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Amphetamine and LSD as Discriminative Stimuli: Alterations Following Neonatal Monoamine Reductions[1]

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MINNEMA, D. J. AND J. A. ROSECRANS. *Amphetamine and LSD as discriminative stimuli: Alterations following neonatal monoamine reductions.* PHARMACOL BIOCHEM BEHAV **20**(1) 95–101, 1984.—Male adult Sprague-Dawley rats (70 days of age), neonatally depleted of either 5-hydroxytryptamine (5HT) via 5,7-dihydroxytryptamine (5,7-DHT; ICS) + desmethylimipramine (DMI; IP) at 3 days of age or dopamine (DA) via 6-hydroxydopamine (6-OHDA; ICS) + DMI at 14 days of age, were trained to discriminate either *d*-LSD-tartrate (80 μg/kg; IP) or *d*-amphetamine (*d*-AMPH) sulfate (0.90 mg/kg; IP) from saline utilizing a two lever drug discrimination paradigm. A neurochemical analysis at the termination of these studies revealed the following in terms of %DA or %5HT (presented in that order) depleted with respect to the appropriate vehicle control group: telencephalon; 96 and 96%, diencephalon; 51 and 31%, and brain stem; 76 and 80%. Rats learned to discriminate either *d*-AMPH or LSD regardless of amine depleted. In addition, the depletion of 5HT had little effects on dose or drug generalizations, or the ability of known antagonists to antagonize the discrimination stimulus (DS) effects of either LSD or *d*-AMPH. The effect of DA depletion, on the other hand, was to increase the sensitivity of the LSD DS at low doses, while decreasing the sensitivity of the *d*-amphetamine DS. DA depletion also had the effect of reducing the effectiveness of the LSD-antagonists, pizotifen maleate (BC105), while the opposite was observed for the *d*-AMPH antagonist, trifluoperazine HCl. These data suggest that: (1) LSD and *d*-amphetamine discrimination stimuli are not mediated and/or influenced via the compromised aspects of the 5HT systems (other central mechanisms may have compromised for these 5HT deficits); (2) the LSD DS is mediated or influenced both by serotonergic and dopaminergic mechanisms; and (3) the *d*-amphetamine DS is mediated by certain aspects of the dopaminergic system with little evidence for the involvement of 5HT systems.

Discriminative stimulus LSD *d*-Amphetamine Dopamine Serotonin

BOTH serotonergic and dopaminergic systems have been indicated in the central actions of the two dissimilar pharmacological agents, lysergic acid diethylamide (LSD) and *d*-amphetamine (*d*-AMPH). The discriminative stimulus (DS) properties of *d*-AMPH are reported to be mediated mainly through central dopaminergic systems [13, 28, 29]. Although not indicated by drug discrimination studies, some studies have suggested a serotonergic role in *d*-AMPH's actions [4,28]. This hypothesized serotonergic component could represent a common mechanism underlying the actions of indolealkylamine and phenethylamine hallucinogens [28]. The actions of LSD appear to be mediated mainly through serotonergic systems [10,12] although some evidence does exist indicating dopaminergic involvement [8]. Involvement of both neurotransmitter systems has been suggested by drug discrimination studies [32].

One means of assessing the role of a particular neurotransmitter process in various behaviors and/or drug actions is to produce selective lesions in that neurochemical system. This technique has been employed in the drug discrimination paradigm [23,33]. Chemically produced lesions appear to be relatively specific for particular neurochemical systems as indicated by selective decreases in neurotransmitter concentration [14]. When exposure to a neurotoxicant occurs early in the animal's life, diminutions in neurotransmitter concentrations can be achieved without incapacitating the animal [5].

In the present study, the brain concentrations of either dopamine (DA) or serotonin (5HT) were selectively reduced in the neonatal rat employing established techniques. As adults, these animals were examined for either LSD or *d*-AMPH discriminative stimulus alterations. An alteration of the DS produced by either *d*-AMPH or LSD in these rats relative to coetaneous controls would provide further evidence as to the neurotransmitter systems involved in that drug's DS.

METHOD

Neonatal Monoamine Reductions

Timed pregnant female Sprague-Dawley rats were ob-

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tained from Flow Research Laboratories in Dublin, VA. Each female rat was individually housed in a 12× 16″ plastic cage, and provided with Purina® rat chow and tap water ad lib. A regular 12-hour light/dark cycle (light; 800–2000 hr) was maintained. The time of birth of each litter was noted. All litters were culled to 8 pups between 24 and 48 hr after birth. At three days of age, the brain serotonin concentration was selectively reduced in the pups of several litters using the procedure of Breese and Mueller [5]. Each pup was administered 20 mg/kg desmethylimipramine (DMI) IP using a 30 gauge needle, followed 60 min later by an intracisternal injection of 5,7-dihydroxytryptamine creatine sulfate (5,7-DHT) (50 μg in 15 μl saline containing 1% ascorbic acid). Control animals were treated in a similar fashion except that 5,7-DHT vehicle only was administered intracisternally. At fourteen days of age, the pups of other litters had brain dopamine concentration selectively reduced using the method described by Breese and Taylor [6]. Each pup was given 25 mg/kg DMI IP, followed 30 min later by an intracisternal injection of 6-hydroxydopamine HCl (6-OHDA) (150 μg in 25 μl saline containing 1% ascorbic acid). The same treatment was given to control animals except that vehicle was substituted for the 6-OHDA solution. All monoamine reductions were carried out in unanesthetized animals. Only male animals were used in the subsequent drug discrimination studies. Following weaning (day 22), the rats were individually housed, maintained on rat chow and tap water (ad lib), and assigned to one of either groups, as shown below: (1) 6-OHDA-DMI, LSD (n=); (2) Controls, LSD (n=6); (3) 6-OHDA-DMI, *d*-AMPH (n=8); (4) Controls, *d*-AMPH (n=6); (5) 5,7-DHT-DMI, LSD (n=9); (6) Controls, LSD (n=6); (7) 5,7-DHT-DMI, *d*-AMPH (n=9); (8) Controls, *d*-AMPH (n=6).

Drug Discrimination Training

At 70 days of age, the rats were removed from free feeding and food deprived to the extent at which 85% normal body weight could be maintained. Operant training began at approximately 75 days of age. Rats were trained to discriminate either LSD tartrate (80 μg/kg, IP, administered 10 min prior to operant session) or *d*-AMPH (0.90 mg/kg, IP, administered 15 min prior to operant session) from saline (1 mg/kg), in a two lever, fixed ratio ten, operant drug discrimination paradigm [2]. Drug lever assignments were determined pseudo-randomly, where approximately half the rats were trained to a left "drug"-lever and a right "saline"-lever. Operant sessions were carried out 7 days/week at the same time each day. Each session was of 15 min duration. The criterion for adequate discrimination defined as a group mean of greater than 90% correct lever responses prior to the first reinforcement over four consecutive sessions (2 drug sessions, 2 saline sessions), with each animal meeting this same criterion in three out of the four sessions.

Drug Discrimination Testing

The same criterion established for drug discrimination training was maintained between each test session. Test sessions were carried out and evaluated in the same fashion as training sessions were terminated (with no reinforcement) following a total of ten responses on either one of the two levers. Each test treatment was performed twice for each animal. The various test treatments were described below:

Dose-effect generalization. Following criterion performance, a dose-effect relationship was determined for all groups of rats, using three half-dose reductions of the training dose. For each group of animals, the test treatment has presented in accordance with a Latin square design, with four training sessions (2 drug, 2 saline, at random) presented between each test session.

Antagonism of the discriminative stimulus. The ability of the DA antagonist, trifluoperazine HCl (0.75, 1.5 and 3.0 mg/kg IP, 30 min prior to the session), and the 5HT antagonist, pizotifen maleate (0.1, 0.3 and 1.0 mg/kg IP, 55 min prior to the session) to antagonize the DS produced by the training dose of *d*-AMPH and LSD, respectively was examined. Trifluoperazine (3.0 mg/kg) was tested to determine whether it could antagonize the LSD DS, and pizotifen (BC105) (1.0 mg/kg IP) was tested to determine whether it could antagonize the *d*-AMPH DS.

Generalization testing. The effectiveness of the DA agonist, apomorphine HCl (0.25 mg/kg IP) and the 5HT agonist, quipazine maleate (2.0 mg/kg IP) to generalize and to potentiate either the LSD or *d*-AMPH DS was examined.

Neurochemical Analysis

At the conclusion of the drug discrimination studies, the extent of the 5HT and DA reduction was determined in the (1) telencephalon, (2) diencephalon and mesencephalon, and (3) brain stem; the mesencephalon and myelencephalon (less cerebellum) using the methods described by Anton and Sayer [1] and Welch and Welch [31]. The rats were sacrificed by decapitation, the brains removed, washed with ice-cold saline, and dissected on an ice-cold surface. Each area was weighed, immediately frozen, and stored at −35°C. The telencephalon was homogenized in 4.0 ml, 0.4 N $HClO_4$ whereas the other two areas were each homogenized in 2.0 ml, 0.4 N $HClO_4$. Following centrifugation at 15,000 rpm for 15 min, a 2 ml aliquot of supernatant was added to 15 ml conical centrifuge tubes containing 500 mg alumina. The pH was adjusted to 8.0 to 8.5 by the addition of 6.5 ml, 0.5 M Tris buffer (pH=9). The tubes were shaken for 15 min, and then briefly centrifuged. The supernatant was removed, of which a 7.5 ml aliquot was saved for serotonin determination. Following two washings of the alumina with distilled water, the dopamine was eluted with 2.5 ml, 0.1 N $HClO_4$.

To develop dopamine fluorescence, a 0.5 ml aliquot of the alumina eluate was added to 0.5 ml, 0.5 M sodium phosphate buffer (pH=7.0). Following the addition of 0.1 ml, 0.1 M sodium iodine and the subsequent addition of 0.2 ml, an alkaline sodium sulfite/EDTA solution, 0.12 ml concentrated HCl:glacial acetic acid (1:1) was added, the sample heated at 95°C for 45 min, cooled to room temperature, and the fluorescence determined (335 nm excitation, 380 nm emission) on an Aminco-Bowman SPF equipped with a Xenon lamp. Tissue blanks were simultaneously prepared by reversing the order of addition of the sodium-iodine and sodium sulfite/EDTA solution. Values were compared to standard stock solutions carried through the same procedure.

To develop serotonin fluorescence, the 7.5 ml aliquot from the original alumina supernatant was added to 15 ml n-butanol, 3 g potassium chloride, and 3 ml, 1 M potassium phosphate buffer saturated with KCl (pH=10). Following 10 min of shaking and a brief centrifugation 12 ml of the supernatant was added to 20 ml cyclohexane and 1.2 ml, 0.1 N HCl. This mixture was shaken, centrifuged, the upper phase discarded, and the lower phase saved. To each ml aliquot of lower phase, 0.3 ml, 12 N HCl (containing 5 mg/ml ascorbic

TABLE 1

BRAIN AREA 5-HYDROXYTRYPTAMINE (5HT) AND DOPAMINE (DA) LEVELS IN RATS ADMINISTERED 6-OHDA or 5,7-DHT NEONATALLY*

	Telencephalon		Diencephalon	Brain Stem
Treatment†	DA ng/g ± S.E.	5HT ng/g ± S.E.	5HT ng/g ± S.E.	5HT ng/g ± S.E.
LSD Trained				
Control	2405 ± 108	238 ± 6	415 ± 13	241 ± 21
DA ↓	1133 ± 163‡ (−53%)	240 ± 6	415 ± 12	248 ± 18
Control	2352 ± 113	227 ± 11	479 ± 27	248 ± 11
5HT ↓	2556 ± 118	10 ± 3‡ (−96%)	233 ± 54‡ (−51%)	60 ± 13‡ (−76%)
d-AMPH Trained				
Control	2507 ± 177	252 ± 7	413 ± 21	222 ± 8
DA ↓	1027 ± 84 (−59%)	245 ± 11	440 ± 18	264 ± 15
Control	2265 ± 144	240 ± 18	430 ± 18	248 ± 5
5HT ↓	2452 ± 98	10 ± 5‡ (−96%)	296 ± 38§ (−31%)	50 ± 17‡ (−80%)

*Dopamine depleted (DA ↓) rats were administered 150 μg 6-hdyroxydopamine (ICS) + 20 mg/kg DMI (IP) at 14 days of age while 5-hydroxytryptamine depleted (5HT ↓) rats were administered 50 μg 5,7 DHT (ICS) plus 25 mg/kg DMI (IP) at 3 days of age; control rats in each group received DMI + 15–25 μl 1% ascorbic acid saline solution (vehicle). Rats were sacrificed by rapid decapitation at approximately 240 days of age. % Values in parenthesis represents the level of amine reduction induced by a specific neurotoxicant.

†DA ↓, 5HT ↓, and the appropriate vehicle control rats were trained to discriminate either LSD tartrate (80 μg/kg, IP) or *d*-AMPH sulfate (0.9 mg/kg, IP) at approximately 70 days of age; each group consisted of an N = 6–9 rats.

‡Significant from the appropriate vehicle control at a minimal of $p<0.01$.

§Significant from the appropriate vehicle control at a minimal of $p<0.05$.

acid) was added and the relative fluorescence determined (295 nm excitation, 550 nm emission). The values were compared to standards carried through the same procedure.

Analysis of Data Collected

Accuracy of discrimination for each animal was expressed as percentage drug lever responses (number drug lever responses/total responses on both levers). Statistical differences between the control animals were determined as a split-plot least-squares factorial analysis (neonatal treatment × drug dose × subject) [15]. Statistical differences between control and treated monoamine concentrations were determined by Student's *t*-tests [15]. Confidence levels at 0.05 were used in all cases.

Drugs and Their Sources

The drugs used and their sources are as follows: d-LSD-tartrate, N.I.D.A.; *d*-amphetamine sulfate, Mallinckrodt Chemical Co.; pizotifen maleate, gift from Sandoz Pharmaceuticals; trifluoperazine HCl (Stelazine), Smith, Kline and French; quipazine maleate, Miles Laboratories; apomorphine HCl, Sigma Chemical Company; desmethylimipramine HCl, USV Pharmaceutical Corporation; 5,7-dihydroxytryptamine creatinine sulfate, Sigma Chemical Company; 6-OH-dopamine HCl, Sigma Chemical Company. All drugs were administered IP and expressed in terms of the salt.

RESULTS

Biogenic Amine Levels in 6-OHDA and 5,7-DHT Treated Rats

Twenty percent of the pups receiving 5,7-DHT died indicating that this neurotoxicant was administered at a dose close to the lethal dose. The fatality rate was less with 6-OHDA (approximately 5 percent). At weaning, a slight depression (5%) in body weight was seen in both groups of neurotoxicant exposed animals. At the time discrimination training began, the body weights of treated and control rats were similar. At the end of the drug discrimination tests (approximately 280 days of age) the rats were sacrificed for neurochemical analysis. As shown in Table 1, the levels of DA in 6-OHDA, DMI treated animals (both LSD and *d*-AMPH groups) were significantly reduced compared to controls. The 5HT levels in those animals were similar to those of controls. The 5,7-DHT, DMI rats exhibited a reduction in 5HT levels with no change in DA levels.

LSD DS

Acquisition of the LSD DS (as defined by the number of session necessary to meet criterion) was similar for all groups of animals. As shown in Fig. 1, no significant difference was observed between the 5,7-DHT, DMI treated rats and controls in the LSD dose-effect curve, $F(1,13)=0.093$. However, the LSD dose-effect curve was significantly different in the 6-OHDA, DMI treated rats, $F(1,12)=4,852$,

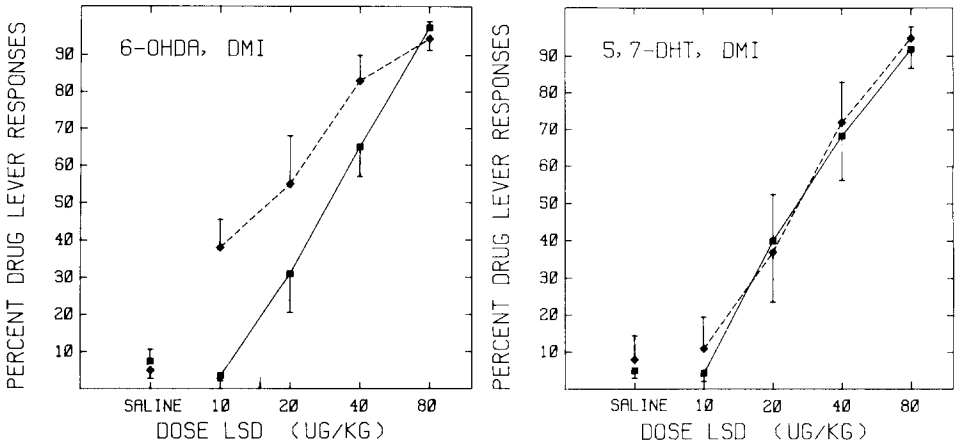

FIG. 1. LSD dose response generalization curves in 6-OHDA, DMI (DA↓) and 5,7-DHT, DMI (5HT↓) treated rats. The square symbols represents data collected from the vehicle controls while the diamond symbols represents data collected from the depleted animal subjects.

$p<0.05$, where higher drug-lever responses (relative to controls) were observed at lower (40, 20 and 10 μg/kg) doses of LSD despite similar performance at the training dose (80 μg/kg) and saline (Fig. 1).

Pizotifen maleate effectively antagonized the LSD DS in a dose-related fashion, $F(2,12)=9.52$ (Fig. 2). Trifluoperazine HCl was without effect on the LSD DS. Although not statistically significant, $F(1,12)=0.40$, F-interaction$(2,12)=3.11$, the 6-OHDA, DMI treated rats tended to be less affected by the 1 mg/kg dose of pizotifen maleate relative to controls (Fig. 2). Quipazine maleate generalized to the LSD DS in all groups of animals. Apomorphine partially generalized to the LSD DS, and significantly potentiated the LSD DS in both control, F-apomorphine treatment$(1,25)=19.55$, $p<0.01$, and 6-OHDA, DMI-treated F-apomorphine treatment$(1,35)=5.88$, $p<0.05$ (Fig.3).

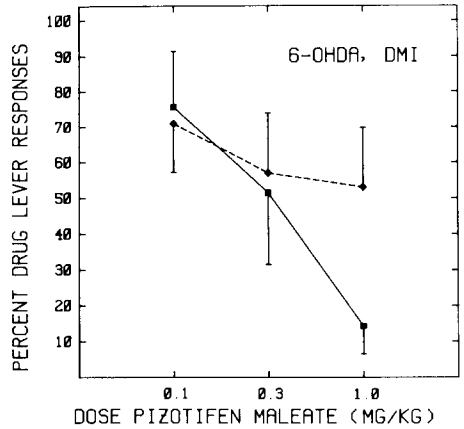

FIG. 2. Dose response antagonism of the LSD DS by pisotifen maleate in 6-OHDA, DMI (DA↓) treated rats. Symbols are similar to those in Fig. 1. The antagonist was administered 55 min prior to LSD (80 μg/kg, IP).

d-*AMPH DS*

Acquisition of the *d*-AMPH DS was similar in all groups of animals. There was no statistically difference in the *d*-AMPH dose-effect curve between the 5,7-DHT, DMI-treated rats and control rats, F-treatment$(1,13)=0.021$ (Fig. 4). The 6-OHDA, DMI treated animals, while exhibiting similar performance under saline and *d*-AMPH training dose conditions, exhibited a significant reduction in percent drug lever responses at the 0.45 mg/kg *d*-AMPH dose, $F(2,12)=5.89$, $p<0.05$ (Fig. 4). The 5HT antagonist, pizotifen maleate, failed to alter the *d*-AMPH DS in any of the treatment groups. While not significantly different, F-treatment$(1,24)=1.25$, the 6-OHDA, DMI-treated rats appeared to be slightly more sensitive to the antagonistic effects of lower dose of trifluoperazine HCl than controls or 5,7-DHT, DMI animals (Fig. 5). Neither quipazine maleate nor apomorphine HCl generalized to the *d*-AMPH DS in any of the treatment groups.

DISCUSSION

Several studies have indicated that the action of *d*-AMPH involves a serotonergic component [4, 11, 18, 27]. The results of the present study provide no support for serotonergic involvement in the *d*-AMPH DS, since (1) no absence DS differences were noted between 5,7-DHT, DMI-treated animal and controls, and (2) neither pizotifen nor quipazine were effective in altering the *d*-AMPH DS. The dose of *d*-AMPH used in the present study, however, was lower than doses used to produce "classical" 5HT-dependent behaviors [17, 27, 29]. The dose of *d*-AMPH is an important factor with respect to the specificity of its CNS actions [16] and may in part explain the observed lack of 5HT involvement noted in the present study.

The altered *d*-AMPH DS dose-effect curve noted in the 6-OHDA, DMI-treated rats, as well as the ability of trifluoperazine to antagonize the *d*-AMPH DS, suggests a major role of the dopaminergic system in the DS properties of *d*-AMPH. This conclusion is consistent with other *d*-AMPH drug discrimination studies [13, 24, 25]. Since the major effect of *d*-AMPH at doses below 1 mg/kg involves the increased release of DA from synaptic DA terminals [3,16], it is interesting to speculate that the altered *d*-AMPH DS dose-response curve observed in the 6-OHDA, DMI-treated rats (which demonstrated an approximately 60% reduction in telencephalic DA levels) may be related to a decrease in functional DA nerve terminals. Support for this hypothesis is

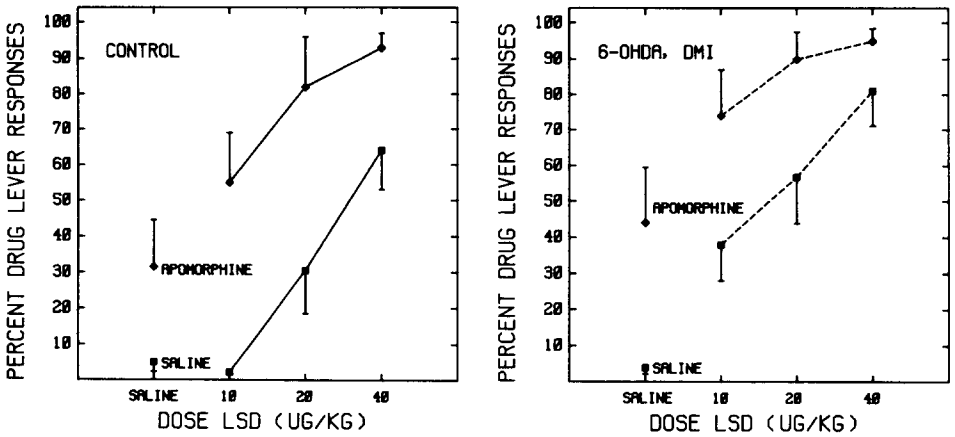

FIG. 3. Potentiation of the LSD DS by apomorphine in vehicle control and 6-OHDA, DMI (DA↓) treated rats. LSD alone is represented by the square symbols while the potentiated effect by apomorphine (250 μg/kg, IP) given 10 min prior to a specific dose of LSD is represented by the diamond symbols. The effects of apomorphine (250 μg/kg, IP) alone is presented to the left of the LSD curves; saline data.

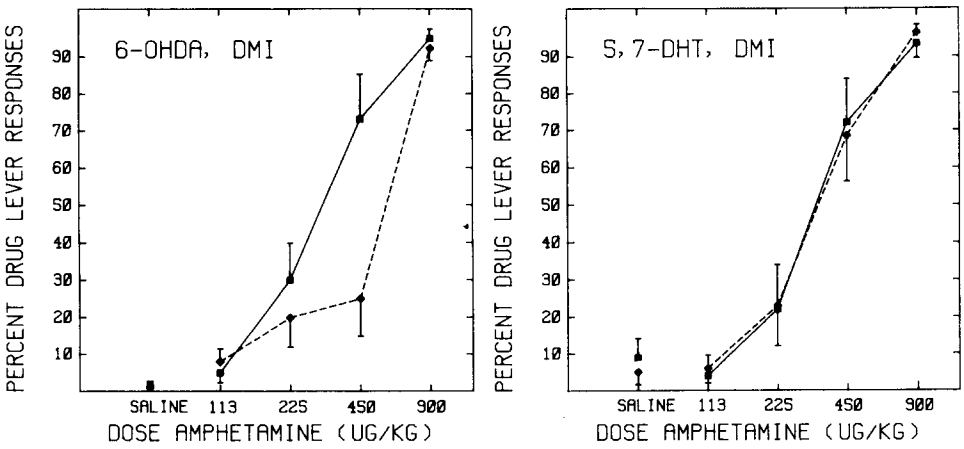

FIG. 4. *d*-AMPH dose response generalization curves in 6-OHDA, DMI (DA↓) and 5,7-DHT, DMI (5HT↓) treated rats. The square symbols represents data collected from vehicle controls while the diamond symbols represents data collected from depleted animal subjects.

provided by rotational studies in which the action of *d*-AMPH is much greater on the non-lesioned side in an unilaterally lesioned animal [9].

If the *d*-AMPH DS is mediated solely by the increased release of DA for dopaminergic nerve terminals, thereby increasing the amount of DA in the synaptic cleft, then one may expect a similar DS action by stimulating DA receptors directly. However, the putative DA receptor agonist apomorphine neither generalized to, nor markedly potentiated the *d*-AMPH DS. The apparent dissimilar DS of these two drugs have been reported [25]. The reason for the dissimilar DS is unclear, although several possibilities are feasible. One possibility is that *d*-AMPH is producing its DS by acting on more than one neurochemical system, of which the dopaminergic system plays a significant but not sole role [7]. Another possibility may be that apomorphine is also acting at receptors not associated with dopaminergic nerve endings or at a subset of dopaminergic receptors [22].

In respect to the major role that 5HT systems reportedly play in the action of LSD [10,28], an unexpected finding in

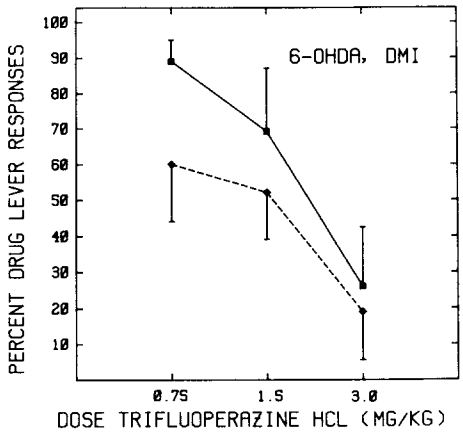

FIG. 5. Dose response antagonism of the *d*-AMPH DS by trifluoperazine HCl in 6-OHDA, DMI (DA↓) treated rats. Symbols are similar to those in Fig. 4. The antagonist was administered 30 min (IP) prior to *D*-AMPH (0.90 mg/kg, IP).

the present study was the lack of effect of the 5,7-DHT, DMI treatment on the LSD DS. These animals exhibited marked reductions in telencephalic 5HT levels (96%) as well as significant diencephalic and brain stem 5HT reductions. The present results conflict with the observation of White *et al.* [33], who described a shift of the LSD DS dose-effect curve to the left following 5,7-DHT treatment. These investigators hypothesized that this shift was the result of 5HT receptor supersensitivity. The lack of apparent 5HT receptor supersensitivity in the present study may be a factor of the age at which 5HT levels were reduced (White *et al.*: as adults, present study: 3-days). At three days of age synaptogenesis is prevalent; 5HT receptor formation and function is not yet totally developed [19]. Since further 5HT receptor development in these 5,7-DHT, DMI-treated animals occurred in a denervated environment, receptor supersensitivity may not have ensued. Alternatively, 5HT receptor supersensitivity in the diencephalon may not have ensued since the extent of 5HT level reduction was only 51%. The studies of Aghajanian and coworkers [12] have suggested that 5HT autoreceptors on the 5HT cell perikarya of the midbrain raphe nuclei are selectively sensitive to LSD. LSD, by interacting with these receptors, reduces the firing rate of these diffusely projecting 5HT neurons, releasing those neurons upon which they impinge from tonic inhibition. It is possible that the lack of effect of 5,7-DHT, DMI treatment in the present study was observed because those tonically inhibited neurons (normally receiving 5HT inhibition) had adjusted to limit 5HT input via a mechanism other than 5HT receptor supersensitively, utilizing those 5HT neurons (particularly diencephalic 5HT neurons) still intact.

The involvement of 5HT receptors in the LSD DS is indicated by the effectiveness of the putative 5HT antagonist, pizotifen, in inhibiting the LSD DS, as well as the ability of the putative 5HT agonist, quipazine, to generalize to the LSD DS, confirm the observations of other drug discrimination studies [2, 34, 35]. The anatomical loci, as well as the specific nature of these 5HT receptors, is yet unclear. The observation that apomorphine (a putative DA agonist) partially generalized to the LSD DS is in agreement with a previous report [2]. That this putative DA agonist significantly potentiated the LSD DS supports the premise that these two pharmacological agents are in part acting at a similar population of receptors, as would be expected based on their structural similarities [20] and their reported cross-tolerance [30]. Receptor binding studies have suggested a subset of receptors having both 5HT and DA affinities [22]. Electrophysiological evidence [8] as well as a recent study with the lisuride DS [32] suggests that LSD may have a strong dopaminergic component. The extent of dopaminergic involvement in the LSD DS in uncertain, as DA receptor antagonists fail to alter the LSD DS ([2], trifluoperazine: present study); a possible receptor subset not influenced by these DA antagonists may also exist. A dopaminergic component in the LSD DS is further indicated by the altered LSD DS dose-effect exhibited by the 6-OHDA, DMI-treated animals. The shift of the LSD DS to the left suggests that these animals are more sensitive to lower doses of LSD. As 6-OHDA, DMI treatment was carried out at 14 days of age when synaptogenesis is partially complete [21], supersensitivity at a particular subset of DA (5HT-like) receptors may have ensued, (although telencephalic DA depletion was only 53%). Alternatively, dopaminergic neurons which act to presynaptically modulate serotonergic neurons by their reduction [26], would alter the serotonergic response to LSD. Another possibility is that these DA neurons normally receive input from 5HT neurons. The incomplete destruction of these neurons may have resulted in an altered (compensatory) activity spectrum of those remaining DA neurons such that they are more sensitive to either 5HT (indirect) or LSD (direct) input.

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