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Changes in Behavior and Monoamine Levels in Microdialysate From Dorsal Striatum After 6-OHDA Infusions Into Ventral Striatum

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TRAN-NGUYEN, L. T. L., E. CASTAÑEDA AND T. MACBETH. *Changes in behavior and monoamine levels in microdialysate from dorsal striatum after 6-OHDA infusions into the ventral striatum.* PHARMACOL BIOCHEM BEHAV **55**(1) 141–150, 1996.—Long–Evans rats received bilateral 6-hydroxydopamine infusions into the nucleus accumbens and were tested immediately (1 and 2 days) or after a recovery period (14 and 15 days) for changes in extracellular levels of dorsal striatal monoamines using in vivo microdialysis. Compared to controls, the monoamine metabolites 3,4-dihydroxyphenylacetic acid, homovanillic acid and 5-hydroxyindoleacetic acid were generally enhanced when tested immediately after 6-hydroxydopamine treatment, including spontaneous levels and those following depolarizing infusions of potassium (60 mM, 20 min) through the microdialysis probes. Following 2 weeks recovery, dopamine metabolite levels were depressed and the serotonin metabolite levels remained enhanced. D-Amphetamine sulfate (1.5 mg/kg, SC) stimulated dopamine overflow was enhanced 2 days after 6-hydroxydopamine administration, but not after 2 weeks recovery. In contrast, potassium increased dopamine overflow to the same extent as control animals regardless of recovery period following 6-hydroxydopamine. The immediate changes in striatal monoamine activity were accompanied by a potentiation of amphetamine-induced stereotyped behaviors. We suggest that transient presynaptic changes within the dorsal striatum following disruption of the ventral striatum may mediate some general aspects of loss and recovery of behavior related to the time course of 6-hydroxydopamine neurotoxicity.

Microdialysis Recovery of function Potassium Dopamine Amphetamine Vesicular pool
Monoamine metabolites Stereotyped behaviors Locomotion 6-Hydroxydopamine Cytoplasmic pool

ALTHOUGH the striatum is similar throughout its structure in neurogenetic embryology, cytoarchitecture, and chemical neuroanatomy (60), much evidence supports the idea that there exists a functional heterogeneity within this structure. The ventral striatum includes the nucleus accumbens (NAc), which is the terminal field for the mesolimbic DA pathway that originates in the ventral tegmental area (VTA), and is particularly important for mechanisms of reward (24). The dorsal striatum contains the caudate-putamen complex (CdN), the terminal field for the nigrostriatal pathway that arises from the substantia nigra (SN), and may have a greater role in motor and sensorimotor function (14,20,33,34,56,59,63). A motor function for the ventral striatum has also been suggested by reductions in spontaneous, drug-induced and schedule-induced locomotor activity following DA depletions within the NAc (22,25,26,66), although such decreases in motor activity could be attributed to changes in reward. Nonetheless, sufficient evidence exists in which changes in behaviors controlled by conditioned reinforcers and discriminative stimuli functionally distinguish the ventral striatum from the dorsal striatum (36,47). For example, 6-hydroxydopamine (6-OHDA) microinfused into the NAc decreases instrumental responding for food, although these animals consume as much, or more, freely available food (11,55), but similar infusions more dorsally in the striatum produce motor deficits that reduce both lever pressing and the amount of freely available food consumed (11,54). In addition, the acute motor stimulant effects of AMPH may also be compartmentalized within the striatum. The mesolimbic pathway primarily mediates the locomotor response to AMPH (10,23,40–42) but the nigrostriatal pathway

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may be more important in the expression of AMPH-induced stereotypy, including sniffing, gnawing, biting, and repetitive head and limb movements (2,10,12,18,23,38). Therefore, the dorsal striatum can be considered functionally distinct from the ventral striatum, even though these two areas are cytoarchitectonically similar. The terms CdN and NAc are used in this report to emphasize the functional distinction between the dorsal striatum and ventral striatum.

Studies that have compared selective infusions of 6-OHDA into the CdN or NAc have provided evidence for a competition between the nigrostriatal and mesolimbic systems to express behavior (9,21,23,35,65). In particular, following DA depletions within the NAc there is an enhancement of stereotyped behavior following systemic AMPH administration, but after DA depletions within the CdN the behavioral response to an AMPH challenge is primarily an enhancement in the locomotor response (21). These increases in behavioral responses to AMPH have been interpreted as a release from competition, but what is not clear is whether there are neurochemical changes that take place in the surviving striatal region that enhance the responsiveness to AMPH or whether all that is required is a diminution in competition due to damage in one DA system. There is evidence to suggest that transient neurochemical changes do occur in intact mesotelencephalic DA systems. For example, it has been shown that the ipsiversive turning evoked by AMPH immediately following hemidecortication is accompanied by a bilateral enhancement in AMPH-stimulated extracellular levels of DA from the CdN, as well as increased spontaneous 3,4-dihydroxyphenylacetic acid (DOPAC) overflow (8). Following a recovery period, the AMPH-evoked ipsiversive turning disappears and extracellular striatal levels of spontaneous DOPAC and AMPH-evoked DA return to normal, indicating that such neurochemical aberrations could be responsible for some aspects of loss of function and subsequent recovery. In an independent study, a decrease in cerebellar NE levels and an attenuated response to AMPH was reported 1 day after contusions of sensorimotor cortex (27), suggesting that immediate alterations in monoaminergic activity from surrounding brain regions may be a general phenomenon of brain damage.

This study sought to determine whether underlying monoaminergic changes within the dorsal striatum could account for transient changes in behaviors immediately following 6-OHDA infusions into the ventral striatum, as well as following a recovery period. To accomplish this goal, in vivo intracerebral microdialysis was used to evaluate whether there are changes in spontaneous, depolarization-induced release using high potassium (K^+) and AMPH-stimulated overflow of DA and monoamine metabolites. It was hypothesized that 6-OHDA infusions into the NAc may induce changes in DA turnover from the CdN. It was further expected that changes in AMPH-evoked behaviors would parallel biochemical changes measured in the CdN.

METHOD

Subjects and Experimental Design

Adult male Long–Evans rats, weighing 300–350 g at the start of the experiment, were maintained in the Arizona State University Psychology Department animal vivarium. Prior to testing, they were housed in groups of three in hanging wire mesh cages but after probe implantation rats were individually caged in a Plexiglas test chamber (31 × 31 × 35 cm) containing a stainless steel bowl (10 cm deep, 27 cm diameter) with a rounded floor which was covered with wood shavings. The animals were kept on a 12 L:12 D cycle (lights on at 0600 h). During testing (about 3 h each test day), food was continuously available and water was not provided, but both were freely available at all other times. All procedures were carried out according to protocol approved by the Animal Care and Use Committee (Arizona State University).

Twenty-nine rats were randomly assigned to a lesion (LX) group that received bilateral infusions of 6-OHDA into the NAc or a control (CTRL) group that was anesthetized but did not receive intra-NAc infusions. The CTRL group consisted of unoperated animals because previous research has indicated no behavioral or neurochemical differences between unoperated and sham-operated controls using the present procedure (7). Animals were also randomly chosen for testing on days 1 and 2 after 6-OHDA infusion (acute group) or on days 14 and 15 postsurgery (chronic group).

For animals in the LX groups, two a priori criteria were imposed. First, in our laboratory postmortem measures of NAc DA are usually well within a 20% range of variance, so we excluded those animals with less than 20% NAc DA depletions. Second, we expected that significant DA depletions in the NAc would not occur without producing some DA depletions in the CdN, because it is well established that 6-OHDA applied to forebrain structures inevitably produces damage to surrounding tissue and other structures further removed from the infusion site (61,62). Therefore, rats with bilateral postmortem DA depletions in the CdN greater than 40% were excluded from further analyses. In addition, depletions within the NAc were required to be more extensive than DA depletions in the CdN. Four animals from the acute LX group and three animals from the chronic LX group were excluded because they did not meet a priori criteria.

In summary, the biochemical analyses included a total of four groups: 1) acute CTRL (n = 3), 2) chronic CTRL (n = 4), 3) acute LX (n = 6), 4) chronic LX (n = 8). For behavioral analyses, only rats with bilateral NAc DA depletions were included. These behavioral analyses included four rats in the acute LX group and five rats in the chronic LX.

Microdialysis Probe Design and In Vitro Calibration of Probe Recovery

The concentric design of the dialysis probes used in this study have been previously described (6,52). The dialysis membrane of the probes consisted of a 4 mm effective length and 250 μm outer diameter. Also, probes were tested for in vitro recovery prior to use and dialysate values were corrected for recovery [for details, see (6,52)]. The mean (± SEM) percent recovery values for the probes used in this experiment were DA, 26.06 ± 0.68%; DOPAC, 24.03 ± 0.74%; HVA, 22.88 ± 0.81%; and 5-HIAA, 24.14 ± 0.79%.

DA Depletion and Dialysis Probe Implantation

Rats were anesthetized with 50 mg/kg sodium pentobarbital (Sigma Chemical Co.), IP. Animals in the LX group received 15–25 mg/kg of desipramine (Sigma Chemical Co.), IP 30 min prior to infusing 6-OHDA·HBr (Sigma Chemical Co.) to protect noradrenergic cells (4). Bilateral 6-OHDA infusions were delivered through a 30 gauge stainless steel cannula into the NAc, and each infusion consisted of 8.0 μg 6-OHDA (weight of the salt) in 2 μl of vehicle (0.9% NaCl with 0.1 mg/ml ascorbic acid). Infusions were delivered over 3-min via polyethylene tubing (PE-20, Coleman Parmer) connected to

a 10 μl capacity Hamilton syringe mounted on a syringe pump (Pump 22, Harvard Inst. Co.). Two infusions were made into each hemisphere for a total of 4 μl of 6-OHDA (16 μg). The stereotaxic coordinates for infusion of 6-OHDA were, from bregma: anterior (A) +1.8 mm, lateral (L) ±1.3 mm, and ventral (V) −7.0 mm from the skull surface, and A +1.8 mm, L ±2.2 mm, and V −7.0 mm from the skull surface, with bregma and lambda horizontal to each other (39). After being lowered, the infusion cannula was left in position for 1 min prior to infusion and for 1 min after infusion.

Animals in the acute LX group received bilateral microdialysis probe implants immediately after 6-OHDA infusions. The stereotaxic coordinates for implanting the microdialysis probes into the CdN were, from bregma: A +0.5 mm, L ±3.0 mm, and V −7.0 mm from the skull surface, with bregma and lambda horizontal to each other (39). The effective surface of the dialysis probe extended the entire 4 mm length of the dorsal–ventral axis of the CdN. The probes were connected to 1.0 ml gastight Hamilton syringes (1001 series) via PE-20 tubing and were mounted on a Pump 22 Harvard syringe pump. A filtered Ringers solution (128.3 mM NaCl, 1.35 mM $CaCl_2$, 2.68 mM KCl, and 2.0 mM $MgCl_2$, pH 7.3) continuously flowed at a rate of 0.15 μl/min through the dialysis probes during the entire surgical procedure. The probes were secured by forming a dental cement cap around the assembly which was anchored to the skull with stainless steel screws. After the wound was sutured, animals were placed in the testing chamber and allowed to recover overnight. Testing began the next day (0700–0800 h), at least 19 h postsurgery, and proceeded across 2 days. Animals in the acute CTRL group underwent surgery only for probe implantation and subsequently were tested on days 1 and 2 postsurgery (tests 1 and 2, respectively). Animals in the chronic LX and chronic CTRL groups were allowed to recover in their home cages from stereotaxic surgery involving 6-OHDA infusion or sham surgery, respectively, and on day 13 postsurgery had probes stereotaxically implanted as described for the acute group in preparation for testing on days 14 and 15 postsurgery (tests 1 and 2, respectively).

In Vivo Microdialysis Procedure

A coiled steel tether attached to a two-channel fluid swivel (Instech Co., 375/D/22) was connected to a flexible steel wire protruding from the dental cement cap on the animal's head to relieve tension from the inlet and outlet lines of the probes. The outlet tubing from the probes was threaded into the hollow coiled tether and inserted into collection vials located 30 cm above the animal's head. Collection vials were, therefore, easily exchanged without significantly interfering with the animal's activity. To change perfusing medium from a normal Ringers to one containing 60 mM K^+, the inlet PE-20 tubing on the dialysis probe extended only 6 cm. In this way, a 24 cm length of PE-20 tubing leaving one commutator could be interchanged with the effluent line from a second commutator containing high K^+. Throughout the experiment, Ringers solution was pumped at a rate of 1.5 μl/min.

On the first day of testing (test 1), 20-min baseline samples were collected until three stable samples were assayed. All samples were stored on ice and assayed no later than 30-min after being collected. Following baseline samples, Ringers solution containing 60 mM K^+ was infused for 20-min, during which time dialysate was collected. Physiological osmolarity was maintained by adjusting the concentration of Na^+ to 70.98 mM. Immediately after this 20-min sample, three additional samples were collected using normal Ringers solution. On the second day of testing (test 2), three 20-min baseline samples were collected. Next, animals received a SC injection of 1.5 mg/kg d-AMPH sulfate (3.0 mg/ml). Six additional 20-min samples were collected after the AMPH challenge. K^+ stimulation was administered during test 1 and AMPH injected during test 2 to minimize carryover effects on the K^+ response due to the long term effects known to take place with AMPH (48). Dialysate samples were assayed for DA, DOPAC, HVA, and 5-HIAA using standard HPLC-EC procedures as described previously (6,7,52).

Behavioral Measures

Behavior during microdialysis testing was recorded by a video recorder and scored on a later occasion. The number of rears, crossovers, and quarter turns were counted. A rear was defined as the animal's two front paws raised up in the air or on the test chamber wall at least 10 cm from the floor, but not placed on the bowl. A crossover was defined as a movement of the animal's head and front paws across the midline of the test chamber. Quarter turns were scored when the longitudinal axis along the dorsal aspect of the animal's body rotated 90°.

During microdialysis testing, overall stereotypy was also measured. Behavior was scored during one baseline sample and each treatment sample thereafter for 1 min starting at the midpoint of the collection interval (at 10 min of a 20-min sample). The scale was a modified version of the stereotypy rating scale by MacLennan and Maier (32): 0 = no activity; 1 = intermittent activity; 2 = continuous activity; 3 = intermittent stereotypy (repetitive sniffing, rearing, or head and limb movements); 4 = continuous stereotypy over a wide area; 5 = continuous stereotypy in a restricted area; 6 = pronounced, continuous stereotypy in a restricted area (with imbalance present from vigorous rearing or sniffing); 7 = stereotyped biting and licking with interspersed exploration; and 8 = continuous stereotyped biting and licking in a restricted area. Additionally, the individual components of stereotypy were examined, including sniffing, oral behavior (biting, gnawing, licking), and repetitive head and limb movements. Each behavioral component was rated on its duration (1 = intermittent behavior, 2 = continuous behavior) and intensity (1 = mild, 2 = moderate, and 3 = intense) during the 1-min observation (46). The product of these two measures was used as an index for individual stereotypy scores.

Brain Tissue Assay

At the termination of the experiment, animals were housed individually in hanging wire mesh cages for at least 1 week to allow recovery from AMPH administration. Next, a postmortem tissue analysis for monoamines was conducted in which CdN and NAc samples were dissected and prepared for HPLC-EC analysis as described elsewhere (49). When possible, probe tracks on the brain slices were examined visually for accuracy of probe placement.

Data Analyses

The statistical analyses for monoamines included repeated measures ANOVAs and a one-way ANOVA was used for the index of total DA overflow. Frequency scores from locomotor and turning behavior were analyzed by repeated measures ANOVAs. When significant *F*-values were obtained, Newman–Keuls post hoc tests were applied. Ordinal values

TABLE 1

POSTMORTEM MONOAMINE LEVELS IN NUCLEUS ACCUMBENS AND CAUDATE NUCLEUS FROM CONTROL AND 6-OHDA INFUSED RATS*

	Group		
Monoamines	Control	Acute Lx	Chronic Lx
Nucleus accumbens			
DA	8.63 ± 0.49	1.83 ± 0.60†	2.03 ± 0.58†
DOPAC	2.28 ± 0.14	0.64 ± 0.24†	0.66 ± 0.12†
HVA	0.96 ± 0.09	0.28 ± 0.13†	0.37 ± 0.07†
NE	0.65 ± 0.13	0.10 ± 0.02†	0.22 ± 0.05†
5-HT	0.52 ± 0.15	0.33 ± 0.09	0.62 ± 0.14
5-HIAA	0.55 ± 0.15	0.57 ± 0.17	0.67 ± 0.13
Caudate nucleus			
DA	10.94 ± 0.50	8.89 ± 0.55	9.42 ± 0.58
DOPAC	1.84 ± 0.13	1.46 ± 0.12	1.69 ± 0.15
HVA	1.28 ± 0.20	0.72 ± 0.06†	0.84 ± 0.07†
NE	0.06 ± 0.01	0.05 ± 0.02	0.05 ± 0.01
5-HT	0.31 ± 0.04	0.32 ± 0.05	0.40 ± 0.07
5-HIAA	0.39 ± 0.07	0.38 ± 0.05	0.51 ± 0.08

*Mean (± SEM) concentrations of monoamines (ng/mg) in postmortem tissue from the nucleus accumbens and caudate nucleus are shown for control animals (average of acute controls and chronic controls) and animals that received 6-OHDA infusions into the nucleus accumbens.

†$p \leq 0.05$, from controls.

obtained from stereotypy ratings were analyzed by pair-wise comparisons using the Kruskal–Wallis test.

RESULTS

Postmortem Measures of Monoamine Tissue Content

There were no differences in postmortem monoamine content between acute and chronic CTRL groups, so their data were combined for comparison to the LX groups. Table 1 displays the average extracellular NAc and CdN concentrations for monoamines and metabolites in the CTRL, acute LX and chronic LX groups. Relative to intact levels from the CTRL group, 6-OHDA produced a mean bilateral DA reduction (± SEM) in the acute LX animals of 83.98% + 6.97 in the NAc and 17.88% ± 5.00 in the CdN. DA depletions in the chronic LX group were 76.43% ± 6.78 in the NAc and 13.85% ± 5.28 in the CdN. Both LX groups had NAc tissue DA, DOPAC, HVA, and NE levels that were significantly depleted from controls, one-way ANOVAs, $Fs \geq 9.17$, $ps \leq 0.0025$; follow-up Newman–Keuls, $p = 0.01$. Only HVA in the CdN was significantly depleted in both LX groups compared to the CTRL group, one-way ANOVA, $F(2, 15) = 4.88$, $p < 0.0232$; follow-up Newman–Keuls, $p = 0.05$. There were no significant depletions of postmortem levels of DA or DOPAC in the CdN of the LX groups compared to the CTRL group (Table 1).

Effect of DA Depletions Within the CdN

It was expected that rats in the LX groups would sustain some DA depletion within the CdN, so the early effect of 6-OHDA-induced damage within the CdN on measures of extracellular DA between all animals assigned to the Acute LX group was analyzed. Rats omitted from this group due to CdN DA depletions > 40% displayed an attenuation in AMPH-stimulated DA release relative to the rest of the rats in the acute LX group, $F(1, 16) = 5.77$, $p = 0.029$, but no other differences were found during basal or K^+-stimulated conditions. Nonetheless, these animals were omitted from the study to comply with previously established a priori criteria. For animals that were retained in the LX group, additional analyses within the acute and chronic groups demonstrated there were no biochemical or behavioral differences between rats with large CdN DA depletions (30–40% range) and the rest of the group.

Extracellular Measures of DA, DOPAC, HVA, and 5-HIAA

The acute CTRL and chronic CTRL groups did not differ in measures of dialysate biochemistry so values for both groups were combined for subsequent analyses. Figure 1 shows the levels (fmol/min) of spontaneous, K^+-stimulated, and AMPH-evoked extracellular DA (Fig. 1A), DOPAC (Fig. 1B), HVA (Fig. 1C), and 5-HIAA (Fig. 1D) in all groups plotted in 20-min blocks of time across 2 successive days of testing (tests 1 and 2). AMPH administration produced an immediate increase in extracellular DA overflow that peaked 40-min after the AMPH injection, and thereafter decreased steadily in all groups, repeated measures, $F(5, 170) = 136.03$, $p < 0.0001$ (Fig. 1A). Moreover, AMPH-stimulated DA overflow was enhanced when animals were tested immediately following 6-OHDA infusions into the NAc (Fig. 1A; test 2, AMPH stimulation). Figure 1A also shows that the enhancement in extracellular DA declined at a significantly slower rate in the acute LX group compared to the other two groups, group, $F(2, 34) = 6.78$, $p = 0.0033$; follow-up Newman–Keuls, $p \leq 0.05$ (Fig. 1A); and this resulted in an overall enhancement of AMPH-induced DA release, calculated as the total sum of DA measured during the entire AMPH phase, in the acute LX group compared to the other two groups, one-way ANOVA, $F(2, 34) = 6.78$, $p = 0.0033$; follow-up Newman–Keuls, $p < 0.05$. During K^+ stimulation, extracellular DA increased by five- to sixfold in all three groups, repeated measures, $F(3, 99) = 223.93$, $p < 0.0001$, and returned to basal levels 20 min later. However, there were no group differences in basal or K^+-stimulated levels of extracellular DA (Fig. 1A).

When testing occurred immediately following 6-OHDA infusion, basal and K^+-stimulated extracellular levels of both DA metabolites were elevated in the acute LX group relative to the other two groups (Fig. 1B and C, test 1). This enhancement in the basal overflow of DOPAC and HVA was evident only during test 1, group $Fs(2, 33) \geq 8.111$, $ps \leq 0.0014$; follow-up Newman–Keuls, $p \leq 0.05$. There was a trend for basal levels of both DOPAC and HVA to be attenuated in the chronic LX group, and this decrease was significant during test 2, group, $Fs(2, 34) \geq 15.20$, $ps < 0.0001$; follow-up Newman–Keuls, $p = 0.01$. Similarly, throughout the K^+ test condition, both DOPAC and HVA levels remained enhanced in the acute LX group and attenuated in the chronic LX group relative to CTRLs, group, $Fs(2, 33) \geq 12.315$, $ps \leq 0.0001$; follow-up Newman–Keuls, $p \leq 0.05$ (Fig. 1B and C, respectively, test 1). During K^+ stimulation all groups displayed an immediate decrease in extracellular DA metabolite concentrations that recovered to baseline levels within 40 min, repeated measures, $Fs(3, 99) = 331.659$, $ps < 0.0001$. During test 2, AMPH administration produced a decrease in both DA metabolites in all groups (Fig. 1B and C, test 2). This decline was evident 40 min after the AMPH injection, repeated measures, $Fs(5, 170) \geq 101.929$, $ps \leq 0.0001$. Moreover, following AMPH administration, both LX groups displayed a significant de-

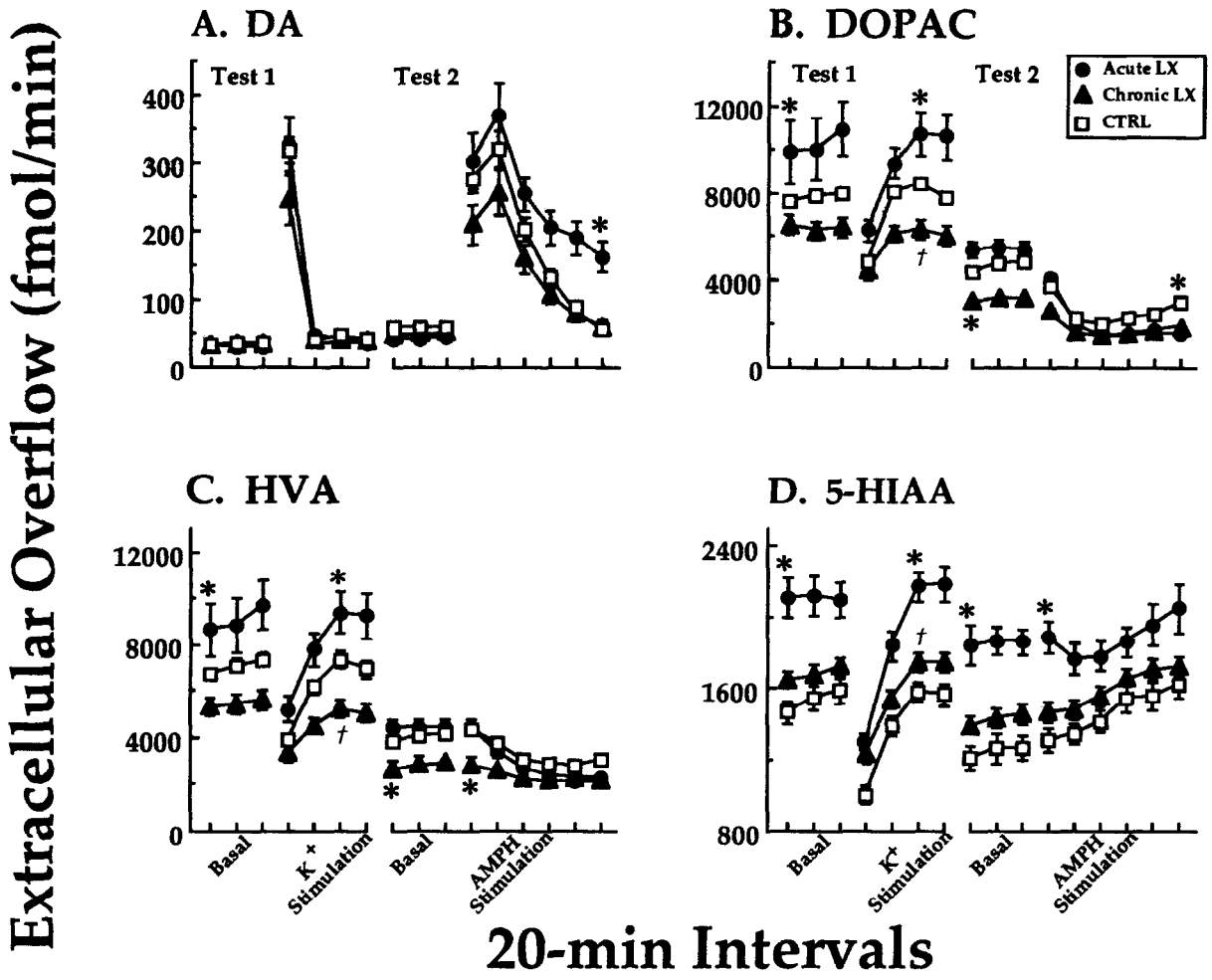

FIG. 1. Concentrations (fmol/min; corrected for recovery) of the extracellular striatal DA (A), DOPAC (B), HVA (C), and 5-HIAA (D), during microdialysis testing in CTRL animals (open squares, $n = 14$ caudates), animals tested immediately following 6-OHDA infusion into the NAc (Acute LX; closed circles, $n = 10$ caudates), and animals tested 2 weeks after 6-OHDA lesion (Chronic LX; closed triangles, $n = 13$ caudates). Dialysate levels of the monoamines are plotted as a function of 20-min intervals during the first and second days of testing (test 1 and test 2, respectively). On test 1, following three baseline samples (basal, test 1), Ringers solution containing 60 mM K^+ was infused through the microdialysis probes for 20 min, during which time a sample was collected; thereafter, three additional samples were collected (K^+ stimulation). On test 2, following three baseline samples (basal, test 2), 1.5 mg/kg AMPH was administered, subcutaneously, and six samples were collected thereafter (AMPH stimulation). The asterisk (*) indicates groups that differed significantly from all other groups (Newman-Keul's, $p \leq 0.05$). The dagger (†) indicates LX groups that differed significantly from the CTRL group only (Newman–Keuls, $p = 0.01$).

crease in DOPAC levels relative to CTRLs, while HVA levels remained attenuated only for the chronic LX group, group, $Fs(2, 34) \geq 8.042$, $ps \leq 0.0014$; follow-up Newman–Keuls, $p \leq 0.05$.

Extracellular levels of 5-HIAA were consistently higher during basal, K^+, and AMPH conditions in the acute LX group compared to other groups, group, $Fs \geq 15.736$, $ps < 0.0001$; follow-up Newman–Keuls, $p = 0.01$ (Fig. 1D). The K^+ challenge produced a decline in extracellular 5-HIAA during the 20-mins of stimulation, repeated measures, $F(3, 99) = 534.112$, $p < 0.0001$, which returned to basal levels 40 min later in all groups. AMPH stimulation produced a significant increase in the extracellular concentration of 5-HIAA, which was evident in the latter samples collected from all groups during test 2, repeated measures, $F(5, 170) = 41.533$, $p < 0.001$ (Fig. 1D).

Behavioral Measures During Dialysis

Concomitant with the enhancement in AMPH-induced DA release from acute LX animals, the intensity of AMPH-induced stereotypy was significantly enhanced in this group beyond the increase displayed by the CTRL and chronic LX groups during the last 40 min of testing, $Hs \geq 4.01$, $ps < 0.045$ (Fig. 2A). In contrast, the intensity of overall stereotypy in the acute LX group was significantly lower relative to the other two groups during baseline testing, $Hs \geq 4.66$, $ps \leq 0.031$ (Fig. 2A), and lower than the chronic LX group during K^+ stimulation, $H = 5.21$, $p < 0.022$.

When the individual behavioral components were examined, the heightened levels of AMPH-induced stereotypy in the acute LX group was comprised primarily of oral behaviors (i.e., licking, gnawing, and biting; Fig. 2B). This enhancement

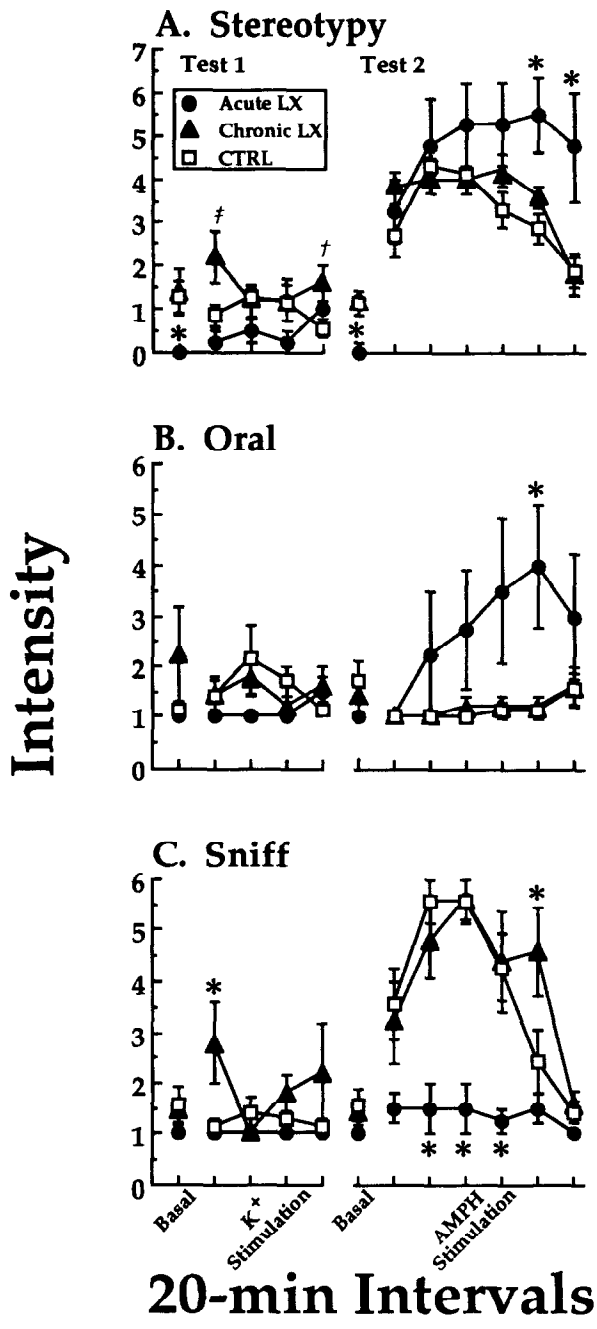

FIG. 2. The intensity of stereotyped behavior (A) and its individual components, oral behavior (B) and sniffing (C), are plotted for CTRL animals (open squares, $n = 7$), animals tested immediately following 6-OHDA infusion into the NAc (acute LX; closed circles, $n = 4$), and animals tested 2 weeks after 6-OHDA lesions (chronic LX; closed triangles, $n = 5$). Behaviors are plotted as a function of 20-min intervals during the first and second days of testing (test 1 and test 2, respectively). On test 1, a 1-min evaluation was taken at midinterval (at 10 min of a 20-min interval) of a dialysis baseline sample (B, test 1) and during each of the four intervals of the K^+ condition (K^+ stimulation). On test 2, a 1-min evaluation was taken at midinterval of a dialysis baseline sample (B, test 2) and during each of the six intervals of the AMPH condition (AMPH stimulation). The asterisk (*) indicates groups that differed significantly from all other groups, including CTRLs (Kruskal–Wallis, $p < 0.05$). The dagger (†) indicates LX groups that differed significantly from the CTRL group only (Kruskal–Wallis, $p < 0.05$). The double dagger (‡) indicates a LX group that differed significantly from the other LX group (Kruskal–Wallis, $p < 0.05$).

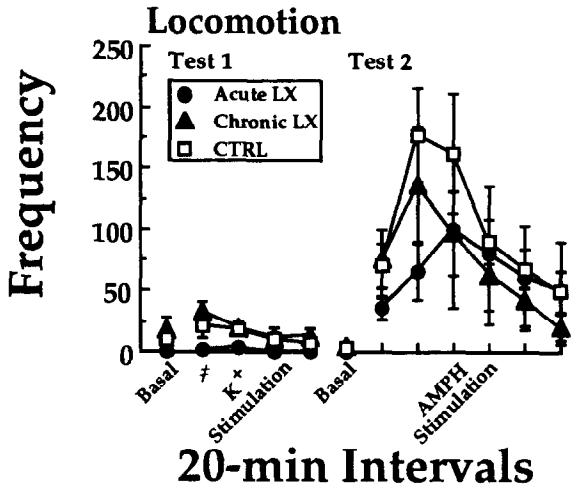

FIG. 3. The frequency of locomotor activity is plotted for CTRL animals (open squares, $n = 7$), animals tested immediately following 6-OHDA infusion into the NAc (acute LX; closed circles, $n = 4$), and animals tested 2 weeks after 6-OHDA lesions (chronic LX; closed triangles, $n = 5$). Scores for general locomotion (sum of rears and crossovers) are plotted as a function of 20-min intervals during the first and second days of testing (test 1 and test 2, respectively). On test 1, the amount of locomotor activity was counted during a 20-min baseline sample (B, test 1) and each of the four intervals of the K^+ condition (K^+ stimulation). On test 2, the amount of locomotor activity (the number of rears and crossovers summed) was counted during a 20-min baseline sample (B, test 2) and each of the six intervals of the AMPH condition (AMPH stimulation). The double dagger (‡) indicates a LX group that differed significantly from the other LX group ($p = 0.05$).

in oral behaviors was significantly higher than the other two groups in the fifth interval of AMPH testing, $Hs \geq 3.56$, $ps < 0.059$. Generally, sniffing behavior evoked by AMPH was significantly lower in the acute LX group compared to the other two groups, $Hs \geq 6.00$, $ps \leq 0.014$ (Fig. 2C). During baseline and K^+ stimulation measures, there were no group differences in oral behaviors. However, sniffing was enhanced during K^+ stimulation in the chronic LX group relative to the other two groups, $Hs = 7.20$, $ps < 0.007$ (Fig. 2C). In general, all groups displayed relatively equal amounts of the individual stereotypy components of repetitive head and limb movements (data not shown) throughout testing, except on the fifth interval post-AMPH in which both LX groups displayed greater levels of this behavior than the CTRL group, $Hs \geq 3.63$, $ps < 0.057$.

The acute LX group consistently displayed lower levels of general locomotor activity (i.e., both crossovers and rears) during test 1 (Fig. 3). During K^+ stimulation, and for the duration of test 1 thereafter, animals in the acute LX group displayed attenuated levels of general locomotor behavior compared to the chronic LX group and a diminution of total quarter turns compared to the other two groups, group, $Fs(2, 13) \geq 4.140$, $ps \leq 0.04$; follow-up Newman–Keuls, $ps \leq 0.05$ (data not shown). All groups displayed relatively equal amounts of locomotor activity during baseline and AMPH stimulation.

DISCUSSION

The present results show that AMPH-induced release of DA from the CdN was augmented in rats tested immediately after bilateral 6-OHDA infusions into the NAc. Concomitant with this augmentation was an enhancement in the intensity of AMPH-evoked stereotypy, especially oral behaviors, which have been shown to be mediated primarily by the CdN. Also during this time, spontaneous and K^+-stimulated levels of the monoamine metabolites DOPAC, HVA, and 5-HIAA were elevated. Two weeks later, the enhancements in AMPH-induced levels of extracellular DA, AMPH-evoked stereotypy, and spontaneous extracellular DA metabolite levels were no longer present. Moreover, extracellular levels of DOPAC and HVA were attenuated in comparison to control levels at this later time. Conversely, K^+-stimulated DA release did not vary from control levels at any time following 6-OHDA infusion.

It was expected that the intensity of AMPH-evoked stereotypy would increase if the DAergic response to AMPH was augmented in the CdN. This was true for stereotyped oral behaviors but not for AMPH-evoked sniffing. In fact, oral stereotypies expressed a faster onset than normal to the exclusion of sniffing (Fig. 2). Stereotyped sniffing is an incipient response to AMPH that is typically supplanted by the more vigorous response of oral behaviors as the pharmacological effects of AMPH peak in rats (9). Therefore, it is reasonable to expect that an enhancement in the nigrostriatal response to AMPH should cause the early phase of AMPH-evoked sniffing to be displaced more rapidly by the earlier onset of the more intense oral stereotypies. In any event, the enhancement in extracellular monoamine metabolites and AMPH-stimulated DA levels that take place in the CdN provide a neurochemical correlate for the augmentation in AMPH-evoked stereotypy that takes place immediately after intra-NAc 6-OHDA treatment. In contrast, the locomotor response was not altered at any time during this experiment. We suggest that sparing of AMPH-evoked locomotor behavior occurred in the acute LX group because animals were tested early after 6-OHDA treatment when DA content has been reported to be partially decreased (68) and well within a range that is associated with sparing of behavior (50). This decrease in terminal density may still be sufficiently large to increase the field of influence of residual DA terminals (69), thus producing the observed changes in AMPH-induced stereotypy.

One possibility that would explain the observed neurochemical and behavioral changes is an enhancement in the presynaptic cytoplasmic pool of DA in the CdN. AMPH and K^+ stimulation were used to produce DA release because their different mechanisms of action may allow insight into presynaptic changes that contribute to behavioral changes. Extracellular DA levels produced by an AMPH challenge are derived primarily from a newly synthesized, cytoplasmic pool (1,16,30,45,57), whereas high K^+ produces an overflow from a vesicular pool in an exocytotic-like manner that is calcium dependent (45,53,57). Based on this understanding, during the second day after 6-OHDA treatment the enhancement in AMPH-stimulated DA release from the CdN probably reflects an augmentation in the cytoplasmic DA pool. Perhaps presynaptic changes in rates of neurotransmitter synthesis, storage into the vesicular pool or reuptake could account for an augmented cytoplasmic pool of DA. For example, tyrosine hydroxylase activity in the striatum has been reported to be increased at 2 days following 6-OHDA treatment (68).

An alternative explanation for the early changes is that denervation-induced overflow of NAc DA diffuses into the CdN to increase extracellular levels of DA there. However, our results show that basal DA overflow and K^+-stimulated DA release remained at control levels for animals tested immediately following 6-OHDA infusions. It is possible that the reuptake system in the striatum is efficient enough to maintain an equilibrium of extracellular neurotransmitter concentrations (13,15,58), thus masking any degeneration-induced increases of extracellular DA. In contrast to K^+ stimulation, AMPH occupies presynaptic reuptake sites, so an additive effect of injury-induced release and the reuptake-blocking action of AMPH may have produced the early enhancement in AMPH-stimulated DA release in the CdN. DA depletion of the CdN after intranigral infusions of 6-OHDA proceeds across approximately 4 days (51,64); so during this time, it is possible for degeneration-induced DA overflow to disrupt extracellular and intracellular DA levels in the CdN. Regardless of the specific source of DA that enhances AMPH-stimulated levels, the present results show that responsivity to AMPH is increased early in the CdN at the same time that the AMPH-evoked behaviors mediated by the CdN are also enhanced.

The augmented extracellular levels of DA metabolites during the first few days after 6-OHDA administration also demonstrate that turnover in the CdN is modified. Enzymatic degradation of DA into DOPAC occurs primarily intraneuronally (28,67). Unfortunately, high dialysate levels of DOPAC and HVA could reflect an increased degradation rate produced by enhanced levels of newly synthesized cytoplasmic DA, or by reuptake of enhanced extracellular DA levels produced by diffusion from nonspecific DA overflow. In the latter case, reuptake of DA provided by nonspecific overflow augments cytoplasmic DA levels to enhance the metabolic rate of DA. Changes in extracellular DA and its metabolites are not always causally linked (37); nonetheless, the present data showing increased extracellular concentrations of DA metabolites in the CdN supports the hypothesis that the cytoplasmic pool of DA is enhanced during degeneration in the NAc from 6-OHDA application.

Interestingly, extracellular levels of 5-HIAA were also elevated immediately after 6-OHDA treatment of the NAc, suggesting that physiological changes that take place within mesotelencephalic DA systems may similarly occur in 5-HT systems. It has been suggested that 5-HT may play a modulatory role in DA release (3,17), so the observed changes may reflect functional alterations that result from damage to DA systems. Future investigations will clarify the role of 5-HT systems on sparing/recovery of DA pathways.

Our data also suggest that there is no change in DA levels in the vesicular pool because K^+-stimulated levels did not differ from controls. However, it is likely that in our paradigm K^+ stimulation was not sufficient to displace the entire vesicular store we sought to quantify because other studies have required much longer (2 h) infusions and higher (100 mM) K^+ concentrations to demonstrate any pharmacological effect (19).

The hypothesis that a diminution in function of one DA system permits an augmentation of behavior mediated by another DA system has been proposed from studies in which behavioral changes were examined following a recovery period from 6-OHDA lesions. This hypothesis predicts that a release from competition to express AMPH-evoked behaviors is sufficient to intensify behavioral responses and requires no change from the primary DA system mediating the intensified response. In this study, after a 2-week recovery period the intensity of AMPH-evoked stereotypy and the amount of

AMPH-stimulated DA from the CdN returned to normal, but spontaneous levels of extracellular DA metabolites were attenuated. The hypothesis for release from competition would not predict the attenuation in extracellular levels of DOPAC and HVA following recovery, especially because no animal sustained DA depletions within the CdN sufficiently large to decrease extracellular levels of the DA metabolites (7). Other studies have reported changes in DA activity after recovery from localized brain damage, including an enhancement in spontaneous and AMPH-stimulated extracellular DA levels from the contralateral CdN in rats with unilateral nigrostriatal 6-OHDA lesions (52), a decrease in extracellular striatal HVA levels from unilateral hemispheric decortication (8), and widespread effects of localized intracerebral 6-OHDA infusions on tissue DA content in areas removed from the site of infusion, including prefrontal cortex, CdN, NAc, and SN (31,44,61,62). Many of the latter changes were depletions that might be due to generalized damage to other DA fibers, but a significant amount of sparing is probably due to compensatory mechanisms that are established following a recovery interval. For example, presynaptic autoreceptors are known to regulate synthesis and release (29) and following DA-depleting lesions these autoreceptors develop supersensitivity (43). Such changes could decrease presynaptic DA turnover, as predicted by the attenuated levels of extracellular DA metabolites 2 weeks after 6-OHDA treatment. Given the present results, the hypothesis for release from competition is not viable, because it does not account for changes in the CdN when the NAc is depleted of DA.

In summary, the present study found that within 2 days after intra-NAc 6-OHDA infusions there was a transient enhancement in extracellular levels of AMPH-stimulated DA, spontaneous and K^+-stimulated DOPAC, HVA and 5-HIAA in the CdN, and AMPH-induced stereotypy. Recent evidence suggests that there is a residual pool of AMPH-releasable DA present in the first few days after intracerebral 6-OHDA administration which mediates behavioral changes during this time (5,51). The present study extends this hypothesis by postulating, based on spontaneous and stimulation-evoked measures of extracellular DA and monoamine metabolites, that the source of the AMPH-releasable pool detected in the CdN after 6-OHDA administration into the NAc is from an increase in presynaptic cytoplasmic DA. An alternative explanation for the enhancement in AMPH-stimulated DA release is that a denervation-induced pool from the NAc may also be important to augment cytoplasmic concentrations. Because the major site for enzymatic degradation occurs in the presynaptic cytoplasm, the enhanced monoamine metabolites also support the idea for augmented cytoplasmic DA levels. After recovery, it is proposed that decrements in extracellular DA metabolites may represent a compensatory downregulation of turnover to modulate behavior within normal limits. The present results establish that it is possible for presynaptic changes within the dorsal striatum to contribute to behavioral changes that take place during the degenerative stages resulting from 6-OHDA infused into the ventral striatum. Therefore, studies that attempt to explain behavioral changes following localized cerebral damage must consider neurochemical changes from parallel systems during the time course of recovery. More generally, understanding the exact source of DA that enhances the extracellular levels of its metabolites and the response to AMPH early after 6-OHDA treatment may provide insights into the functional significance, if any, for these neurochemical changes. Perhaps such changes can be harnessed to improve treatment of neurodegenerative diseases such as Parkinson's disease.

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