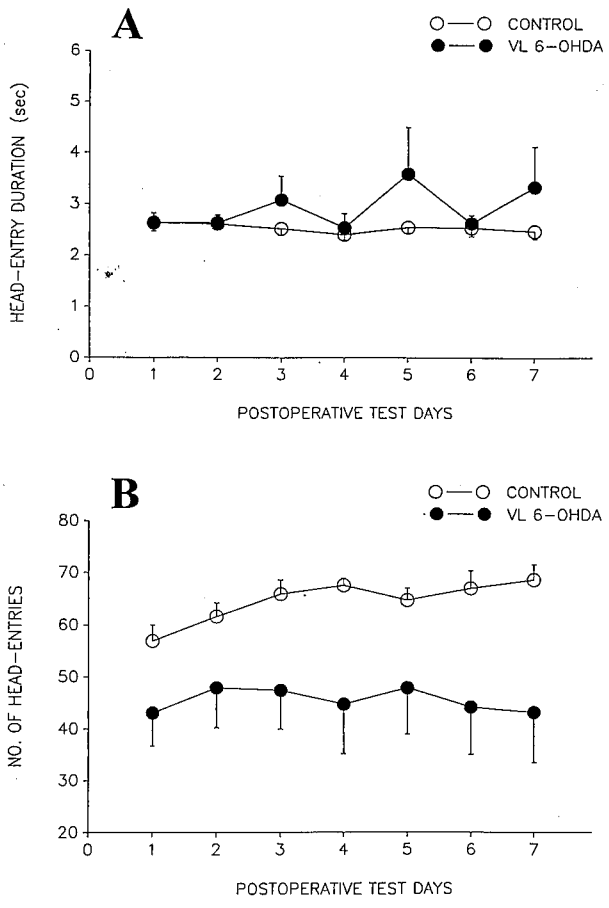

Fig. 3. The average duration (panel A) and number of head entries (panel B) for the sham control and 6-OHDA lesion groups across 7 postoperative test days. Each data point denotes group mean and 1 SEM

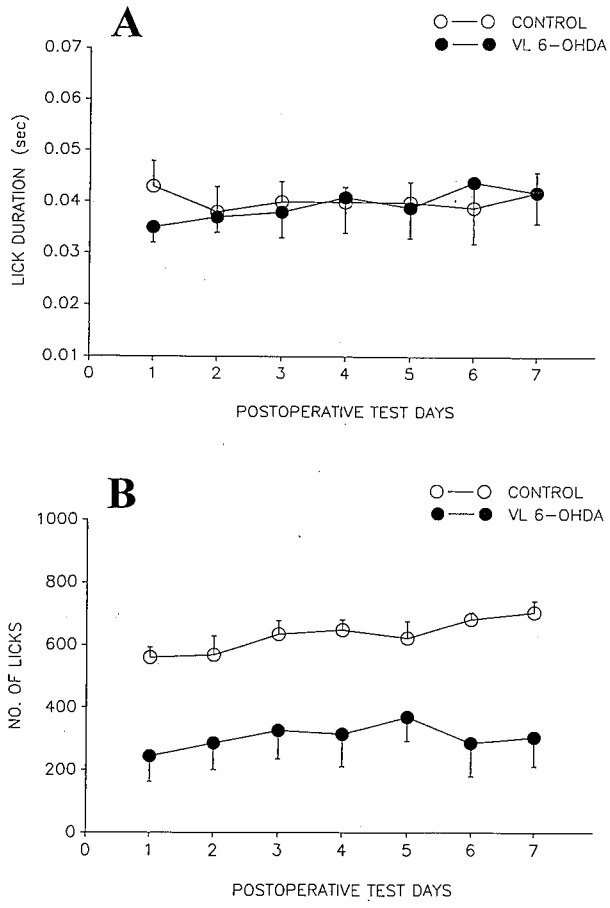

Fig. 4. The average duration (panel A) and number of licks (panel B) for both experimental groups across 7 postoperative test days. Each data point denotes group mean and 1 SEM.

showed that the 6-OHDA lesion decreased the numbers of head entries and licks and increased duration of forelimb operant responses. The sequences of specific acts constituting operant behavior were disrupted by 6-OHDA lesions in terms of a decrease in the number of consecutive events as well as increasing the intervals between different acts. The largest effects on the latency measures were for the FH, HL, and LH latencies.

Discussion

The present study demonstrated the impairment of operant behavior after bilateral depletion of DA by infusion of 6-OHDA into the ventrolateral striatum in rats. The rats which received 6-OHDA lesions tended to make fewer head entries and fewer licks than the control rats did. However, this was not the case for the number of forelimb responses on the force transducer to measure the operant responding. In general, these results are in agreement with the findings that interference with dopaminergic transmission in the brain seems to impair performance in the operant environment (9, 32). The source of this impairment in operant behavior has been a problematic issue.

Regarding the force and duration of the forelimb responding, 6-OHDA lesions produced various degrees of dysfunction. The present 6-OHDA treatment increased operant duration, but it did not significantly affect force. The increase in forelimb response duration was similar to those produced by peripherally administered neuroleptics (10, 11, 16). The duration-increasing and rate-decreasing effects of haloperidol suggest that neuroleptic action slows behavioral processes. In other words, rats treated with haloperidol make each response longer in the temporal domain, and these longer duration responses contribute to the drop in the number of responses (16). The operant deficits of forelimb response rate (responses in 4 min) after the present lesions are less in degrees than those observed in the previous work using relatively low dose (0.08 mg/kg) of haloperidol.

When the data in the first postoperative test

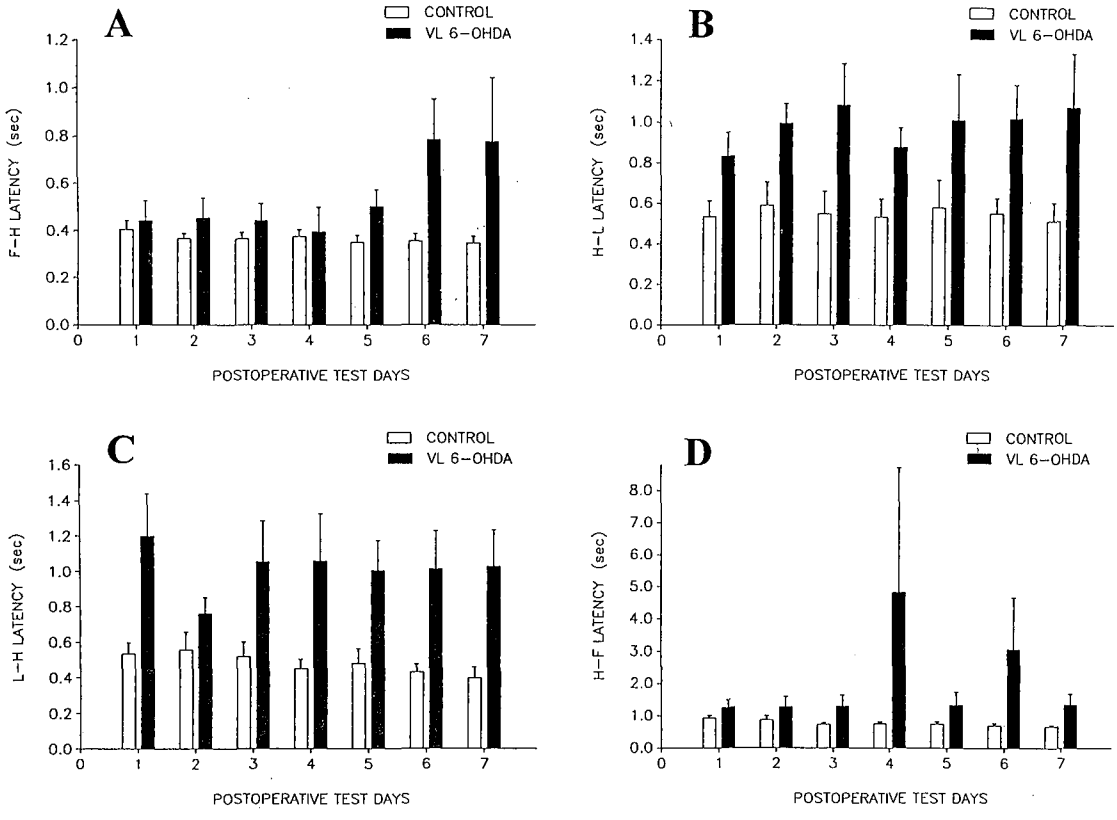

Fig. 5. The FH (panel A), HL (panel B), LH (panel C), and HF (panel D) latencies as defined in Figure 1 for both experimental groups. The 6-OHDA lesion resulted in a general increase in the latencies to switch from one behavior to another. Each data point denotes group mean and 1 SEM.

week for the lesion group are combined and compared to the control group, the lesioned subjects as a group displayed the numbers of forelimb responses, head entries, and licks that were, respectively, 93%, 70% and 48% of control level. Thus, the 6-OHDA lesions in the ventrolateral striatum had relatively more impact on reducing the licks than the head entries and the forelimb responses. Further, the head entries were suppressed more than the forelimb responses following the treatment with 6-OHDA. This ordering of effects may be understood by considering the behavioral coordination of forelimb, head entry, and lick responding in the sequences performed in the modified operant chamber of current study. First, the lesioned rats in the present study were still apparently motivated to initiate forelimb responding on the force transducer. Nevertheless, the forelimbs of the lesioned rats exhibited dysfunctions which caused the response force and duration to be higher than in the control rats. Second, motoric function was impaired for these lesioned rats when they had to shift movement after a forelimb response was made, thereby affecting the following consumption-related behavioral processes including head entries and licks. Finally, although the lesioned rats were deficient in the speed of getting the reinforcer, their motivational state was still sufficient for them to maintain responding. In other words, they are only partially impaired in the execution of sequences of operant behavior. Together, the above reasoning from the forelimb measurements suggest that initially the motivation to perform in the lesioned rats was at least partially intact, but more dysfunctions led to an inability to perform well enough to keep reinforcement levels adequate to maintain responding at control levels.

The behavioral alterations in forelimb and lick responding for the lesioned group in the current study may have resulted from functional impairments in bodily movements and slowing of responses. The behavioral impairments of forelimb and tongue which resulted from the ventrolateral striatal lesion were congruent with the findings of others localized lesions of the rodent striatum (21, 22, 23). In that cited series of reports, forelimb and tongue reaching movement for food were assessed in rats with several different ibotenic acid lesion sites in the striatum. Pisa and colleagues found that: 1) the most significant impairments on the initiation and execution of forelimb and tongue movement were derived from the ventrolateral lesion, 2) the dorsolateral lesion produced similar behavioral deficit but with less severity, and 3) no chronic effects on either task was

obtained for the dorsomedial lesion group. Such behavioral disturbances have also been seen in rats with selective lesions of the dopaminergic pathway projecting to the lateral or ventral caudate or striatum (6, 26). Together with the previous reports, the present study supports the hypothesis that the DA of the ventrolateral striatum is involved in the control of psychomotor functions.

It may further be hypothesized that the ventrolateral striatal area is more specifically involved in the motor control of the tongue licking than the forelimb responding. One of the most important results in the present study is that the lesioned rats reliably showed longer HL and LH latencies than the controls, and these specific effects were consistently larger than FH and HF latencies across the postoperative test days. Lesioned rats were apparently impaired in initiating tongue movement and in withdrawing the head (and body) from the reward well after a lick bout. These observations are consistent with Schallert's (29) view that the rodent striatum integrates the orienting and ingestive acts required for drinking behavior.

In conclusion, the behavioral impairments measured from the operant response and its associated consummatory behavior showed that the 6-OHDA lesions may have produced a lack of forelimb motor control and at the same time slowed the execution of sequential movement. Among the three behavioral components in the specialized operant chamber, the 6-OHDA lesions quantitatively affected forelimb responding, head entry, and licking in an increasing order. The pattern of these behavioral changes is somewhat similar to the motoric deficits induced by neuroleptics. In fact, the effects of striatal DA depletion have been shown to be additive with the effects of neuroleptic blockade of DA receptors (15). According to Jicha and Salamone (15), vacuous chewing responses specifically resulted from the depletion in the ventrolateral striatum, and these vacuous chewing movement were increased by systemic administration of haloperidol. Taken together, these data support the idea that behaviors impaired by 6-OHDA lesion in the striatum may be analogous to the behavioral deficits of Parkinson's disease resulting from degeneration of the DA system. Further evidence is needed to reveal more precisely the behavioral functions of the striatum. The methods used here should contribute to this end.

Acknowledgements

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