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Serotonin Depletion Causes Long-Term Reduction of Exploration in the Rat

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LIPSKA, B. K., G. E. JASKIW, A. ARYA, AND D. R. WEINBERGER. *Serotonin depletion causes long-term reduction of exploration in the rat.* PHARMACOL BIOCHEM BEHAV 43(4) 1247–1252, 1992.—This study assessed the effects of central serotonergic depletion on exploratory activity at baseline, as well as after administration of *d*-amphetamine or the anxiogenic β-carboline FG-7142. Intraventricular 5,7-dihydroxytryptamine (5,7-DHT) induced an almost complete depletion of serotonin [5-hydroxytryptamine (5-HT)] in the medial prefrontal cortex, nucleus accumbens, medial corpus striatum, and hippocampus with no changes in norepinephrine, dopamine or dihydroxyphenylacetic acid concentrations. 5-HT-depleted rats demonstrated reduced spontaneous and *d*-amphetamine-augmented exploration 3–10 weeks postoperatively. An effect on FG-7142-induced inhibition of exploratory activity was not apparent. These data implicate 5-HT systems in the expression of different aspects of exploratory and amphetamine-augmented motor behaviors.

Serotonin 5,7-Dihydroxytryptamine Amphetamine FG-7142 Exploration Locomotor activity

THE role of brain serotonin [5-hydroxytryptamine (5-HT)] in regulation of locomotor activity has been the subject of considerable investigation. While depletion of 5-HT in the brain of the rat has been in general associated with locomotor activation (12,16,25,31,34,36), no change (6,11,29) or even a reduction in locomotion have also been reported (21,22). Indeed, behavioral changes may depend upon the method of 5-HT depletion, as well as on the testing conditions and post-depletion testing interval (29).

The role of 5-HT systems in *d*-amphetamine-induced motor activity is also poorly understood. Several 5-HT depletion studies have suggested that 5-HT neurons inhibit *d*-amphetamine-induced hyperactivity (5,7,23), while others found little evidence of 5-HT involvement (32,41). The wide range in the extent of 5-HT depletion and the frequent omission of data on other neurotransmitters that can be depleted by 5-HT-directed neurotoxins preclude simple comparisons between these studies (6,10,11,15,30). To obviate these problems, we induced a selective, prolonged, and diffuse serotonergic depletion and then assessed spontaneous and *d*-amphetamine-induced motor exploration.

Earlier experiments also suggested that reduction of exploratory activity following administration of the anxiogenic β-carboline FG-7142 might be mediated by its actions at GABA/benzodiazepine (BDZ) receptor complexes on 5-HT terminals in the dorsal hippocampus (26,28). Such complexes modulate 5-HT release (27). Accordingly, we also tested the hypothesis that FG-7142-induced attenuation of exploratory activity could be mediated by 5-HT release and would be abolished in the 5-HT-depleted rat.

METHOD

Surgery and Handling

Adult, male Sprague-Dawley rats (Zivic Miller Labs, 200–250 g) were housed three to a cage with free access to food and water in a temperature-controlled environment with a 12 L : 12 D cycle (lights on 7:00 a.m.–7:00 p.m.). To enhance specificity of the neurotoxin (3,4) animals were pretreated with the dopamine (DA) uptake blocker nomifensine (15 mg/kg, IP, divided into 2 doses, 50 and 30 min before infusion) and the noradrenaline (NE) uptake blocker desipramine (15 mg/kg, divided into two doses, 60 and 40 min before surgery). Following induction of anesthesia with ketamine (40 mg/kg, IP) and sodium pentobarbital (Somnifer) (25 mg/kg, IP), animals were placed in a Köpf stereotaxic instrument (Köpf, Topanga, CA) with the tooth bar at 2.5 mm below the interaural line. Freshly prepared 5,7-dihydroxytryptamine creatinine sulfate (5,7-DHT, 7.5 μg/μl free base) or an equal volume of vehicle (saline containing 0.1% ascorbic acid purged with ni-

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trogen) was infused by pump (Harvard Apparatus, South Natick, MA) through a stainless steel 26-ga cannula implanted in the left ventricle at the coordinates: AP −0.8 mm, ML + 1.5, VD −3.7 mm, with respect to bregma (37), at a rate of 4 μl/min (total volume 20 μl). The cannula remained in place for 5 min after the end of infusion.

Behavioral Testing

Three weeks postoperatively, rats were brought to the testing area in their home cages and acclimatized overnight. At 10:30 a.m. FG-7142 (Schering AG, Berlin, Germany, 15 mg/kg, IP) or its suspension vehicle (VEH) (3 drops Tween-80/10 ml distilled water) were administered and 20 min later animals were placed in clear Plexiglas activity monitors (42 × 42 × 30 cm) [Omnitech Model RXYZCM 16 (43), Omnitech Electronics, Columbus, OH]. Activity was measured at 15-min intervals for 60 min. The distance traveled, vertical activity, and time spent in the center of the monitor were analyzed by analysis of variance (ANOVA) with drug (FG or VEH) and lesion status (5-HT depletion or sham) as independent factors.

Rats that did not receive FG-7142 were tested again 6 and 10 weeks postoperatively. Each time, unacclimatized rats were brought to the testing area at 9:00 a.m. and immediately placed in activity monitors for a 60-min habituation period. After a saline injection (1 ml/kg, IP) each animal was returned to the photocell monitor for an additional 60-min period. At that point, *d*-amphetamine (1.5 mg/kg, IP) (Sigma Chemical Co., St. Louis, MO) was administered and activity was recorded for a final 60 min. The distance traveled, vertical activity, and time spent in the center of the monitor by sham and 5-HT-depleted groups of rats were compared in each treatment condition (habituation, saline, *d*-amphetamine) by Student's *t*-tests with a Bonferroni correction.

Neurochemistry

Six weeks postoperatively, animals that had received an injection of FG-7142 3 weeks earlier but had not been retested with *d*-amphetamine were acclimatized to the dissection area for 24 h. After decapitation, the medial prefrontal cortex (MPFC), anteromedial corpus striatum (MCS), and nucleus accumbens (NAC) were dissected over ice from 2-mm sections as described previously (24), while the dorsal (DH) and ventral hippocampus (VH) were dissected from two 2-mm sections as shown in Fig. 1 and frozen at −70°C until analysis. Concentrations of DA, dihydroxyphenylacetic acid (DOPAC), homovanilic acid (HVA), NE, 5-HT, and 5-hydroxyindoleacetic acid (5-HIAA) were assayed by high-pressure liquid chromatography with electrochemical detection as previously described (33). Data were analyzed by Student's *t*-test.

RESULTS

Almost complete depletions of 5-HT (93–99%, $p < 0.0001$) and its main metabolite 5-HIAA (52–93%, $p < 0.02$) were achieved in all regions assayed (Table 1). There were no significant changes of NE, DA, or DOPAC concentrations. HVA was, however, reduced in the NAC (20%, $p < 0.05$) and DH (67%, $p < 0.01$) and completely depleted in the VH (99.9%, $p < 0.0001$, Table 1).

Analysis of distance traveled and vertical activity following administration of FG-7142 3 weeks postoperatively showed significant main drug ($F = 3.64$, $p < 0.05$; $F = 5.11$, $p < 0.05$, respectively) and lesion ($F = 6.35$, $p < 0.05$; $F = 6.14$, $p < 0.05$, respectively) effects but no drug × lesion interaction ($F = 1.74$, $p > 0.1$; $F = 0.459$, $p > 0.5$, respectively). Analysis of center time did not show any significant effects (drug, $F = 2.6$, $p > 0.1$; lesion, $F = 0.3$, $p > 0.5$; drug × lesion, $F = 0.9$, $p > 0.1$). Posthoc tests revealed that FG-7142 reduced both total distance traveled and vertical activity in sham animals ($p < 0.05$). Vehicle-treated 5-HT-depleted rats were hypoactive compared to their sham counterparts ($p < 0.05$), but additional motor inhibition following FG-7142 was not significant in 5-HT-depleted animals (Fig. 2).

Three different components of motor activity of sham and 5-HT-depleted rats were then assessed 6 and 10 weeks postoperatively in three testing conditions: after exposure to a novel

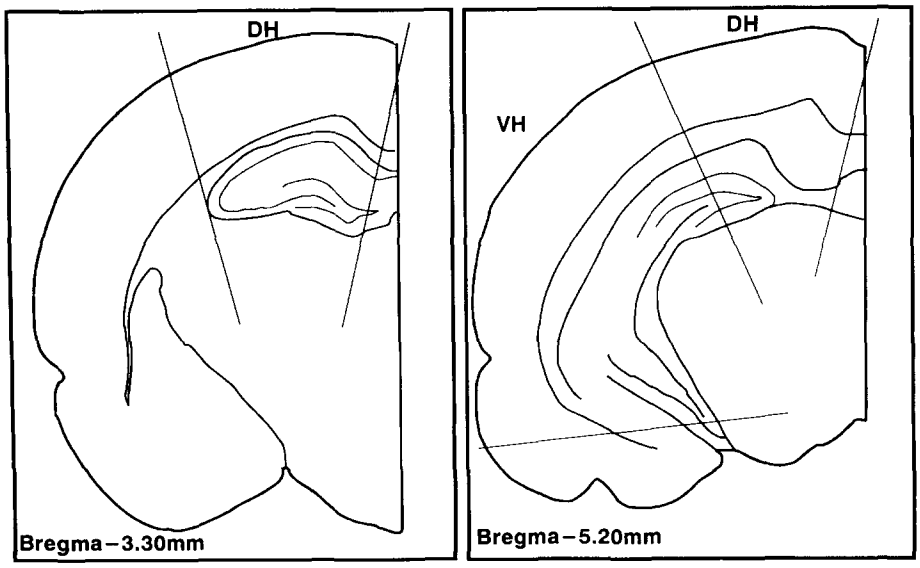

FIG. 1. Dissection of the dorsal (DH) and ventral hippocampus (VH) from two 2-mm slices. Coordinates refer to distances posterior to bregma (37).

TABLE 1

LEVELS OF BIOGENIC AMINES AND METABOLITES

	NE	DOPAC	DA	HVA	(%)	5-HIAA	(%)	5-HT	(%)
MPFC									
Sham	2.14 ± 0.31	0.29 ± 0.10	0.91 ± 0.21	0.54 ± 0.14		2.38 ± 0.58		3.89 ± 0.44	
5,7-DHT	2.20 ± 0.27	0.25 ± 0.09	1.00 ± 0.06	0.43 ± 0.11		0.32 ± 0.15	(87)*	0.19 ± 0.03	(95)*
NAC									
Sham	2.12 ± 0.43	16.12 ± 4.44	64.88 ± 8.75	6.36 ± 1.33		3.37 ± 0.41		4.44 ± 0.65	
5,7-DHT	2.17 ± 0.46	12.80 ± 2.28	62.23 ± 6.48	5.03 ± 0.93	(20)*	0.29 ± 0.37	(91)*	0.15 ± 0.11	(97)*
MCS									
Sham	2.97 ± 0.79	8.02 ± 1.17	59.85 ± 12.4	4.42 ± 1.05		4.55 ± 1.51		3.26 ± 1.20	
5,7-DHT	3.42 ± 0.97	6.81 ± 1.77	55.07 ± 9.05	3.62 ± 1.06		2.19 ± 2.35	(52)*	0.12 ± 0.07	(96)*
DH									
Sham	1.83 ± 0.54	NA	0.19 ± 0.05	0.06 ± 0.04		1.53 ± 0.60		1.15 ± 0.46	
5,7-DHT	1.58 ± 0.35		0.16 ± 0.03	0.02 ± 0.02	(67)*	0.11 ± 0.04	(92)*	0.08 ± 0.03	(93)*
VH									
Sham	2.93 ± 0.55	NA	0.23 ± 0.05	0.06 ± 0.03		1.75 ± 0.46		1.72 ± 0.49	
5,7-DHT	2.77 ± 0.58		0.22 ± 0.05	0	(100)*	0.13 ± 0.08	(93)*	0.02 ± 0.03	(99)*

Groups of sham-operated and 5-HT-depleted animals were sacrificed 6 weeks after surgery. Brain regions were dissected: medial prefrontal cortex (MPFC), nucleus accumbens (NAC), anteromedial corpus striatum (MCS), and dorsal (DH) and ventral (VH) hippocampus. Concentrations are expressed as pM/mg tissue, wet weight. %, percent of depletion. NA, data not available (below limit of detection).

*$p < 0.05$.

environment (habituation), after saline, and after amphetamine injection.

Six weeks postoperatively, 5-HT-depleted rats showed reductions in comparison with sham-operated controls in all three components of motor activity (total distance traveled, vertical activity, and time spent in the center of the monitor) during the habituation period ($p < 0.001$, $p < 0.01$, $p < 0.01$, respectively), as well as after saline injection ($p < 0.01$ for all three measures). Vertical activity ($p < 0.01$) and center time ($p < 0.0001$) were also reduced following *d*-amphetamine administration, while there was no difference in total distance traveled ($p > 0.1$) between sham and 5-HT-depleted rats (Fig. 3) under this testing condition.

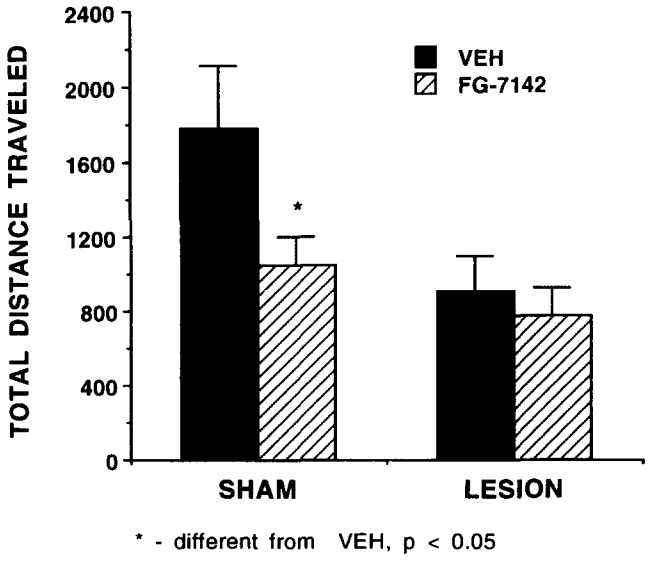

FIG. 2. Distance traveled over 60 min by the four groups of rats (n = 10 per group), starting 20 min after injection of either FG-7142 (15 mg/kg, IP) or vehicle (VEH) (distilled water with three drops of Tween-80). Rats received either saline (SHAM) or IVC 5,7-dihydroxytryptamine (5,7-DHT) injection (LESION) 3 weeks earlier.

Ten weeks postoperatively, almost all measures of motor activity returned to control levels in 5-HT-depleted rats tested during a habituation period and after saline injection. The exception, vertical activity, was still reduced in the lesioned group during habituation ($p < 0.01$). As was the case at the first testing session, the total distance traveled by sham and 5-HT-depleted rats was similar after *d*-amphetamine administration. However, vertical activity ($p < 0.01$) and time spent in the center ($p < 0.001$) after *d*-amphetamine were still profoundly decreased in the 5-HT-depleted group (Fig. 4).

DISCUSSION

ICV administration of 5,7-DHT with appropriate pretreatment produced a near complete depletion of forebrain 5-HT and 5-HIAA while sparing DA and NE. Several investigators, using similar doses of 5,7-DHT, achieved partial 5-HT depletions (6,10,15,30) and did not protect NE or DA systems. Lyness and Moore (30) reported a 70% reduction in 5-HT levels in the NAC and 54% in the striatum with no change in DA, NE, or DOPAC concentrations by using 5,7-DHT with desmethylimipramine pretreatment. They did not assay, however, cortical regions known to also modulate motor behaviors.

The significant HVA decreases in the NAC and in both the DH and VH are difficult to interpret in the face of normal DA, DOPAC, and NE levels. HVA may be a product of either DAergic or NEergic terminals (9). While some minimal damage to DA or NE terminals cannot be precluded, it should be noted that because the hippocampal HVA levels were close to the limit of detection of our assay the reduction in hippocampal HVA levels may be spuriously exaggerated.

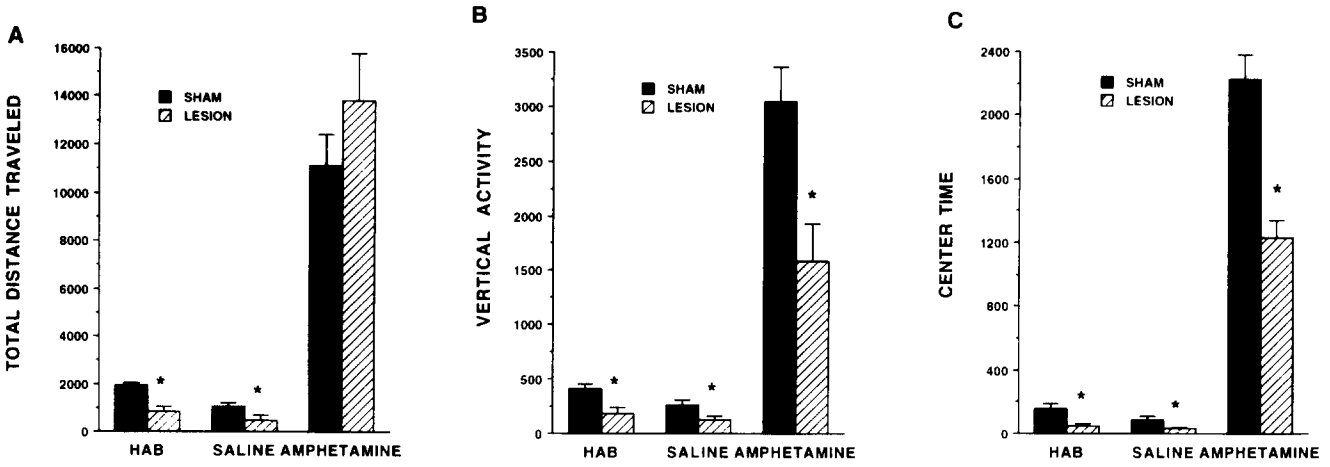

FIG. 3. Saline (SHAM) or 5,7-dihydroxytryptamine (5,7-DHT)-injected (LESION) groups were tested 6 weeks postoperatively. After overnight acclimatization to the testing area, rats were placed in the apparatus for a 60-min habituation period (HAB). Then, saline (1 ml/kg, IP) was administered and activity recorded for a further 60 min (SALINE). Rats then received *d*-amphetamine (1.5 mg/kg, IP) and had their activity recorded for a further 90 min (AMPHETAMINE). (A). Total distance (cm) traveled by rats in a Digiscan photocell apparatus (means ± SD, n = 12/group). (B). Vertical activity (total number of beam interruptions of the vertical sensor). (C). Center time (seconds). *Lesion significantly different from SHAM, $p < 0.05$.

As anticipated, FG-7142 decreased locomotor activity in sham-operated rats. The absence of a significant drug × lesion interaction might suggest that a similar reduction in locomotor activity would be evident following FG-7142 administration to 5-HT-depleted rats, but the trend toward such a reduction was not significant on posthoc tests. The latter may reflect the difficulty of detecting significant activity reductions in animals already rendered hypoactive by central 5-HT depletion (i.e., the so-called floor effect). Thus, the data do not provide robust evidence for or against our initial hypothesis that FG-7142-induced attenuation of exploratory activity is mediated by hippocampal 5-HT release.

Several other possible confounds must be considered. Sprouting and regeneration of 5-HT axons and terminals following chemical axotomy has been reported to lead to recovery from 5-HT depletion-induced behavioral deficits (2,13, 42). Some studies suggest that such recovery can occur by the 21st day after central 5,7-DHT lesions despite persistently low levels of 5-HT (14,40). Such an explanation is unlikely in the current study, where 5-HT depletion was severe and other enduring behavioral effects of 5-HT depletion were evident. A more serious problem may lie in extrapolating from effects of central 5-HT depletion to the role of 5-HT in the dorsal hippocampus. Brain 5-HT systems show considerable anatomic, pharmacological, and functional heterogeneity (1,19, 35). The possibility that a 5-HT lesion confined exclusively to the dorsal hippocampus might block behavioral effects of FG-7142 cannot be precluded (46). Further, because the de-

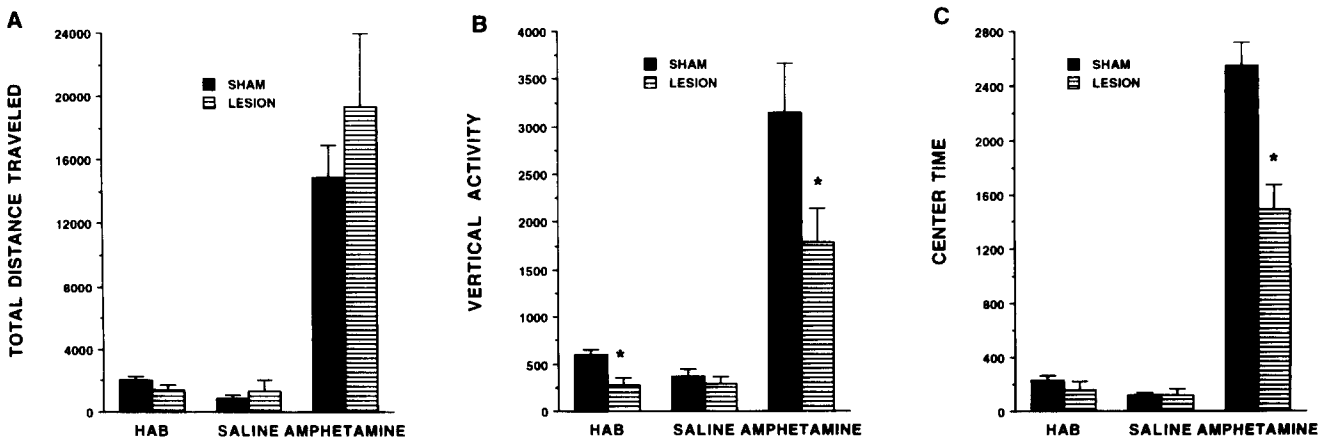

FIG. 4. Saline (SHAM) or 5,7-dihydroxytryptamine (5,7-DHT)-injected (LESION) groups were tested 10 weeks postoperatively. After overnight acclimatization to the testing area, rats were placed in the apparatus for a 60-min habituation period (HAB). Then, saline (1 ml/kg, IP) was administered and activity recorded for a further 60 min (SALINE). Rats then received *d*-amphetamine (1.5 mg/kg, IP) and had their activity recorded for a further 90 min (AMPHETAMINE). (A). Total distance (cm) traveled by rats in a novel photocell apparatus (means ± SD, n = 12/group). (B). Vertical activity (total number of beam interruptions of the vertical sensor). (C). Center time (seconds). *Lesion significantly different from SHAM, $p < 0.05$.

gree to which 5-HT transmission is altered may determine whether behavioral indices of anxiety are reduced or increased (20) our findings may not be applicable to animals with modest 5-HT depletion.

The persistent reductions of locomotor and exploratory behaviors in 5-HT-depleted animals in this study were surprising in light of most previous investigations. Central 5,7-DHT administration has been reported to increase spontaneous and *d*-amphetamine-stimulated locomotor hyperactivity, albeit at a shorter postoperative interval (30). One group (16) commented that reduced or unchanged locomotion is sometimes observed when partially 5-HT-depleted animals are tested in "emotional" situations (e.g., in a novel open field). The latter cannot be easily reconciled with the putative anxiolytic effects of 5,7-DHT lesions demonstrated in several behavioral paradigms (6). Under the latter premise, augmented rather than reduced locomotor exploration might be expected after 5,7-DHT lesions.

Spontaneous locomotor activity returned to control levels 10 weeks postoperatively, while rearing activity and entries to the center continued to be reduced in 5-HT-depleted rats. Because there was no neurochemical evidence of recovery 6 weeks postoperatively, other compensatory mechanisms specifically affecting locomotion must be suspected. Insofar as we measured only gross distance traveled, and not the pattern of locomotion, which can provide evidence of more subtle abnormalities (17), the degree to which locomotion is truly "normalized" is not known.

d-Amphetamine increased overall locomotion (distance traveled) in 5-HT-depleted rats but did not, however, affect other components of exploratory behavior (rearing, center activity). While the neural basis of rearing and center activity are poorly delineated, NAC DA systems have been well implicated in the control of gross spontaneous and *d*-amphetamine-augmented locomotor behavior (38,39,44). A number of studies suggest that mesolimbic 5-HT terminals primarily inhibit mesolimbic DA-mediated behaviors [(8); for review, see (45)]. In light of such data, the consistent ability of *d*-amphetamine to increase gross locomotion to control levels, despite near total mesolimbic 5-HT depletion, cannot be easily explained. Concomitant 5-HT depletion of other brain regions known to affect locomotor behavior may be involved (18).

In summary, our data show that virtually complete and selective 5-HT depletion can be achieved by appropriate pretreatment and ICV infusion of 5,7-DHT. Such 5-HT-depleted rats show a transient attenuation of spontaneous locomotor exploration and a persistent reduction in vertical activity and center time 3–10 weeks after the lesion. In such animals, *d*-amphetamine can augment locomotion but fails to stimulate other components of exploratory behavior. These data implicate brain 5-HT systems in the expression and integration of different components of normal and drug-augmented exploratory motor behaviors.

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