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6-Hydroxydopamine and Avoidance: Possible Role of Response Suppression[1]

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LENARD, L. G. AND B. BEER. *6-Hydroxydopamine and avoidance: possible role of response suppression.* PHARMAC. BIOCHEM. BEHAV. 3(5)873–878, 1975.– The intraventricular administration of 6-HD to rats pretreated with pargyline resulted in severe, long-lasting decreases in avoidance responding with little or no effect on escape responding. Despite the fact that the rats failed to avoid, they appeared to be able to discriminate the CS, as was evident from freezing behavior and other symptoms of an apparent fear reaction during the CS. The increase in freezing, a response that was incompatible with avoidance was seen during the first few test sessions after 6-HD treatment and seemed to be largely responsible for a gradual decline in avoidance responding during this same period. The role of CA depletion in the animal's response to aversive stimuli thus appears to be a significant aspect of the avoidance decrement that follows 6-HD administration.

6-Hydroxydopamine Norepinephrine Catecholamines Dopamine Response suppression Avoidance

AVOIDANCE behavior has typically been employed as a convenient behavioral assay for studying the relationship between norepinephrine (NE), dopamine (DA), and behavior. Recently, much research in this area has involved the use of 6-hydroxydopamine (6-HD), an agent that produces permanent depletion of NE and DA in the brain, apparently in consequence of the destruction of central catecholamine (CA) containing neurons [4, 21].

Long-term decrements in avoidance behavior are produced by 6-HD when it is administered to rats by direct injection into the cerebral ventricular system [9, 13] or into specific cerebral structures [12, 14]. Having obtained these results, however, researchers have invariably stopped short of an adequate description and analysis of the behavioral changes. Despite the unique ability of 6-HD to produce a depletion of NE and DA in the brain that is permanent, most studies of the effects of 6-HD on avoidance behavior have examined animals for only very short periods of time, often beginning immediately after treatment. Results from experiments such as these may not only give an incomplete picture of the behavioral effects of permanent depletion of CA, but, if based on data obtained immediately after treatment with 6-HD, may reflect the acute pharmacological and toxicological effects of 6-HD, and therefore, actually be misleading. Because of these shortcomings, the most interesting and important aspects of the interaction between 6-HD-induced depletion of CA and avoidance behavior may have been overlooked.

In this experiment, rats that had been trained on a one-way discriminated avoidance procedure were subsequently treated with 6-HD and pargyline and tested regularly for more than 10 weeks. Several aspects of avoidance behavior were studied, including the time course of the decrease in responding, the occasional recovery of responding after an initial decrease, and the topography of the response itself. It was hoped that such extended observations would provide a fuller understanding of the nature of the effects of 6-HD-induced depletion of CA on avoidance behavior.

METHOD

Animals

Twelve male Sprague-Dawley rats (Holtzman) 200–250 g were housed in individual cages and were maintained on a 12 hr light–dark cycle. The rats were allowed food and water ad lib.

Procedure

Surgery. The rats were each implanted with a permanent cannula in either the left or right lateral ventricle. Each cannula (Plastic Products Co.) consisted of 3 parts: (1) a guide cannula permanently implanted in the brain, consisted of a length of 22 ga stainless steel tubing mounted in a base of threaded nylon; the tubing extended 4 mm

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[2] Much of these data were used by L. G. Lenard to partially fulfill the requirements for the Ph.D. degree at Rutgers, The State University.

beyond the base into the ventricle; (2) an injection cannula, which consisted of a length of 27 ga stainless steel tubing with a small nylon stop mounted on the outside near one end. The injection cannula was inserted into the guide cannula during intraventricular injection, and, when locked in place by a cap that screwed onto the nylon base, extended 0.5 mm beyond the end of the guide cannula into the ventricle; (3) a dummy cannula, consisting of a length of 22 ga needle filler wire mounted in a threaded nylon cap, could be inserted into the guide cannula and the cap screwed onto the nylon base so that the filler wire extended 0.5 mm beyond the guide cannula. The dummy cannula served to keep the guide cannula open and was kept in place at all times, except during intraventricular injections.

Rats to be implanted with a cannula were deprived of food the night before surgery. Prior to surgery the rats were anesthetized by intraperitoneal injections of sodium pentobarbital (Nembutal® – Abbott) 25 mg/kg and chloral hydrate, 150 mg/kg. After their heads had been shaved, the rats were placed in the sterotaxic instrument using ear bars designed to avoid puncture of the ear drum. The bite bar was placed at the height of the interaural line (i.e., 0) according to the stereotaxic atlas of Albe-Fessard *et al.* [1]. The coordinates for implantation into the lateral ventricle were: A-P = +7 mm, Lat = ±2 mm, DV = +7 mm. Training did not begin until at least 7 days after surgery.

Avoidance procedure. Avoidance behavior was measured in a shelf-jump avoidance chamber based on a design by Tenen [19]. Each chamber was constructed of Plexiglas and had a stainless steel grid floor (24.5 × 19.5 cm). At one end of the grid floor and 17 cm above it was a shelf (12 × 19.5 cm). A black wall the width and height (shelf-to-top) of the box was mounted on a gear strip that, in turn, was meshed with a gear mounted on the shaft of a reversible motor anchored to an external surface of the box. When the wall was fully extended in one direction, it covered the shelf completely, preventing a rat on the grid from jumping onto the shelf. When the motor was activated, the wall drew back, exposing the shelf. Reversing the motor moved the wall out, gently pushing the rat off the shelf and back onto the grid, again concealing the shelf. Shock (2.0 mA, provided by a BRS/Foringer SG-901 shock generator) was delivered to the grid at appropriate times via a shock-scrambler circuit.

Each test session consisted of 50 trials. A trial was initiated by the presentation of the conditioned stimulus (CS) i.e. withdrawal of the wall and consequent exposure of the shelf, with accompanying noise and vibration. If the rat jumped onto the shelf within 10 sec of the start of the CS presentation, thus tripping a microswitch under the shelf, shock was avoided and the trial ended. A 20 sec inter-trial interval (ITI) followed. For the first 10 sec of the ITI, the rat was allowed to remain on the shelf. The rat was then gently pushed off the shelf back onto the grid by the moving wall where it was allowed 10 sec more before the start of the next trial. If the rat failed to jump onto the shelf within 10 sec of the CS, a series of shock pulses (each 0.5 sec in duration, with a 2 sec shock-shock interval) was initiated. If the rat then jumped onto the shelf, it escaped from the shock, ending the trial and initiating an ITI, as described above. A maximum of 10 shocks was presented if no escape-response occurred.

The rats were trained in either of 2 shelf-jump avoidance chambers to a criterion of at least 90 percent avoidance during two consecutive sessions.

Drug administration. When the behavioral criterion had been met, the rats were injected intraperitoneally with pargyline (Eutonyl® – Abbott), 50 mg/kg, 30 min prior to an intraventricular injection of 250 μg of 6-HD (Regis). A second intraventricular injection of 250 μg of 6-HD, not preceded by pargyline was given 24 hr later. The combination of pargyline and 6-HD has been shown to produce maximal depletion of both NE and DA [5].

Intraventricular injections were given as follows: One end of a 40 cm length of polyethylene tubing (PE-50) was fitted over the upper portion of the injection cannula. The other end of the tubing was connected through a plastic tubing adapter to a 50 μl syringe (Hamilton) mounted in a Hamilton Repeating Dispenser. 6-HD was dissolved in a solution of 0.9 percent saline and 0.05 percent ascorbic acid. The injection cannula and PE tubing were filled with this solution from a 1 ml syringe. The 50 μl syringe, filled with distilled water, was then attached to the plastic tubing adapter, which had been disconnected from the 1 ml syringe. At this point, a small air bubble was introduced into the PE tubing at the syringe end so that the flow of solution into the brain could be checked visually by observing the movement of the bubble down the tube. The dummy cannula was removed from the guide cannula and the injection cannula was inserted and anchored with the screw cap. The compound was then injected at a rate of 1 μl/5 sec. This rate was easily maintained since each depression of the dispenser button released 1/50 of the total volume of the syringe, i.e., 1 μl. About 60 sec after the last depression of the dispenser button, the injection cannula was removed from the guide cannula and immediately replaced with the dummy cannula. The volume for each 6-HD injection was 20 μl. Injections were always given to awake, freely moving animals. Doses of drugs were calculated as the weight of the salt.

In the course of testing, some of the rats were given injections of a catecholaminergic agonist and a dopaminergic antagonist. The effects of these agents were temporary and will not be discussed in this paper. Data from sessions during which control injections were given were pooled with data from sessions with no treatment because these injections had no measurable effect on performance.

After the rats had been allowed to recover for 5 days, avoidance testing resumed, with a frequency of 2–3 daily session/week for about 10 weeks.

Biochemical assay. For the purposes of the biochemical assay, 4 rats of the same age and weight as those receiving 6-HD received no drug treatment and were designated as controls. Two of these rats, each with an implanted cannula, were tested in the shelf-jump procedure in the standard manner. The other 2 rats were housed in individual cages for the duration of the experiment, but were never tested. Since no significant differences in levels of CA were found among these control rats, the data from the assays of their brains were pooled.

About 3 weeks after the conclusion of the experiment, all the rats were decapitated and their brains were excised and frozen immediately on dry ice. NE and DA were measured fluorometrically by the trihydroxyindole procedure [6]. Whole brains were homogenized in 4 volumes of fresh 0.4N perchloric acid at 0–4°C. The homogenized samples were centrifuged at 0–4°C for 20 min at 9000 rpm. The CA were adsorbed onto alumina at pH 8.5, then eluted into 0.1N acetic acid and oxidized according to the method described by Chang [7]. After they had been

oxidized, the samples were analyzed for NE on a spectrophotofluorometer (Aminco-Bowman) at excitation wavelength 385 mμ/ emission wavelength 485 mμ. The samples were stored overnight under a fluorescent light and then analyzed the next day for DA at 320/380 mμ.

RESULTS

Figure 1 shows the mean percent avoidance and escape for the 11 animals that survived the 6-HD-pargyline treatment. When compared with pretreatment performance levels, avoidance responding was severely depressed from the start of posttreatment testing and remained low for most rats throughout the 10 wk of the experiment. Escape behavior, on the other hand, was largely unaffected except during the early sessions, when a few rats occasionally failed to escape.

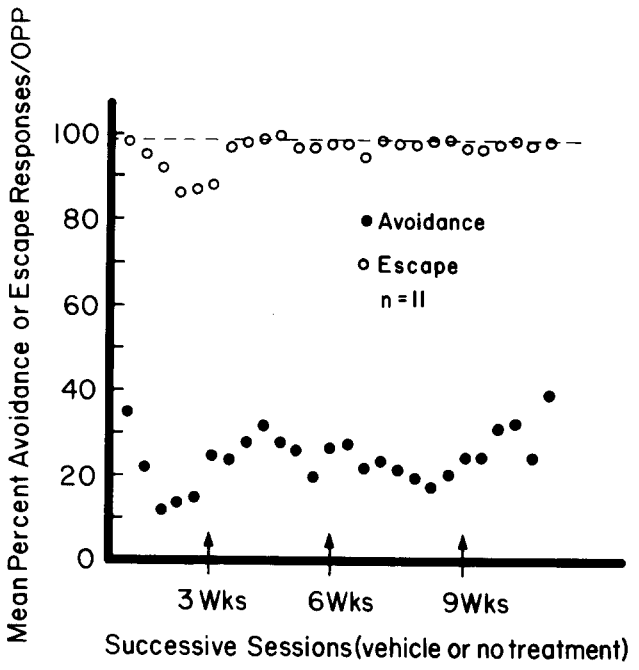

FIG. 1. Mean percent avoidance or escape per opportunity for pretrained rats after intraventricular injection of 6-HD. Each trial was an opportunity to avoid. Escape opportunities occurred only when rats failed to avoid shock. Broken line represents the mean percent avoidance for the last 2 sessions before treatment with 6-HD. Only sessions during which vehicle was injected or no treatment was given are shown; drug-treatment sessions are omitted (see text for details).

The magnitude of the escape decrement almost never approached that of the avoidance decrement for any rat. In many cases, rats that rarely avoided shock had nearly perfect escape records. Examples of this can be seen in the data from Rats 490 and 493 in Fig. 2, which shows avoidance and escape records for individual animals. These two animals usually avoided on only 10 percent or less of their trials, and often did not avoid at all during a 50 trial session. However, they failed to escape only a few times throughout the experiment. In only one instance (Rat 486) did a rat fail to escape throughout an entire session; it also exhibited a particularly severe avoidance decrement, not avoiding at all during 22 of 26 sessions. Despite this poor avoidance record, its escape responding in most sessions was greater than 80 percent.

A noteworthy aspect of the behavior of most rats treated with 6-HD was a progressive decline in the frequency of avoidance responses during the first 3–4 test sessions after treatment. Figure 1 shows that the mean avoidance level was about 35 percent during the first post-treatment session, 22 percent during the second, 11 percent during the third, and about 13 percent during the fourth session. Escape behavior also declined, but to a much lesser extent over this same period. This effect, which was observed in nearly every animal, can be seen most clearly in the data from some of the individual animals shown in Fig 2. Rat 492, for example, went from 50 to 0 percent avoidance during the first four sessions before leveling off at a mean of about 10 percent. This animal's escape responding declined from 100 to 86 percent by the fifth posttreatment session, but eventually returned to normal after several more sessions.

After the initial decline in avoidance responding, some rats showed a greater tendency to avoid during further testing. This tendency is evidenced as a gradual increase in the mean percent avoidance seen in Fig 1, and is most notable during 2 separate phases of testing. The largest and most widespread improvement occurred in many rats soon after the minimum level of avoidance had been reached during Sessions 3–4, e.g., Rats 489, 494, and 495. Some rats tended to show additional improvement much later on in testing, e.g. Rats 487 and 496. The level of avoidance for Rat 487 remained about 10 percent until approximately 6 weeks after 6-HD treatment, after which its baseline suddenly rose to about 30 percent. After about 3 weeks of fairly stable responding at this rate, its baseline rose again to 60–75 percent avoidance. Rat 496 avoided on about 10 percent of the trials until nearly 9 weeks after treatment, when its avoidance performance began to improve with nearly every session. At the time testing was terminated, Rat 496 was avoiding on about 62 percent of the trials.

The avoidance behavior of a few rats recovered dramatically after an initial decrement. For example, Rat 491 avoided at pretreatment levels during Sessions 7–10, following a large decrease that had occurred during the first 6 sessions. In succeeding sessions, this rat continued to perform erratically, with avoidance levels ranging from 8 to 96 percent. Rat 494 showed early improvement in responding after an initial decline to a low of 15 percent avoidance during the first 4 sessions. By about the fifth week of testing, this rat was usually avoiding at least 80 percent of the time and eventually reached over 90 percent avoidance by Weeks 8–9.

Direct observation of 6-HD treated rats in the shelf-jump procedure revealed that many rats, though not responding to avoid shock, nevertheless appeared to be discriminating the CS. These rats typically turned their heads away from the shelf, vocalized loudly, became rigid, urinated and defecated when presented with the CS. Some rats became so rigid that they tended to fall over backwards. Rats exhibiting this behavior pattern rarely avoided on the trial during which it appeared, but, when shocked, usually escaped immediately. Once the animal was on the shelf, these symptoms of what appeared to be a fear response to the CS subsided immediately, only to begin again at the next presentation of the CS.

Some rats consistently showed a delayed fear response,

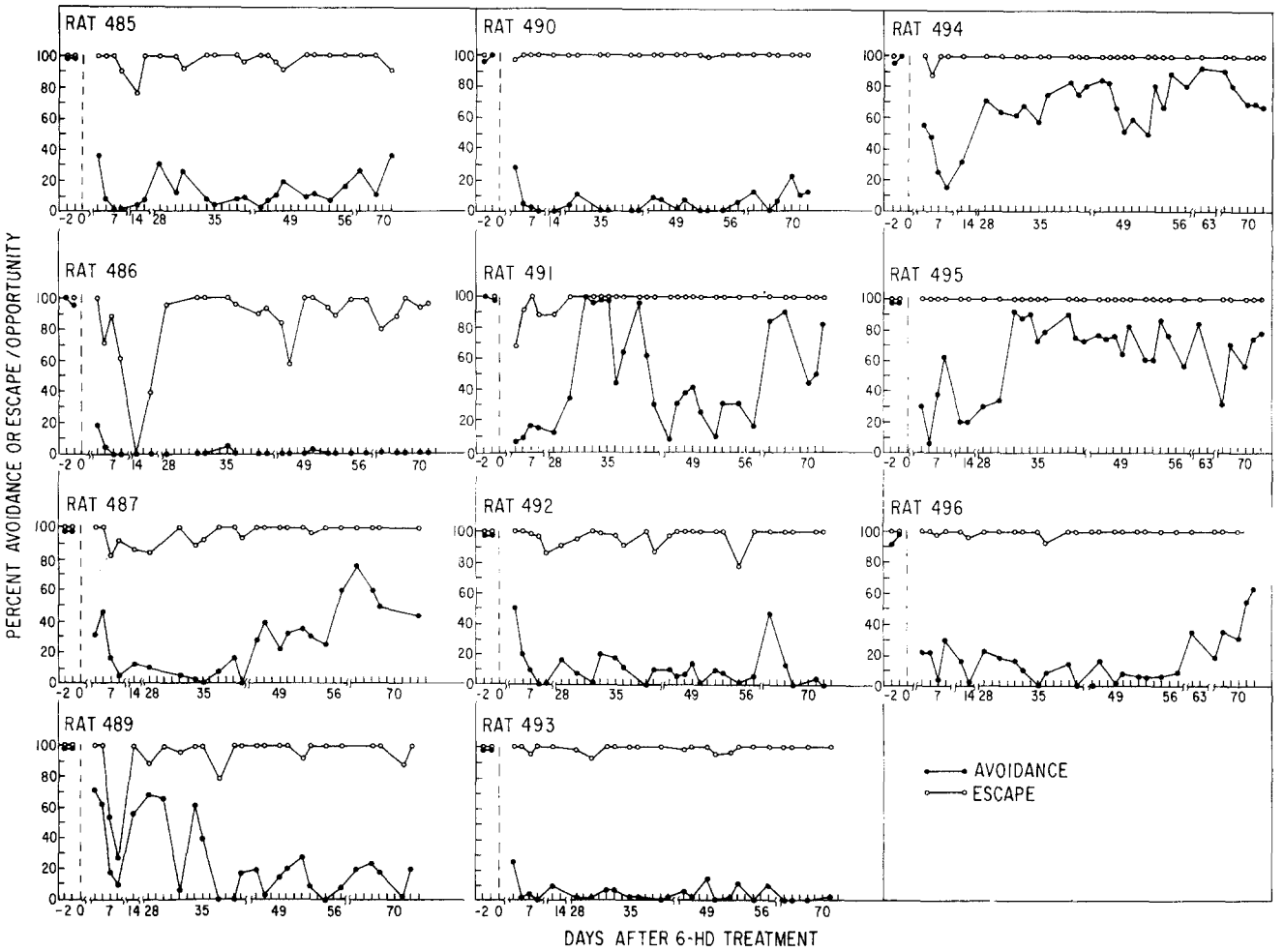

FIG. 2. Percent avoidance or escape per opportunity for individual pretrained rats after intraventricular injection of 6-HD. Each trial represents an opportunity to avoid shock. Escape opportunities occurred only when rats failed to avoid. Broken vertical line indicates administration of 6-HD.

i.e. they did not respond immediately at the start of the CS presentation, but waited until several seconds had elapsed and they were closer to actually being shocked. Some animals seemed to react during the CS presentation as though they were being shocked. They flinched and jumped rhythmically, as though they were receiving a series of shock pulses.

This apparent fear response to the CS was not evident during the first test session after the administration of 6-HD, but developed gradually, growing in intensity during the first few sessions as the frequency of avoidance responses decreased.

Results of Catecholamine Assay

The median levels of NE and DA for the 11 animals in this experiment were 9 and 12 percent of control, respectively. Depletion levels for individual animals are shown in Table 1. Of those rats showing greater than median avoidance preformance after treatment with 6-HD (Rats 487, 489, 491, 494, and 495) all but 489 had above-median levels of NE, DA, or both. Avoidance by Rat 486 was below median value but its NE level was above the median.

DISCUSSION

Intraventricular administration of 6-HD to 11 rats produced a selective decrease in avoidance responding with little or no effect on escape responding. In nearly every case, the frequency of avoidance responses decreased with each successive test session during the first few sessions after treatment with 6-HD. A similar decrease in avoidance responding has been reported for pretrained animals but was not discussed [8].

It is highly unlikely that this decrease could have resulted from a continuing process of depletion of CA or of nerve degeneration because, retesting was begun 5 days after treatment with 6-HD in the present experiment and at least 14 days after treatment in the study by Cooper *et al.* [8]. Furthermore, a similar effect has been observed in animals that were tested more than 4 weeks after treatment with 6-HD [3].

Despite the failure to make an avoidance response, the rats did seem able to discriminate the CS, as evidenced by an apparent fear response that appeared in many rats treated with 6-HD during presentation of the CS after the initial one or two sessions. Seiden and Hanson [18] described similar behavior in an avoidance situation by cats

TABLE 1

MEDIAN PERCENT AVOIDANCE AND LEVELS OF NE AND DA IN WHOLE BRAINS OF RATS AFTER THE ADMINISTRATION OF 6-HD + PARGYLINE

Rat	Median Percent Avoidance	NE		DA	
		ng/g	Percent of Control	ng/g	Percent of Control
485	11	13.6	3	89.2	12
486	0	142.8	32	89.2	12
487	25	176.7	40	175.5	24
489	16	23.8	5	75.9	10
490	4	34.0	8	89.2	12
491	33	57.8	13	138.5	19
492	8	40.1	9	38.0	5
493	2	23.8	5	75.9	10
494	69	57.8	13	127.2	17
495	73	328.0	73	100.6	14
496	16	17.0	4	n.d.*	0
Control (n = 4)	–	447.0 ± 18.8	–	707.0 ± 49.5	–

*Not detectable; below the level of sensitivity of the assay

treated with reserpine. They observed that " . . . the cats often growled, hissed, crouched and spat at the CS or the UCS and made motions as if to avoid or escape, but when this pattern of 'defensive' behavior had emerged, no avoidance or escape responses occurred . . ." Similarly, in the present study, the appearance of such responses, which were incompatible with avoidance, seemed to preclude the occurrence of an avoidance response, although escape responses did occur.

Others have also attributed avoidance decrements to the predominance of freezing responses over avoidance responses. Thomas *et al.* [20], for example, suggested that avoidance decrements observed after ablation of the cingulate gyrus resulted from a lowering of the threshold of an innate crouching or freezing reflex. Similarly, Barrett *et al.* [2] noted that the poor avoidance behavior characteristic of rats of the Zivic-Miller (ZM) strain seemed to result from the tendency of these rats to exhibit "freezing, crouching and general behavioral suppression" in response to shock and was neither a function of greater shock sensitivity nor of the rats' making the wrong choice in the Y-maze.

It is apparent from the present data that during the first few sessions after treatment with 6-HD there was an increase in the frequency of a new series of responses, including freezing, that was incompatible with the avoidance response and was correlated with a decline in the frequency of avoidance behavior. It is possible that the rats had learned to suppress avoidance responses. It is significant, in this regard, that rats treated with 6-HD have often been observed in our laboratory to acquire at least two different unprogrammed avoidance responses that were not incompatible with freezing. Some rats learned to hang onto the top of the moving wall as it pushed them off the shelf, thereby avoiding falling onto the grid. If they were able to remain hanging there through the ITI, they could successfully avoid the next shock. Other rats learned to hold down the shelf with their front paws as they were pushed off the shelf. Holding down the shelf in this way depressed the microswitch signaling the animal's response and automatically ended the next trial as soon as it had begun, despite the rat's failure to jump. In each of these cases, the animals could avoid the next shock while remaining frozen during the presentation of the CS. The fact that such responses were acquired after treatment with 6-HD and were often extremely difficult to eliminate suggests that the ability per se of the rat to acquire new responses was not hampered by this treatment.

The role of the animal's reaction to aversive stimuli seems relevant to its ability to perform in an avoidance situation. Both NE and DA neurons in the brain have been shown to be active during aversive stimulation [10,11]. Depletion of NE by the injection of 6-hydroxydopa seems to increase emotionality in rats in aversive situations [16,17]. Moreover, it has often been noted that animals

treated with 6-HD, although while generally indistinguishable under normal circumstances from untreated rats after some initial recovery period, appear to have a long-lasting abnormal response to aversive stimuli [15]. One interesting example of this is the observation by Young and Smith [22] that rats treated with 6-HD tended to freeze in the open field (usually an aversive situation for a rat) despite normal activity in their home cages.

From the present data, we deduce that decrements in avoidance behavior after the administration of 6-HD should not be explained as a failure to learn the new response or to recall a previously acquired one. Such explanations contain the inference that some central learning or memory mechanism has been disrupted by treatment with 6-HD. In fact, this seems not to be the case. Animals were still capable of escaping and could avoid provided that such avoidance responses were compatible with immobility. These results indicate, however, that the long-term avoidance decrement may be largely a function of active suppression of avoidance responses. Significantly, there have been no reports of decrements in withholding punished responses after intraventricular administration of 6-HD, where correct performances are compatible with immobility.

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