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Reversal of 6HD-Induced Neonatal Brain Catecholamine Depletion After Operant Training

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TESSEL, R. E., S. R. SCHROEDER, P. S. LOUPE AND C. J. STODGELL. *Reversal of 6HD-induced neonatal brain catecholamine depletion after operant training.* PHARMACOL BIOCHEM BEHAV 51(4) 861-867, 1995. – Rats received either vehicle (controls) or 100 μg of 6-hydroxydopamine (6HD) base intracisternally on postnatal day 5. At 3 mo of age, striatal and cortical catecholamine and metabolite levels were determined in some animals. Others were subjected to 4.5 mo of training on incrementally more difficult fixed-ratio (FR) discriminations; 2 mo later, their levels were determined. Learning was essentially unaffected by 6HD even though errors in all animals increased with increases in discrimination difficulty and 6HD had markedly depleted levels in the 3-mo-old animals. Moreover, an initial response-rate deficit in 6HD-treated rats disappeared with training. However, after training, levels in 6HD-treated rats were not only not depleted, they were as much as 661% of those in controls. These and others of our findings indicate that FR discrimination training can induce persistent increases in brain catecholamine utilization. They also appear to be the first to suggest that at least some neurochemical effects of neonatal 6HD are not necessarily irreversible, and that such a reversal can be experientially induced and possibly functionally beneficial.

Fixed-ratio discrimination learning Neonatal 6-hydroxydopamine Striatal and cortical catecholamines
Dopaminergic neuronal plasticity

THE COGNITIVE and behavioral dysfunctions present in developmentally disabled individuals such as those with mental retardation last indefinitely (19). The mechanisms mediating these dysfunctions are poorly understood but, at least in individuals with Lesch-Nyhan syndrome, appear to involve lesions of central dopamine (DA)-containing neurons (6,26). Central administration of 6-hydroxydopamine (6HD) to rats also induces a loss of cortical and striatal DA that lasts indefinitely (32). In addition, such rats often have spatial learning deficits (3,13,31) and respond to repeated DA agonist administration by manifesting aberrant behaviors (e.g., self-injurious behavior) comparable to those emitted by some developmentally disabled individuals (6). Consequently, these animals have been proposed to model aspects of human mental retardation (4).

Almost by definition, learning in individuals with retardation is more susceptible to variations in task difficulty. For example, persons with mental retardation often have difficulty learning when arbitrary matching-to-sample procedures are used (39). However, the extent to which adult animals neonatally treated with 6HD are susceptible to variations in task difficulty does not appear to have been directly evaluated.

One arbitrary matching-to-sample procedure that has been used successfully in rats is food-maintained fixed-ratio (FR) discrimination (28). In addition, FR discriminations are readily amenable to changes in difficulty and are not absolutely dependent on visual or auditory acuity. Thus, they may be more useful than some other tasks for estimating learning deficits in developmentally disabled organisms.

The original purpose of the present study was to assess the effect of incremental variations in FR discrimination difficulty on learning in adult, neonatal 6HD-treated and control rats.

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However, we now report that such treatment has little effect on the ability of adult (3-mo-old) animals to learn and perform such discriminations or a subsequent position reversal relative to controls, despite findings that increases in task difficulty were effective in reducing learning rates in all animals and that 6HD treatment impaired response rates early in training. In addition, this 4.5-mo-long training regimen was unexpectedly associated with a long-lasting reversal of the large striatal and cortical DA and metabolite depletion present in other 3-mo-old neonatally 6HD-treated rats. Our data suggest that this reversal may function to mitigate the motor and/or cognitive consequences of such depletion and that this or related training regimens may be clinically useful in the treatment of individuals whose developmental disabilities are mediated by prior loss of brain catecholamines.

METHODS

Male Sprague-Dawley rat pups from at least three separate litters were removed from their mothers and either injected intracisternally with 6HD hydrobromide (100 μg of free base in 10 μl of saline containing 0.1% ascorbic acid) or vehicle (controls) 5 days after birth. After weaning at 21 days of age, the pups were housed three per cage per group until use. At 3 mo of age and on a random basis, some animals from each litter were housed individually and their weights reduced to approximately 85% of free-feeding weights for subsequent FR discrimination training; others were sacrificed for catecholamine and metabolite determinations.

Apparatus

Six 29 × 25.3 × 28-cm experimental operant chambers housed in larger insulated shells with ventilation fans (Coulbourn Instruments Co., Allentown, PA) were used. A center retractable lever and two side levers were located 2 cm from the grid floor on one side of each chambers with a three-diode cue-light panel located above each lever. A food trough was located above the center retractable lever and its cue light, approximately 9.5 cm from the floor whereas a houselight was located 26.5 cm from the floor to the right of the food trough on the same side of the chamber.

Training

FR discrimination training involved several steps. In the first step, the weight-reduced animals were trained to complete ratios of gradually increasing magnitude (FR1, FR2, FR4, FR6, FR8, and FR16) on the center lever when cue lights above it were illuminated; responding was reinforced by presentation of a 45-mg food pellet (P.J. Noyes, Lancaster, NH). Upon completion of each ratio, the center lever retracted and its cue lights were extinguished before the food pellet was dropped into the food trough, after which the lever was represented.

After one to two sessions at FR16, the next step was performed. This involved adding a single nonretractable lever, located on the right side of the retractable lever, to the chamber for one session. Completion of the FR16 now also illuminated cue lights over the side lever, and a single side-lever press was required for food presentation. During the next session, a second nonretractable lever located to the left of the retractable lever was added, and cue lights above it also illuminated after lever retraction. However, a press on the right side lever was still required for food presentation; left-side lever presses had no programmed consequences.

This two-session sequence was then repeated, except that during the first of these sessions only the left-side lever was present, and the center lever retracted after a single press (FR1). During subsequent sessions both FR requirements were made available such that if the ratio was 16 on a given trial, a response on the right lever was reinforced by food presentation; if the ratio was 1, a response on the left lever was reinforced. The intertrial interval was 0.5 s. Errors (i.e., responding on an incorrect side lever) resulted in a 5-s timeout during which the house- and all stimulus lights were extinguished, and the center lever was retracted. In addition, each side lever response emitted during this period reset the duration of the timeout. Furthermore, a ratio associated with an error continued to be represented following the timeout until a correct response was made. However, this correction procedure was rapidly eliminated and the probability that the lever retracted after completion of an FR1 or an FR16 on any particular trial became 0.5.

When the proportion of side-lever selections in which errors occurred stabilized, the lower FR value was sequentially increased to 4 and then 8 to increase discrimination difficulty. The lower value was then reduced to an FR4 and the positions of the particular side levers associated with the FR4 and FR16 requirements were reversed. Error rates were allowed to stabilize between each of these FR changes. After training had been completed, the animals were maintained at 85% free-feeding weights but allowed to remain in their home cages for 2 mo before sacrifice for catecholamine and metabolite determinations.

Catecholamine and Metabolite Determinations

Rats were rendered unconscious by exposure to a carbon dioxide–saturated environment, and decapitated, and the striata and cerebral cortices were rapidly isolated over ice, separately weighed, and sonicated on ice in high performance liquid chromatography (HPLC) mobile phase containing 10^{-5} M dihydroxybenzylamine (DHBA) as an internal standard, and 0.17 U of ascorbic acid oxidase activity. Mobile phase (pH 3.9) consisted of 0.05 M sodium acetate, 0.05 M citric acid, 0.2 M 1-sodium octane sulfonic acid, 269 μM EDTA, 0.6% (v/v) methanol, and 0.04 M tetrahydrofuran in distilled water. After sample centrifugation, an aliquot of the supernatant fluid (with further dilution in mobile phase if necessary) was subjected to HPLC with electrochemical detection (EC) using a Beckman Absorbosphere (4.8 mm × 250 mm) C18 reverse-phase column (Altech, Deerfield, IL) connected to a Bioanalytical Systems LC-4B amperometric detector (West Lafayette, IN) and quantified using a Shimadzu CR501 Chromatopac integrator (Columbia, MD) and area under the peak (AUP) analysis. Catecholamines and metabolites were detected using a working electrode potential of 800 mV vs. an Ag/AgCl reference electrode. Cortical 3-methoxytyramine concentrations were below our limit of detection. External standard AUPs were determined before each day's HPLC-EC determinations.

Chemicals

6HD hydrobromide, norepinephrine (NE) bitartrate, DA hydrochloride, 3,4-dihydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA), 3-methoxytyramine (3MT), and DHBA were purchased from Sigma (St. Louis, MO); disodium EDTA, tetrahydrofuran, sodium acetate, and citric acid were purchased from Fischer (Fairlawn, NJ); and 1-sodium octane sulfonic acid was purchased from Aldrich (Milwaukee, WI).

Statistical Analyses

Statistical analyses were conducted using a repeated measures ANOVA (BMDP4V) with 6HD treatment as the between-subject factor and the varying levels of task difficulty and sessions as the repeated measures. Performance in the discrimination procedures was assessed in terms of percent error (ratio of incorrect to total side lever selections; error rate) and response rate (number of responses on the center lever per minute of center lever presentation) for each session per animal. The statistical significance of changes in the concentrations of each catecholamine and metabolite in cortex and striatum were separately assessed by one-way ANOVA.

RESULTS

Both control and 6HD-treated animals rapidly learned to perform the initial 1v16 discrimination and did not differ in the numbers of error made during this period (Fig. 1). In addition, subsequent changes in discrimination difficulty in general induced monotonically related and significant changes in errors in both animal groups (Fig. 1): for 6HD-treated and controls rats, respectively, 1 vs. 16 without correction × 4 vs. 16: [$F(1, 10) = 18.49$, $p < 0.002$ and $F(1, 10) = 6.34$, $p < 0.05$]; 4 vs. 16 × 8 vs. 16: [$F(1, 10) = 1.00$, $p > 0.34$ and $F(1, 10) = 26.59$, $p < 0.001$]; 8 vs. 16 × 4 vs. 16: [$F(1, 10) = 93.39$, $p < 0.0001$ and $F(1, 10) = 210$, $p < 0.0001$]; 4 vs. 16 × 4 vs. 16 reversal: [$F(1, 10) = 21.34$, $p < 0.001$ and $F(1, 10) = 171$, $p < 0.0001$]. Nevertheless, these increases in difficulty did not induce a preferential increase in errors emitted by the 6HD-treated animals. However, 6HD-treated animals did tend to make more errors during the position reversal ($p = 0.13$) (Fig. 1).

Response rates increased in both groups of animals during training (Table 1). However, in contrast to errors, response rates in 6HD-treated animals during the FR1–FR16 and the initial FR4–FR16 discriminations were modestly but significantly impaired relative to those in controls ($p < 0.05$); these differences disappeared in subsequent discriminations (Table 1).

The failure of 6HD markedly to affect learning or response rates during FR discrimination training was not due to a lack of effect of 6HD treatment. Indeed, striatal dopamine (DA) levels and those of its major metabolites, DOPAC, HVA, and 3-MT, in other adult (3-mo-old) untrained animals were severely depleted relative to those in age-matched untrained controls (Fig. 2) (DA: $p < 0.01$; DOPAC: $p < 0.001$; HVA: $p < 0.01$; 3-MT: $p < 0.02$; 96%, 91, 92, and 88% reductions, respectively). Striatal NE was also depleted by 90%

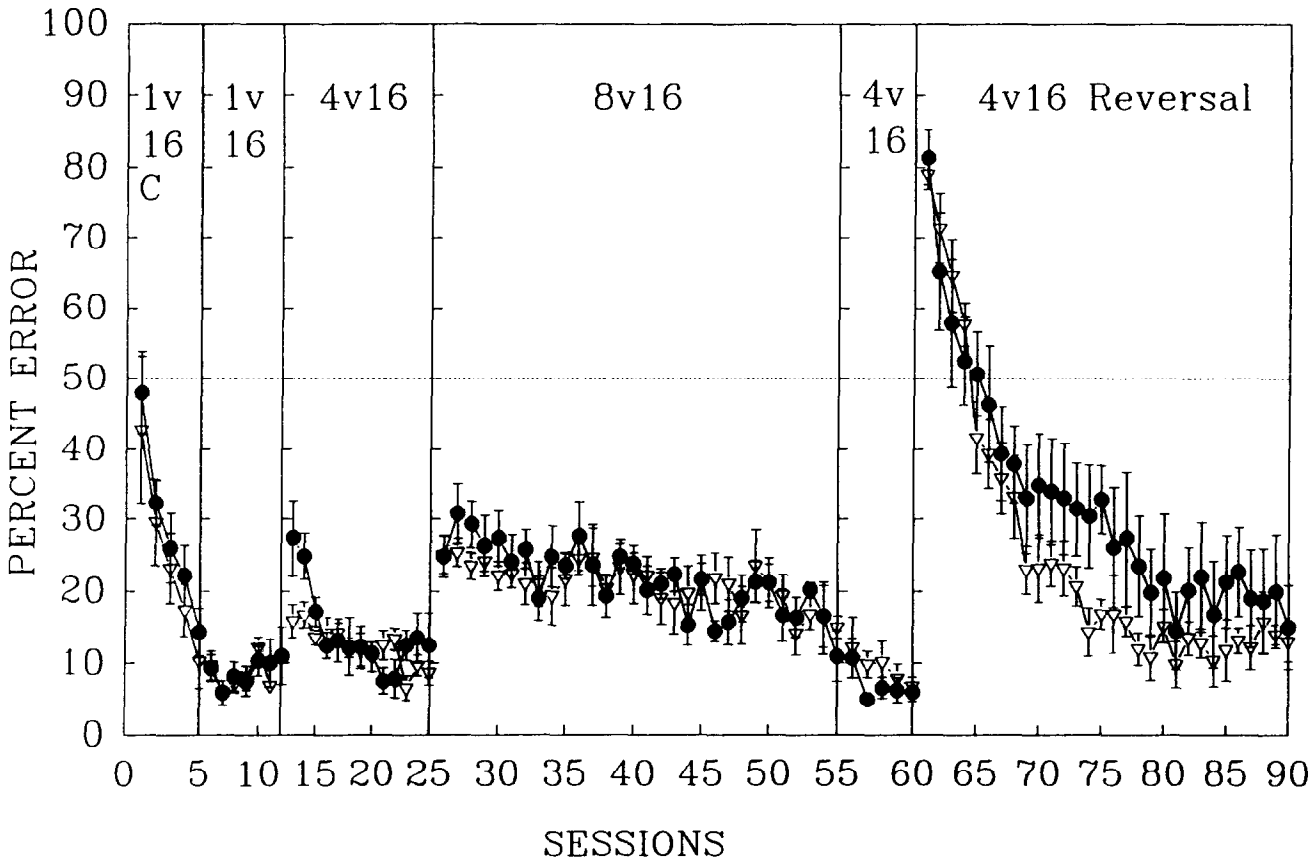

FIG. 1. Food-maintained fixed-ratio (FR) discrimination learning and performance in adult rats neonatally treated intracranially on postnatal day 5 with either 100 μg of 6HD base or vehicle. Training began when the animals were 3 mo of age, using once-daily sessions conducted 5 days/week. The ordinate, percent error, indicates the ratio of incorrect side lever presses to total side lever presses per session; the abscissa indicates the number of sequential training sessions. ∇ and ● (and brackets) represent the means (± SEM) of observations in six vehicle- and 6HD-treated rats. The numbers above each panel (e.g., 1v16) indicate the FR discrimination being learned. C, A correction procedure (see Methods) was used during this portion of the experiment.

TABLE 1

EFFECT OF NEONATAL 6HD TREATMENT ON CENTER-LEVER RESPONSE RATES DURING FIXED-RATIO DISCRIMINATION TRAINING

	Discrimination Difficulty				
Neonatal Treatment	1 vs. 16	4 vs. 16	8 vs. 16	4 vs. 16	4 vs. 16R
Vehicle	82 (4)*	112 (8)	131 (8)	112 (7)	119 (11)
6HD	66 (5)*†	89 (4)†	116 (11)	112 (13)	132 (15)

Numbers indicate the mean (± SEM) of center-lever response rates (responses per minute) averaged across the first and last session at each level of discrimination difficulty in six rats. R, Data were obtained during the 4 vs. 16 position reversal.

*$p < 0.05$ compared to rates at subsequent levels of discrimination difficulty in the same treatment group.

†$p < 0.05$ compared to rates in animals treated neonatally with vehicle at the same level of discrimination difficulty.

(0.09 ± 0.03 and 0.98 ± 0.24 μg/g tissue, respectively, in untrained 6HD- and vehicle-treated rats; $p < 0.005$).

Despite such apparent effectiveness, striatal DA, DOPAC, HVA, and 3-MT concentrations in trained 6HD-treated animals 2 mo after the end of training were not only significantly elevated above those in untrained 6HD-treated rats; they were, respectively, 326, 326, 286, and 601% of those in untrained controls and, respectively, 661, 326, 286, and 524% of those in trained controls (each $p < 0.01$) (Fig. 2). In contrast, striatal DA in trained control animals was modestly but significantly reduced by 51% following training ($p < 0.02$), although metabolite concentrations were unchanged compared to those in untrained controls (Fig. 2).

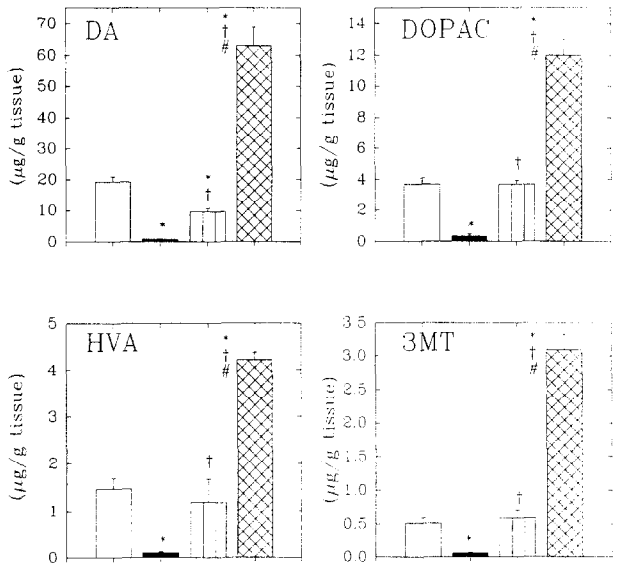

FIG. 2. Striatal tissue concentrations of DA and its metabolites in FR-discrimination trained or untrained vehicle- and 6HD-treated rats. Untrained rats (open and solid bars: vehicle- and 6HD-treated rats, respectively) were sacrificed at 3 mo of age; trained rats were sacrificed 2 mo following the FR discrimination training indicated in Fig. 1 when the animals were 9.5 mo old (vertically lined and cross-hatched bars: vehicle- and 6HD-treated rats, respectively). Bars (and brackets) represent the means (± SEM) of observations in striata in each of six animals. *, †, # Significant differences ($p < 0.01$) from values associated with untrained vehicle-injected rats, untrained 6HD-treated rats, and trained vehicle-injected rats, respectively.

Similarly long-lasting but smaller training-associated increases also occurred in cortex. DA concentrations in trained, lesioned animals were significantly higher than those in untrained 6HD-treated animals ($p < 0.01$) (Fig. 3), comparable to those in trained controls, and only slightly though significantly ($p < 0.05$) below those of untrained controls. In addition, cortical HVA concentrations in trained 6HD-treated animals were markedly elevated ($p < 0.01$ compared to all other groups; 461 and 275% increases compared to untrained and trained controls, respectively) (Fig. 3). However, unlike those in the striatum, cortical DA, DOPAC, or HVA levels in trained control animals were not significantly altered compared to untrained controls (Fig. 3). Striatal and cortical NE levels were also elevated in trained compared to untrained 6HD animals (striatum: 1.57 ± 0.54 and 0.09 ± 0.03 μg/g tissue in trained and untrained animals, respectively, $p < 0.01$; cortex: 0.43 ± 0.19 and 0.016 ± 0.003 μg/g tissue in trained and untrained animals, respectively, $p < 0.05$) but did not differ significantly from those in either trained (striatum: 0.86 ± 0.11 μg/g tissue; cortex: 0.65 ± 0.04 μg/g tissue) or untrained (striatum: 0.96 ± 0.24 μg/g tissue; cortex: 0.42 ± 0.05 μg/g tissue) control animals.

DISCUSSION

In the present study, neonatal 6HD treatment had little effect on FR discrimination learning or lasting effects on response rates even though evidence was obtained that such treatment markedly depleted cortical and striatal catecholamines and metabolites and was associated with a significant initial deficit in operant response rate. In addition, the lack of effect of neonatal 6HD treatment on learning was not attributable simply to the use of a task that was insufficiently difficult, because incremental increases in discrimination difficulty were effective in incrementally increasing errors in these as well as control animals.

The occurrence of the initial response-rate deficit is consistent with a previously reported reduction in the acquisition of FR responding by adolescent neonatal 6HD-treated rats (17) and, because 1 vs. 16 discrimination learning in the present study was unaffected by 6HD treatment, it may reflect a motor rather than a learning deficit. However, numerous findings indicate that rats neonatally treated intracranially with 6HD display spatial learning deficits (3,4,13,31,33). In addition,

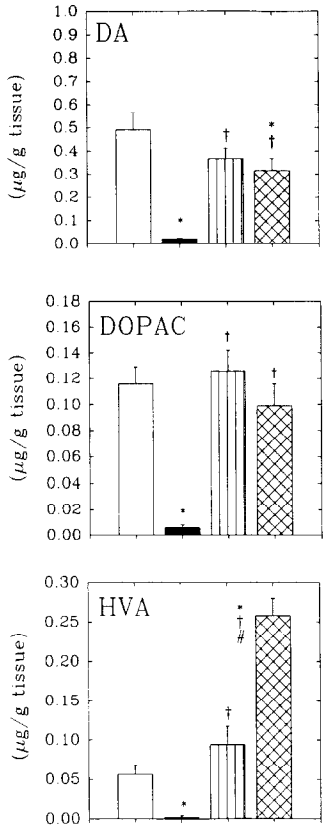

FIG. 3. Cortical tissue concentrations of DA and its metabolites in FR-discrimination trained or untrained vehicle- and 6HD-treated rats. See Fig. 2 for details.

neonatal 6HD treatment has been associated with response-rate elevations in some operant schedules in adult animals (24,34). Comparable results were not obtained in the present study.

The reasons for these disparities are not clear. They may be at least partially accounted for by procedural differences (6HD dose, route and postnatal time of administration, operant schedule used, type of reward, etc.). However, 2 mo following FR discrimination training, striatal tissue concentrations of dopamine and its metabolites in adult rats neonatally treated with 6HD were not only not depleted, they were markedly elevated relative to those in adult (3-mo-old), untrained 6HD- and vehicle-injected animals and in age-matched trained vehicle-injected animals. Qualitatively similar but quantitatively smaller training-associated recoveries in cortical DA and metabolite levels as well as those of striatal and cortical NE were manifested. Furthermore, prolonged reductions in at least striatal dopamine occurred in trained control animals.

These changes suggest that training had induced large increases in cortical and striatal DA release but that in the striatum, DA synthesis was able to keep pace with release only in the 6HD-treated rats. They also suggest that the magnitude of training-associated striatal DA recovery could be inversely related to the magnitude of initial striatal DA depletion. This is because as the magnitude of initial depletion decreases, the neurochemical responses of residual DA neurons at some point presumably would begin to approximate those in trained control animals. Nevertheless, despite their magnitude, the increased availability of catecholamines in trained 6HD-treated animals did not induce any detrimental effects on the behavioral measures of the present study. Instead, such increases were associated with a normalization of the response-rate deficits initially manifested by the 6HD-treated rats. Although other explanations are possible (e.g., preferential reinforcement of high response rates and of correct responses by the procedure used), it is also conceivable that the selective absence of learning defects and elevated response rates (as well as the improvement in the animals' response rates during training) in 6HD-treated animals of the present study were also contributed to by these changes.

Because the effects of 6HD on catecholaminergic neuronal function are generally viewed as being irreversible [e.g., (12)], to the best of our knowledge, the occurrence of significant recovery from severe, neonatal 6HD-induced striatal and cortical DA depletion has not been previously reported and was therefore unexpected. In addition, the experiments described in the present study were designed to examine the effects of variations in FR discrimination difficulty on learning in adult, neonatal 6HD-treated rats. Consequently, it was not originally evident that controls for the potential neurochemical effects of confounding variables (e.g., food deprivation, age at time of sacrifice, lever pressing, food presentation, frequency and consumption, etc.) would be needed.

The absence of such controls makes it impossible to identify the variables responsible for the recovery with any certainty. Nevertheless, in what appears to be the only study involving the measurement of catecholamines in mature neonatal, 6HD-treated rats, Oke et al. (32) reported that striatal and cortical DA concentrations, as well as those of NE in certain parts of the cortex, were still reduced in 12-mo-old rats when the same 6HD dose and route of administration as in the present study had been used. Thus, it seems unlikely that the recovery phenomenon observed in the present study is attributable to age alone, and several lines of evidence support the possibility that experientially induced reversal of neonatal, 6HD-induced catecholamine depletion is possible.

First, DA synthesis, release, and metabolism can be increased by neuronal electrical stimulation (20,42). They can also be elevated by both the nonassociative (e.g., food deprivation, lever pressing, intermittent food presentation) and associative aspects of food-maintained operant training (5,8,18, 21,37) presumably through similar mechanisms, although the latter aspects may make a larger and/or longer-lived contribution than the former (40).

Second, residual dopaminergic neurons in rats lesioned with 6HD as adults compensate for the neuronal loss through increased firing rates and elevations in DA synthesis, release, and turnover [e.g., (7,43)] in concert with a reduction in the responsiveness of D_2 autoreceptors (41). The extent to which similar compensatory processes operate in adult rats lesioned with 6HD as neonates has not been well investigated. However, in the present study, in contrast to the marked training-associated increases in DA and its metabolites in 6HD-treated rats, striatal DA turnover in trained control animals was significantly increased relative to that in untrained controls although striatal DA levels were reduced. These data indicate that DA neurons in both 6HD-treated and control animals had been markedly activated by training. However, as in animals lesioned with 6HD as adults (41), they also suggest that regulation of striatal DA synthesis and release in residual striatal (and cortical) DA neurons by D_2 autoreceptors may also have be reduced in neonatally lesioned animals.

Furthermore, the same 12-mo-old neonatal 6HD-treated

animals mentioned earlier in which striatal and cortical catecholamines remained depleted also had higher DA concentrations in the globus pallidus, septum, and preoptic regions than age-matched controls (32). These latter observations suggest that the magnitude of "spontaneous" compensation in such animals can be sufficient to induce increases in DA levels in some noncortical, nonstriatal DA-innervated brain regions. Because compensatory processes have not been found to be associated with significant increases in brain-regional DA tissue levels in animals lesioned as adults (43), the magnitude of these processes in animals lesioned as neonates may therefore be greater and/or more responsive to training than in those lesioned as adults. Thus, the stimulation provided by FR discrimination training to residual dopaminergic neurons together with their elevated capacity for compensation and a reduction in autoreceptor function could be sufficient to account for recovery from neonatal 6HD-induced DA depletion.

Finally, recovery from lesion-induced DA depletion could also involve neurotropic-factor induced increases in dopaminergic neuronal activity and/or reinnervation. Several different neurotropic factors are either found in striatal DA neurons and/or can increase indices of DA neuronal function in adult animals in vivo (2,9,11,15,16,25,35). Furthermore, experiential factors can increase nerve growth factor (NGF) use, whereas lesions of DA neurons innervating the striatum can increase its availability and result in selective increases in striatal DA synthesis and release. Thus, reminiscent of the present findings, intraventricular administration of NGF has been reported to increase striatal DA and HVA concentrations in adult mice whose striatal DA and HVA had been reduced by prior exposure to the DA neuronal toxin MPTP, but not in untreated controls (15). In addition, environmental enrichment housing combined with behavioral training has also been found to decrease, whereas intranigral 6HD administration has been found to increase NGF concentrations in some rat brain regions (29,30).

Regardless of the exact mechanisms through which recovery from neonatal 6HD depletion occurs, however, our findings suggest that prolonged exposure to a food-maintained operant FR discrimination procedure may have profound and long-lasting neurobiologic consequences in organisms with preexisting perinatal brain insults. This contention is further supported by our finding that the magnitude of hippocampal hypoplasia present in rats made microencephalic by prenatal exposure to methylazoxymethanol (MAM) is selectively reduced following FR discrimination training compared to that in age-matched, food-deprived untrained MAM animals (see companion study). Because such brain insults are commonly associated with developmental disability (27), our data also suggest that experience could be therapeutically beneficial to affected individuals and aid in reducing the need for pharmacotherapy.

Whether levels of recovery comparable to those observed in the present study can also occur when central DA or other neuronal populations are damaged during adulthood is unknown. Such damage could be more resistant, because several weeks of exposure to a simple (FR-5) schedule of food presentation does not reverse the DA depletion produced by intrastriatal 6HD administration in adult rats (10,38). However, the possibility that at least a partial recovery from adult brain damage can be experientially induced cannot be currently eliminated. For example, the extent to which exposure to simple operant schedules may have at least decreased the magnitude of 6HD-induced DA depletion in prior studies (10,38) cannot be determined because, as in the present report, appropriate controls were not included. In addition, residual serotonergic, noradrenergic, and cholinergic neurons, like dopaminergic neurons, have the capacity to partially compensate for damage in adulthood (1,23,36), and experiments in adult-lesioned animals involving operant learning procedures comparable to those used in the present study have not been performed. Moreover, more central DA neurons are activated in adult animals during learning of a complex operant task than during its performance following such learning (40). This observation suggests that operant tasks requiring continued learning might be more likely to result in recovery than during the performance of tasks that are more easily learned. It is thus conceivable that exposure to procedures related to those used in the present study might eventually be used to reverse or at least delay the onset of symptoms caused by central neuronal damage occurring in adult organisms (e.g., patients with Alzheimer's or Parkinson's disease), and to reduce the need for pharmacotherapy and other, more invasive procedures such as fetal tissue transplants in such patients (14,22).

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