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DRL Performance in 6-Hydroxydopamine-Treated Rats[1]

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LEVINE, T. E., P. S. McGUIRE, T. G. HEFFNER AND L. S. SEIDEN. *DRL performance in 6-hydroxydopamine-treated rats.* PHARMAC. BIOCHEM. BEHAV. 12(2) 287–291, 1980.—Adult rats were given intraventricular injections of 6-hydroxydopamine (6-HDA) or saline-ascorbate vehicle prior to exposure to a differential-reinforcement-of-low-rate (DRL) 18-sec schedule of water reinforcement. The 6-HDA treatment did not alter the acquisition or maintenance of DRL performance despite large depletions of dopamine and norepinephrine in brain. The 6-HDA treatment completely blocked the response rate-increasing effects of amphetamine but did not alter the rate-decreasing effects of amphetamine on DRL performance. These findings suggest that 6-HDA-treated rats are able to respond to the contingencies necessary to maintain reinforcement on a DRL schedule.

6-Hydroxydopamine DRL Operant behavior Amphetamine Catecholamines

ALTHOUGH considerable evidence exists for a relationship between brain catecholamine systems and operant behavior [13, 14, 18], selective destruction of these systems via central injections of the neurotoxin 6-hydroxydopamine (6-HDA) produces relatively few long-lasting effects on schedule-controlled behavior. Studies of fixed interval performance [12], continuous reinforcement and T-maze performance [1,2] and most studies of fixed ratio performance [6, 11, 12], have revealed essentially no differences between 6-HDA-treated and control animals beyond a temporary disruption in performance immediately following treatment. However, rats given 6-HDA display apparently permanent increases in responding when performing on variable interval [10], random interval [8], and on some fixed ratio [9] schedules of reinforcement. Thus, the ability of 6-HDA to affect operant responding appears to be dependent upon the operant paradigm examined. One explanation for such schedule-specific effects would be that, as has been shown for many drugs (see review [7]), the effects of 6-HDA on operant behavior are dependent upon the baseline rate of operant responding. Thus, 6-HDA may increase responding which normally occurs at a low rate while not influencing responding which normally occurs at high rates. Alternatively, the effects of 6-HDA on operant behavior may depend upon properties of the operant schedule other than rate of responding.

The present experiments were conducted in order to further examine the determinants of the effects of brain catecholamine-depleting 6-HDA injections on operant behavior. A DRL schedule of reinforcement generates low rates of responding and has been shown to be susceptible to response-rate increasing effects of drugs such as amphetamine which selectively increase low rate operant performance [15]. However, the results of these experiments indicate that a 6-HDA treatment which causes a large depletion of catecholamines in brain does not alter the rate at which rats respond on the DRL schedule. The 6-HDA treatment was sufficient, however, to eliminate the response-rate increasing effects of amphetamine.

METHOD

Subjects and Treatments

Male Sprague-Dawley rats (Holtzman, Madison, WI) weighing 200–250 g were anesthetized with ether and were treated as follows: 10 rats were given pargyline HCl (Saber Labs, Morton Grove, IL) (50 mg/kg, IP) 45 min prior to an intraventricular injection of 6-HDA (Regis Chemical Co., Chicago, IL) (200 μg/20 μl, dose as free base; 10 μl in each ventricle); 8 vehicle control rats were given pargyline prior to intraventricular injection of a 20 μl volume of the 6-HDA

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vehicle solution (0.9% saline containing 0.1% ascorbic acid); 8 rats received no treatment. All rats were given free access to food and a 0.01% solution of tetracycline in tap water for 2 weeks. Rats were then placed on a water deprivation schedule consisting of 15 min access to tap water each day.

Apparatus

Ten modified Gerbrands rat operant chambers (Model C), served as experimental enclosures. Each chamber was equipped with a houselight and a Lehigh Valley response lever. A static force of 20–30 g was required to operate the lever. A solenoid-operated dipper delivered 0.05 ml of water. Each chamber was enclosed in a modified Coleman camping cooler equipped with ventilating fan.

The chamber devices were interfaced to a PDP/8e computer which controlled the reinforcement contingencies and stored the data [16]. The data were recorded as interresponse times (IRTs), defined as the interval between two successive lever presses. IRTs were recorded with a resolution of 0.1 sec. The data were analyzed off-line by a PDP/8a computer.

Procedure

After 5 days of adaptation to the water deprivation schedule, training was begun. Rats were placed in the chambers and allowed to acquire the lever press response during a one hour exposure to a continuous reinforcement schedule. When the animals emitted at least 75 responses during a one hour session, training on a DRL 18-sec schedule was begun. On this schedule, responses occurring at least 18 sec apart were reinforced. Rats were exposed to the DRL schedule for one hour per day, 7 days per week. Drug testing was begun after 12 weeks of exposure to the DRL 18-sec schedule. d-Amphetamine sulfate (Smith Kline and French Labs, Philadelphia, PA) was dissolved in 0.9% NaCl and injected IP 30 min prior to the session. Drug doses were tested in a varied sequence with 2–3 non-drug days between each drug test. Control data were collected from the non-drug day preceeding each test day. Amphetamine doses were expressed as micromoles per kilogram body weight; 1 mg of amphetamine is equivalent to 7.4 micromoles.

Neurochemistry

The levels of norepinephrine and dopamine in the brains of all rats used in these studies were determined in order to assess the destruction of central catecholaminergic neurons caused by the 6-HDA treatment. After completion of behavioral testing, rats were maintained with free access to both food and water for at least two weeks. Each rat was then killed by decapitation and the brain rostral to the parietal bone was placed on a cold glass plate. A coronal brain slice extending from the level of the optic chiasm to the rostral aspects of the olfactory tubercle was obtained. The corpus striatum was dissected bilaterally from this coronal slice by cutting along the cortical and septal borders of this tissue. The residual telencephalon included the tissue rostral to the coronal slice (excluding the olfactory bulbs), the cortical tissue dorsal to the rhinal sulcus from the coronal slice and the remaining telencephalon caudal to the coronal slice. After removing the cerebellum, the diencephalon was separated from the brainstem by a vertically-directed cut at the posterior aspects of the mammillary body. Tissues were stored in liquid nitrogen for 1–4 weeks prior to assay of norepinephrine and dopamine by a radioenzymatic procedure described elsewhere [3]. Levels of catecholamines in tissue (corrected for recoveries) were expressed as micrograms per g wet tissue weight.

TABLE 1

EFFECT OF 6-HDA ON RESPONSE RATE OF RATS PERFORMING ON THE DRL SCHEDULE

Week	Group: Untreated controls (n=8)	Vehicle treated controls (n=8)	6-HDA treated (n=10)
1	292 ± 39	316 ± 42	357 ± 31
2	256 ± 35	279 ± 31	312 ± 16
3	220 ± 35	273 ± 25	303 ± 20
4	232 ± 20	247 ± 13	271 ± 15
5	250 ± 22	218 ± 20	264 ± 17
6	252 ± 30	243 ± 16	230 ± 15
7	265 ± 28	219 ± 17	227 ± 15
8	263 ± 25	222 ± 16	243 ± 16

*Rats received no treatment (untreated controls) or IP injections of pargyline (50 mg/kg) prior to IVT injections of 6-HDA (200 μg) or the vehicle solution (vehicle-treated controls).

Data shown are mean (± SEM) weekly response rates (expressed as lever presses per hour). The number of rats tested is indicated in parentheses.

RESULTS

The acquisition of stable DRL performance was not altered by treatment with 6-HDA. Throughout training, the 6-HDA treated rats showed performance comparable to that of vehicle or untreated rats on the basis of response rate (Table 1), reinforcement rate (Fig. 1), and IRT distribution (Fig. 3; see control and saline treatments).

Vehicle-treated rats showed a dose-dependent increase in response rate following 1–16 μmol/kg of amphetamine (Fig. 2, left). At the highest dose tested (32 μmol/kg), responding was depressed. Despite the biphasic effect of amphetamine on response rate, there was a dose-dependent decrease in reinforcement frequency in control rats (Fig. 2, right). In contrast to the effects of amphetamine on control rats, 6-HDA-treated rats showed no increases in response rate following administration of amphetamine. However, like controls, 6-HDA-treated rats showed decreases in reinforcement rate after all amphetamine doses tested (Fig. 2). The IRT distributions also demonstrate resistance to the effects of amphetamine on DRL performance in the 6-HDA-treated rats (Fig. 3). Vehicle-treated rats (shown on the left of Fig. 3) showed a dose-dependent shift towards shorter IRTs following 1–6 μmol/kg amphetamine. In contrast, there was no such shift to shorter IRTs in the 6-HDA-treated rats (shown on the right of Fig. 3). Both control and 6-HDA-treated rats showed a general flattening of the distribution after 32 μmol/kg amphetamine.

The levels of catecholamines in the brains of 6-HDA-treated rats are shown in Table 2. Vehicle-treated con-

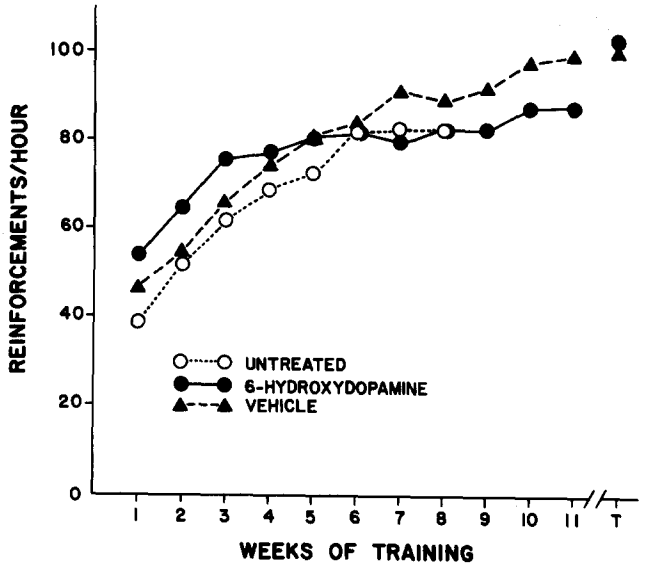

FIG. 1. Effects of 6-HDA treatment of the number of reinforcements obtained on the DRL-18 sec schedule. Three weeks prior to exposure to the DRL schedule, groups of rats received no treatment (untreated, n=8) or IP injections of pargyline (50 mg/kg) prior to IVT injections of 6-HDA (200 μg, n=10) or the vehicle solution (vehicle, n=8). Each point represents the mean number of reinforcements obtained during seven consecutive hour-long sessions.

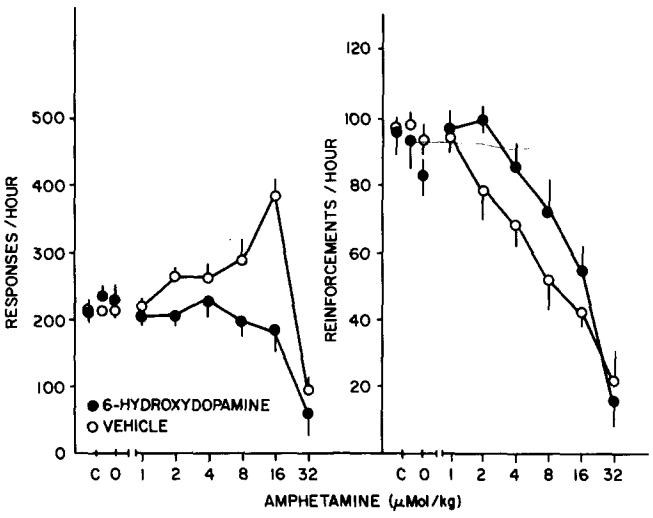

FIG. 2. Effects of d-amphetamine on response rate (left panel) and reinforcement rate (right panel) in rats performing on the DRL-18 sec schedule. Rats previously received either the vehicle treatment (n=8) or the 6-HDA treatment (n=10) described in Fig. 1 legend. Each point represents mean ± SEM results of one determination. C: non-drug baseline performance; O: IP injection of 0.9% saline.

trol rats showed no significant alterations in the regional levels of catecholamines in brain compared to untreated control rats. Norepinephrine levels in 6-HDA-treated rats were significantly reduced by 76% in the telencephalon, by 62% in the diencephalon, and by 63% in the brainstem. Dopamine levels in the corpus-striatum from 6-HDA-treated rats were significantly reduced by 84%.

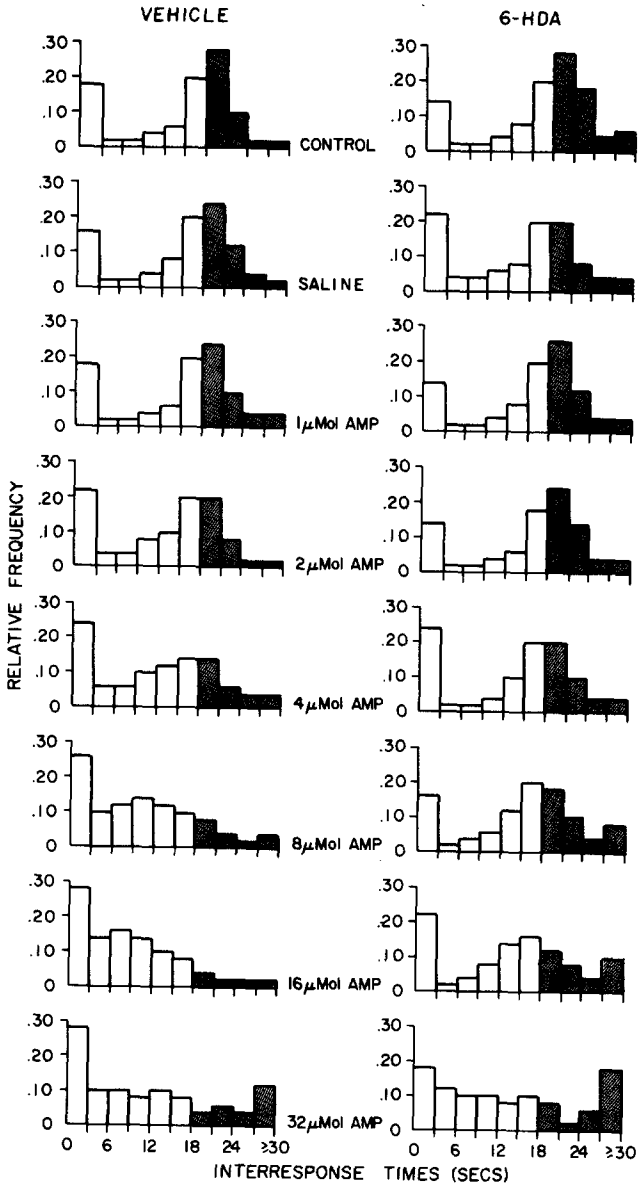

FIG. 3. Effect of d-amphetamine on the interresponse time distributions in rats performing on the DRL-18 sec schedule. Rats previously received either the vehicle treatment (left column, n=8) or the 6-HDA treatment (right column, n=10) described in Fig. 1 legend. Saline or d-amphetamine was injected IP 30 min prior to the start of the one hour test session. Each bar represents the mean relative frequency of responses which occurred with an interresponse time less than or equal to the interval indicated on the abscissa. Shaded bars indicate reinforced IRTs.

DISCUSSION

The 6-HDA treatment used in these studies did not affect the acquisition or maintenance of DRL performance in rats, despite considerable depletion of dopamine and norepinephrine in brain. This result differs from the response-rate increasing effect of similar 6-HDA treatments on variable interval and random interval operant performance [8,10]. These differences in the effects of 6-HDA on operant performance do not appear to be related to differences in the

TABLE 2

EFFECT OF 6-HDA ON THE REGIONAL LEVELS OF CATECHOLAMINES IN BRAIN*

Group	N	Striatum (DA)	Telencephalon (NE)	Diencephalon (NE)	Brainstem (NE)
Untreated controls	8	8.40 ± 0.72	0.25 ± 0.01	0.77 ± 0.06	0.40 ± 0.01
Vehicle-treated controls	8	7.66 ± 0.40	0.27 ± 0.02	0.74 ± 0.02	0.40 ± 0.01
6-HDA-treated	10	1.24 ± 0.07†	0.06 ± 0.01†	0.29 ± 0.04†	0.15 ± 0.01†

*Rats received no treatment (untreated controls) or IP injections of pargyline (50 mg/kg) prior to IVT injections of 6-HDA (200 μg) or the vehicle solution (vehicle-treated controls).

Data shown are mean ± SEM results expressed as μg/g brain tissue.

†Significantly lower than vehicle-treated control group ($p<0.01$).

baseline rate of responding since the mean response rates on the DRL schedule used in the present studies (200 resp/hr) was lower than the response rates typically generated by VI schedules on which response rates are increased by 6-HDA treatment (approximately 800 resp/hr). Schoenfeld and Zigmond [12], noting the failure of 6-HDA treatment to affect fixed ratio or fixed interval operant performance, proposed that the sensitivity of the variable interval schedule to 6-HDA may be related to the loose relationship between reinforcement and responding on this schedule. That is, except when responding is very low on the VI schedule, reinforcement frequency is fairly consistent over a wide range of response rates. The absence of response rate changes in the 6-HDA-treated rats performing on the DRL schedule may therefore stem from the more tightly defined response contingencies associated with DRL schedules. Thus, if rats increase responding on the DRL schedule, the reinforcement frequency is immediately reduced. Schoenfeld and Uretsky [10] have reported decreases in VI responding in 6-HDA-treated rats when the schedule contingencies have been made stricter by the addition of a time-out period or FR for shock.

Despite the absence of changes in baseline DRL performance, the 6-HDA treatment completely blocked the response rate-increasing effects of amphetamine on this schedule. Such an antagonism of amphetamine's effects by 6-HDA has been previously demonstrated with regard to the locomotor stimulatory [3] and anorexic [5] effects of amphetamine. Schoenfeld and Zigmond [12] have reported that 6-HDA treatment attenuates the response-rate increasing effects of amphetamine on low rate operant responding seen in the first half of a fixed interval 3 min schedule of reinforcement but that 6-HDA does not block the response rate-decreasing effects of amphetamine [12]. The present results are consistent with these data. Collectively, these findings suggest that the rate increasing effects of amphetamine on operant performance are mediated by central catecholamine neurons while the rate decreasing actions may be due to some other effect of this drug.

The present results, together with the results of studies on other schedules of reinforcement, suggest that rats are able to respond to the contingencies necessary to maintain reinforcement despite large-scale losses of central catecholamine neurons. This ability of lesioned rats to maintain performance may stem from compensatory changes at central catecholamine synapses which serve to reinstate behavioral function after subtotal lesions (see [17]). Preliminary results from this laboratory indicate that more severe depletions of dopamine (>90%) interfere with the capacity to adjust behavior to the contingencies of reinforcement (see also [3]). Thus, the capacity for compensation following loss of central catecholamine neurons may depend on the sparing of some critical subpopulation of these neurons.

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