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Behavioral Effects of Xylamine-Induced Depletions of Brain Norepinephrine: Interaction With LSD

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GEYER, M. A., J. GORDON AND L. M. ADAMS. *Behavioral effects of xylamine-induced depletions of brain norepinephrine: Interaction with LSD.* PHARMACOL BIOCHEM BEHAV 23(4) 619–625, 1985.—Male rats were treated with a combination of systemic fluoxetine and intraventricular xylamine (under ether anesthesia) to deplete brain norepinephrine (NE) in the projection areas of the locus coeruleus. Four days later, control and lesioned rats were tested following injections of either saline or 80 μg/kg LSD in a Behavioral Pattern Monitor which recorded the sequential patterns of their locomotor and investigatory (holepokes) responses. Liquid chromatographic measures of brain monoamines confirmed that xylamine reduced hippocampal NE by 80.8% and hypothalamic NE by 26% without affecting levels of serotonin or dopamine. Relative to controls, NE-depleted rats exhibited repetitive spatial patterns of locomotion with no alteration in the amount or rate of habituation of locomotor activity. Lesioned animals made fewer rearings and holepokes, particularly early in the hour test session. When given 80 μg/kg LSD, sham-lesioned rats exhibited the expected decreases in entries into and time spent in the center of the chamber, an increase in time spent in the corners, and fewer holepokes and rearings early in the session. With the exception of the effect on rearings and holepokes, the effects of LSD were diminished in rats depleted of brain NE. These results indicate that this profile of behavioral effects of LSD, which has been interpreted as a potentiation of neophobia, may be dependent upon the noradrenergic projections of the locus coeruleus.

Norepinephrine Xylamine LSD Hippocampus Neophobia Locomotor patterns Holepokes Exploration

THE contribution of central noradrenergic systems to spontaneous and drug-induced behavior in rats has been studied in a variety of contexts and with a variety of manipulations. As extensively reviewed elsewhere [27], brain noradrenergic systems, particularly that originating in the pontine locus coeruleus (LC), have been implicated in the modulation of behavioral arousal, exploration, stimulus sampling, responsiveness to sensory stimuli, and neophobia [1, 11, 16].

Because of the ill health associated with electrolytic lesions of the LC [19] and the difficulty of producing consistent and symmetric 6-hydroxydopamine (6OHDA) lesions of the LC [1], much of the literature on this system has relied on 6OHDA lesions of the dorsal noradrenergic bundle (DNB). However, lesions of the DNB, which carries fibers from the LC to limbic and cortical structures, also produce increased levels of norepinephrine (NE) in the other projection sites of LC neurons [34], an effect which complicates the interpretation of behavioral changes induced by this manipulation. Hence, the recent development of the benzylamine-derived depletors of NE, DSP4 and xylamine, which appear to have selective effects on noradrenergic fibers originating in LC [12, 14, 18, 21], has provided a new way to address questions regarding the behavioral functions of central NE. When given systemically, DSP4 and xylamine produce massive depletions of both peripheral and central NE. While the peripheral stores of NE are replenished in about ten days, the central depletion appears to be permanent [14,21]. In addition to the fibers derived from LC, DSP4 and xylamine also deplete central serotonin, at least within the hippocampus [18,21], unless a serotonergic uptake blocker is used.

Although significant behavioral effects which are largely consistent with the effects of DNB lesions have been found after DSP4 [11], these effects may have been related to the noradrenergic hypersensitivity which has been demonstrated to develop during the ten days required for the recovery of peripheral NE stores [13]. Unfortunately, virtually all studies of the effects of DNB lesions also included a comparable period for post-operative recovery before the initiation of behavioral testing [27]. To overcome this limitation, we developed a procedure for intraventricular injections of xylamine in etherized rats which produces massive and rapid depletions of central, but not peripheral NE, and permits the assessment of behavioral changes as soon as 48 hours after lesioning [18]. Following pretreatment with fluoxetine to protect hippocampal serotonin, intraventricular administration of 100 μg xylamine produces a roughly 88% depletion of hippocampal and cortical NE which is maximal within 48 hours and persists for at least three weeks [18]. The lesioned animals remain healthy and gain weight normally.

The present report describes the behavioral effects of xylamine-induced depletions of brain NE, as detected by a Behavioral Pattern Monitor (BPM) which characterizes in

detail the frequencies and spatiotemporal patterns of the locomotor and investigatory responses of rats. The effects of NE depletions are compared with our previous reports of behavioral changes associated with increased levels of hippocampal NE [16].

The second aspect of this report considers the possibility that the potentiation of neophobia induced by LSD in rats [2,4] may be mediated in part by the noradrenergic system originating in the LC. A variety of hallucinogens have been shown to intensify the normal neophobia exhibited by rats when introduced into a novel environment [2–4]. The LC noradrenergic system has been implicated in the modulation of neophobia in particular as well as other behavioral responses associated with fear or anxiety [9, 10, 11, 26, 31], although important questions regarding possible species differences and the specification of relevant environmental stimuli remain to be answered. Though scant, there is also clinical evidence to suggest that beta-noradrenergic blockers such as propranolol may be specifically effective in ameliorating anxiety attacks induced by LSD in humans [25]. Propranolol has also been reported to block some of the behavioral effects of hallucinogens in animals [11,30]; and phenoxybenzamine has been found to block the suppression of holepoking produced by LSD [22].

METHOD

Animals

Male Sprague-Dawley rats weighing 250–275 g (Charles River Breeding Laboratories) were housed two per cage on a reversed 12-hour light/dark cycle and allowed to acclimate for one week prior to any experimental manipulation. Wayne Lab Blox and water were available ad lib. Following surgery, animals were housed individually.

Surgery

Approximately one hour prior to surgery all animals received an intraperitoneal (IP) injection of fluoxetine (25 mg/kg). Animals were anesthetized using anhydrous ether and placed in the stereotaxic apparatus (David Kopf Co.). The injection needle was lowered through holes in the cranium into the lateral ventricles and a 10 μl injection was given on each side [18]. Sham animals received a total of 20 μl of saline while the experimental group were given a total of 100 μg of xylamine per 20 μl.

Drugs

Fluoxetine, a serotonin uptake blocker, was generously supplied by Lilly, and dissolved in saline for IP injections. Xylamine was provided by Dr. Arthur Cho, UCLA. The National Institute on Drug Abuse supplied d-lysergic acid diethylamide-25 (LSD), which was dissolved in saline and injected subcutaneously (SC).

Apparatus

The Behavioral Pattern Monitor (BPM) chambers have been described elsewhere [2,16]. Briefly, each chamber is a 30.5 by 61 by 38 cm box of black plastic with a stainless steel floor and wall touchplate (located 15 cm above the floor). Each chamber has three floor holes and seven wall holes. Holepokes are detected by an infrared photobeam in each hole. A 4 by 8 perpendicular array of photobeams is used to localize the animal's position with 3.8 cm resolution. A microprocessor system checks the status of all beams every 100 msec. As changes occur in the photobeam patterns a data reading is taken with a time value recorded for each change. The data are stored in a linear stream on cassettes which are later used for data reduction and analysis [2,16].

Behavioral Measures

The dependent variables included the number, duration and mean duration of holepokes and rearings, cumulated over either 10 or 30 min blocks. Holepokes were divided into varied or repeated holepokes depending on whether there had been an intervening rearing or holepoke into a different hole between two holepokes into the same hole. The total number of photobeam interruptions was used as a measure of overall motor activity. From the state of the 4 by 8 array of photobeams, the animal's (x,y) position was calculated and used to assign the rat to one of eight square "sectors" and one of nine unequally sized "regions," as described elsewhere [16]. "Crossovers" were defined as the total number of sector entries, and used as the most standard measure of horizontal locomotion. The durations and frequencies of entries into the nine regions, particularly the four corners and center, were used for more descriptive assessments of the animals' behavior.

The spatial distribution and sequential patterns of the animals' locomotor activity were also examined graphically. Based upon the (x,y) position data, a real-time, variable-speed plot program displayed the successive positions of the animal by the movement of a cursor inside a two-dimensional reconstruction of the chamber on a video terminal. Together with visual observations, this method provided a comprehensive description of the experimental animals' patterns of movement and permitted the detection of effects upon that pattern *per se*. For analyses of the degree of redundancy in these spatial patterns, the transition frequencies between any of five large areas (two ends, center, and two long wall areas) were calculated, as was the coefficient of variation (CV) of the distribution of these transition frequencies, as detailed elsewhere [17]. As an animal preferentially repeats certain transitions, the CV increases, while a more random pattern produces a lower CV. Thus the CV reflects the extent to which an animal establishes a preferred pattern of locomotor activity over time.

Behavioral Testing

Two days after surgery, the animals were brought up to the laboratory during their dark cycle (under black cloth) for weighing, handling, and 20 min acclimation period in the behavioral laboratory. Behavioral testing took place during the animals' dark cycle, four days following surgery. Animals were brought to the laboratory one hour before testing. Ten min before testing, animals received a SC injection of either saline or 80 μg/kg LSD and returned to their cages. The test session was 60 min in duration, after which the animals were removed and all chambers were thoroughly cleaned.

Lesion Verification

Animals were sacrificed by decapitation 21 days after surgery. The brains were rapidly removed and cooled on ice. The hippocampus, hypothalamus, and caudate were dissected on an ice-cold plate using a brain slicer and tissue was stored at −60°C until monoamine determinations could

TABLE 1
EFFECTS OF XYLAMINE ON BRAIN MONOAMINES

	Hippocampus		Hypothalamus
	NE	5HT	NE
Sham (N = 21)	0.54 ± 0.03	0.77 ± 0.03	1.77 ± 0.09
Xylamine (N = 19)	0.11 ± 0.01*	0.71 ± 0.02	1.31 ± 0.11*
% Control	19.8	91.7	74

Values are expressed as ng/mg tissue ± S.E.M.
* $p < 0.01$.

be done. Previous studies have shown that the effects of xylamine on monoamines do not differ significantly from two to 21 days [18]. Therefore, the depletions reported for this study at day 21 are reflective of those at day 4, when the animals were tested behaviorally.

High Performance Liquid Chromatography (HPLC)

The chromatographic system used was the Bioanalytical Systems LC-17 equipped with a "μBondapack" C-18 reverse-phase column (3.9 × 30 cm; Waters Assoc.), an Altex pump and an LC-4 amperometric detector coupled to a TL-5 glassy carbon electrode (Bioanalytical Systems) and an Ag/AgCl reference electrode. Output from this system was recorded with a Shimadzu Integrator and a Houston dual-pen recorder. Water for the solvent was deionized using a Millipore "Milli-Q" water purification system. Amines and their metabolites were estimated according to the methods of Mefford [29]. As described earlier, slight modifications have been made for 5-HT assays [23] and for dopamine and NE assays [24].

Statistics

Behavioral results were assessed using mixed design ANOVAs in which treatments were between group factors and blocks of time were the within subjects factor. These ANOVAs were followed by *t*-tests or one-way ANOVAs to assess the main effects underlying significant interactions. Chemistry results were analyzed with *t*-tests.

RESULTS

Chemistry

Intraventricular administration of 100 μl/20 μl of xylamine following systemic fluoxetine (25 mg/kg) markedly reduced hippocampal NE levels without significantly altering hippocampal 5HT levels (see Table 1). Relative to sham animals, hippocampal NE was depleted by 80.8%, $t(38) = 13.7$, $p<0.01$, while hippocampal 5HT was only reduced by 9.3% (non-significant) at 21 days following xylamine administration. Hypothalamic NE levels were depleted by 26% in xylamine treated animals relative to shams, $t(20) = 3.4$, $p<0.01$. This relatively small depletion of hypothalamic NE is consistent with the suggestion that xylamine preferentially affects the noradrenergic projections of the LC [21]. As expected [18], caudate dopamine and 5HT levels were unaffected by intraventricular xylamine (data not shown).

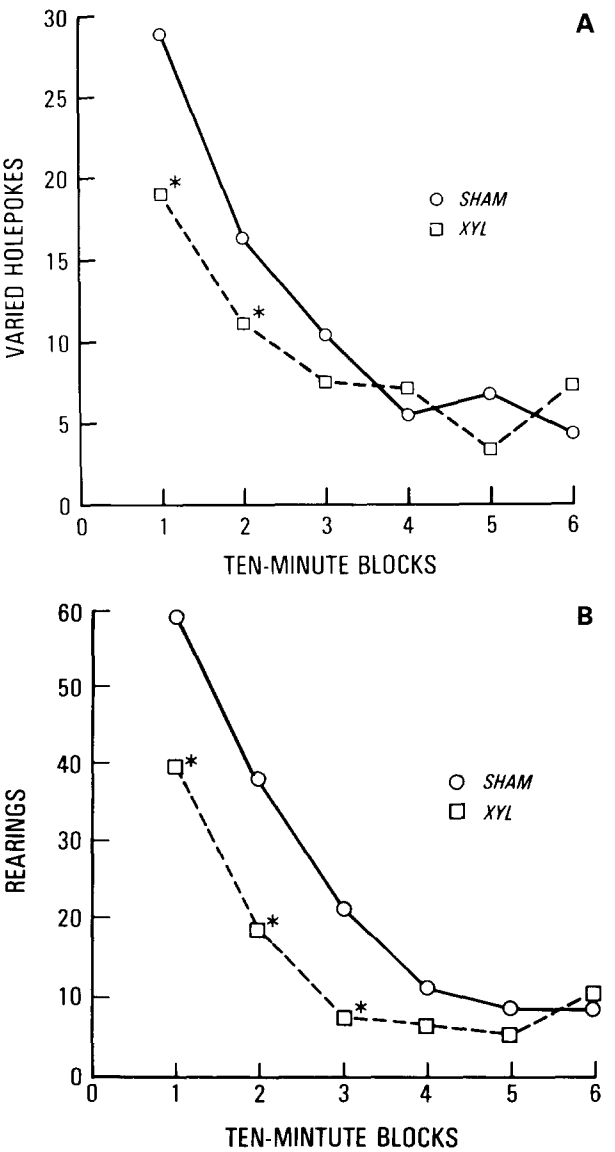

FIG. 1. The effects of xylamine-induced depletions of brain NE on (A) Varied Holepokes and (B) Rearings are shown for successive 10-minute blocks of an hour test session. *Significantly less than corresponding control value.

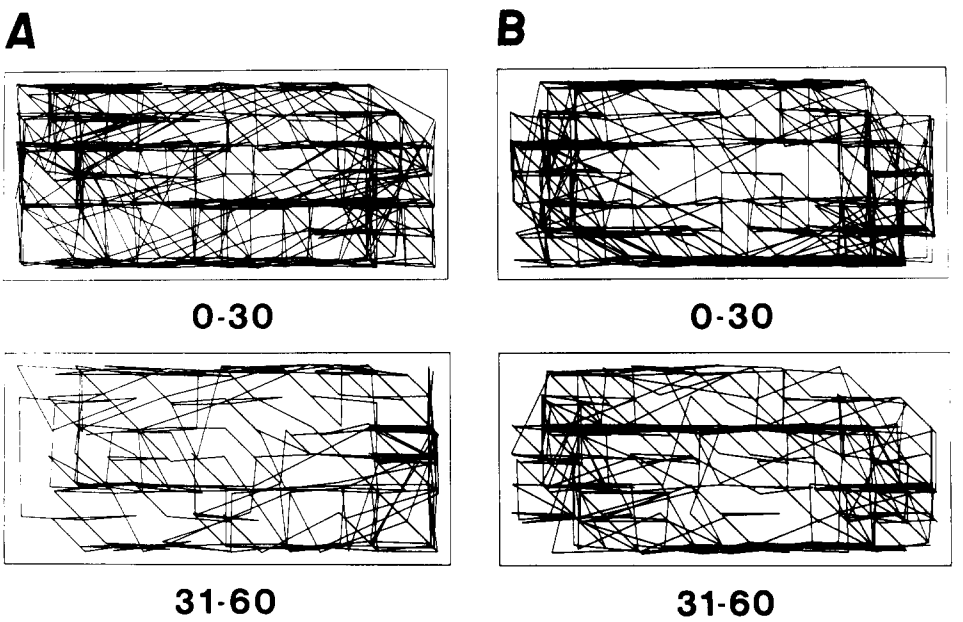

FIG. 2. Computer reconstructions of the spatial patterns of locomotion exhibited by representative animals treated with (A) Vehicle or (B) Xylamine are shown for successive 30-minute intervals.

Behavioral Effects of Xylamine

The rats treated with xylamine were healthy and gained weight at the same rate as did the controls. When tested in the BPM, xylamine treated rats did not differ from controls on any measure of the amount of locomotor activity, including total photobeam breaks and crossovers from one sector to another. As shown in Fig. 1A, however, lesioned rats made significantly fewer varied holepokes (successive pokes into different holes) during the first half of the hour test session, as reflected by the treatment-by-trials interaction, $F(5,70) = 2.44$, $p<0.05$. Similarly, rearing responses were significantly reduced in the NE-depleted rats throughout most of the test session (Fig. 1B), resulting in a significant main effect of treatment, $F(1,15) = 7.25$, $p<0.02$, and another treatment-by-trials interaction, $F(5,75) = 3.72$, $p<0.005$.

Spatial Patterns of Locomotion

Despite the absence of any significant difference in the amount of locomotion between control and lesioned rats, computer-generated video displays revealed a consistent alteration in the spatial patterns of locomotion exhibited by xylamine-treated animals. As described previously [2, 4, 17], control animals explore the chamber in a somewhat structured manner, their behavior being organized into stays in a "home" corner and excursions out from the corner to various parts of the chamber and back. Rats with NE depletions tended to exhibit this structure even more consistently than did controls. That is, the locomotor patterns of the lesioned rats were more repetitive, with longer and more consistent excursions around the perimeter and back to the home corner. Computer reconstructions of the locomotor patterns of representative animals are shown in Fig. 2. These observations were confirmed statistically using the CV measure on transitions between various areas of the chamber

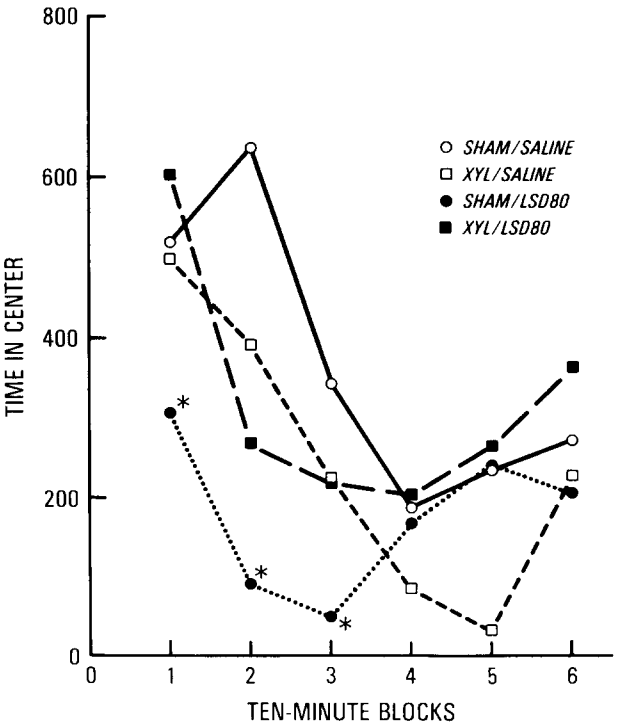

FIG. 3. The effects of xylamine, LSD, and the combination on time spent in the center region (in tenths of seconds) are shown for successive 10-minute intervals. *Significantly less than corresponding control value.

[17]. To the extent that an animal preferentially moves through the same areas in the same direction, the CV measure increases. For sham-lesioned animals, the CV ($\pm$S.E.M.)

TABLE 2
INTERACTION OF XYLAMINE WITH LSD ON BEHAVIOR

Group	N	Cross-overs		Varied Holepokes		Total Rearings	
		1-st half	2-nd half	1-st half	2-nd half	1-st half	2-nd half
Sham + Saline	10	1337 ±95	423 ±88	55 +6	16 ±5	106 ±14	23 ±6
Xylamine + Saline	8	1164 ±221	339 ±138	37* ±6	17 ±6	64* ±9	21
Sham + LSD	9	837* ±87	390 ±79	32* ±3	18 ±3	38* ±6	28 ±9
Xylamine + LSD	8	1128 ±169	555 ±121	33* ±3	15 ±3	56*† ±6	41† ±8

Values are expressed as group means ± S.E.M.
* Significantly below SHAM + SALINE group.
† Significantly above SHAM + LSD group.

was 0.411 ± 0.05; for xylamine-treated animals, the CV was 0.569 ± 0.06 ($t = 2.17$, $p < 0.05$). This difference was most pronounced during the first half of the session (Sham 0.437 ± 0.05; Lesion 0.615 ± 0.05; $t = 2.72$, $p < 0.02$).

Effects of LSD in Xylamine-Treated Rats

Previous studies with LSD [4] and other hallucinogens [3] revealed that the behavioral effects most strongly and consistently produced by hallucinogens were a decrease in entries into and time spent in the center of the chamber (agoraphobia), a corresponding increase in time spent in the corners, and a decrease in crossovers and holepokes that was specific to testing in a novel chamber (neophobia). These effects are generally most marked during the first half of the hour session, opposite effects being observed in the last half hour with some doses of some hallucinogens.

In general, this profile of effects was confirmed in the sham-lesioned rats given 80 μg/kg LSD in the present experiment. However, rats depleted of brain NE by the xylamine pretreatment failed to exhibit these characteristic effects of LSD. As shown in Fig. 3, xylamine pretreatment blocked the decrease in time spent in the center produced by LSD, resulting in significant pretreatment-by-treatment interactions for both entries into and time in the center, $F(1,31) = 4.3, 5.7$, $p < 0.05$. The reciprocal increase in time spent in the corners produced by LSD was also diminished in the lesioned rats given LSD, yielding another pretreatment-by-treatment interaction, $F(1,31) = 5.1$, $p < 0.05$; data not shown. While xylamine also blocked the LSD-induced reduction of crossovers early in the session (Table 2; $F(1,31) = 4.2$, $p < 0.05$), the interaction between xylamine and LSD on holepoking was more difficult to assess. Specifically, rats treated with either xylamine or LSD alone exhibited a reduction in holepoking specific to the initial portion of the session. Therefore, the finding that animals which received combined treatments also exhibited an early decrease in holepoking (Table 2) could reflect additivity or a floor effect. In contrast, the LSD-induced suppression of rearings, an effect which is neither specific to nor characteristic of hallucinogens [3], was attenuated by the xylamine pretreatment (Table 2; $F(1,31) = 13.2$, $p < 0.001$).

DISCUSSION

The intraventricular administration of xylamine following pretreatment with fluoxetine produced the expected preferential depletion of hippocampal NE relative to hypothalamic NE, with no alteration in hippocampal serotonin or caudate dopamine. This pattern of depletions is consistent with the suggestion that, like DSP4, xylamine predominately affects the noradrenergic projections from the LC [12, 14, 18, 21]. Since xylamine was injected centrally in a form that does not pass the blood-brain-barrier [14], no peripheral NE depletions prevented the behavioral characterization of the animals soon after the lesion [18].

When tested four days after surgery, NE-depleted animals exhibited a consistent alteration in the spatial patterns of their locomotion despite being comparable to controls in the amount of locomotor activity. The locomotion of xylamine-treated rats was more repetitive and structured than that of controls, being organized into a home corner and periodic excursions therefrom even more consistently than has been reported for untreated rats [4,17]. This effect is exactly the opposite of that produced by intrahippocampal microinfusions of low doses of NE, which disrupted the normal structure of the rats' locomotor patterns at doses having no effect on the amount of activity [16]. While NE depletions with DSP4 have occasionally been found to decrease the amount of locomotion in a novel environment [11], most studies find no general alteration in the level of activity in NE-depleted rats [6, 7, 26]. Our results are con-

sistent with these observations. It should also be noted that, like studies with DSP4 [11], our results provide no evidence for an alteration in the rate of habituation of exploratory locomotion in a novel environment.

Consistent with its effects on spatial patterns of locomotion, the xylamine-treated rats exhibited significant reductions on both varied holepokes and rearings against the wall, two measures of investigatory responding that are augmented by increasing levels of hippocampal NE [16]. Similarly, DSP4 has been shown to reduce rearings and the investigation of novel objects [11]. Lesions of the DNB with 6OHDA have also been reported to reduce behavioral responses to novelty [26], though only in some situations [7]. However, while hippocampal microinfusions of NE significantly increase the amount of time spent in the center of the chamber late in the test session, the effect of xylamine on this measure was not significant despite a trend toward a reduction (Fig. 3). Comparable depletions of NE induced by DSP4 have also been reported to produce a tendency toward fewer center entries [11]. While such effects have been interpreted as reflective of increased neophobia [11], our results are not consistent with that interpretation because the reduction in center activity produced by xylamine was specific to the last rather than the first part of the session (Fig. 3). Furthermore, xylamine-treated rats given a choice between a familiar homecage and a larger novel chamber do not avoid the novel chamber (M. A. Geyer, unpublished observations).

Xylamine-treated rats failed to explore the holes or rear as frequently as controls and, although they exhibited normal levels of locomotor activity, the paths they took were relatively rigid and they failed to spatially explore the chamber as thoroughly as did the controls. Hence, these results, like others [32], appear to conflict with the suggestion that rats with 6OHDA lesions of the DNB exhibit a deficit in selective attention which leads to an increase in the sampling of irrelevant stimuli [27]. Additional studies will be required to establish whether this seeming contradiction is related to the definition of "irrelevant," the nature of the specific stimuli being presented to the animal in the various experimental paradigms [15], the distinction between proximal and distal stimuli (or inspective versus diversive exploration), or some compensatory changes that may develop during the recovery period typically included in studies with DNB lesions. The present results are consistent with the finding that rats with DNB lesions exhibit an impairment of spontaneous alternation in a T-maze, a phenomenon which can be interpreted as indicative of a reduction in the tendency to approach and explore novel stimuli [32].

Together with our previous report of the effects of intrahippocampal microinfusions of NE [16], the present results indicate that the noradrenergic projections of the LC contribute importantly to the modulation of an animal's responsiveness to environmental stimuli. It appears from these studies that at least some aspects of the propensity to explore a novel environment are regulated by central NE. As discussed in detail elsewhere [16], the profile of effects produced by administering NE directly to the hippocampus was interpreted as reflective of an increase in the diversity of stimulus sampling. The opposite effects of xylamine, reported here, appear to corroborate that interpretation, despite the fact that the infusions produce short-term increases in hippocampal NE while the lesions produce long-term changes. The simplest interpretation of these results is that the propensity to sample environmental stimuli is directly related to the functional activity of hippocampal NE. However, it may be that neither microinfusions nor lesions replicate physiological changes in the functioning of the noradrenergic input to the hippocampus. Hence, it is relevant to note that similar conclusions regarding the behavioral influence of this neuronal system have been drawn from physiological studies in rats [8].

In addition to the more global theories of the role of the LC in the modulation of stimulus responsivity, the LC has been implicated specifically in mediating responsiveness to threatening stimuli [1, 9, 20, 31]. As detailed in our previous reports [2–4], the most characteristic effect of hallucinogens in rats is to potentiate their normal tendencies to avoid novel and open areas. Hence, the finding that xylamine attenuated those effects of LSD associated with neophobia and agoraphobia provides further evidence that LC activation plays an important role in mediating defensive responding to threatening stimuli. In addition to the effects of LSD and other hallucinogens on behavior during the initial period of time in a novel chamber, LSD also disrupts the spatial patterns of locomotion late in the test sessions [2,4], an effect that has been tentatively interpreted as related to changes in stimulus sampling. Concomitantly, LSD often produces an increase in activity late in the session. In the present study, animals treated with both xylamine and LSD exhibited markedly disrupted patterns of locomotion (data not shown) and a tendency toward increased levels of activity and rearing during the last half of the session (Table 2). Further experiments will be needed to determine whether or not this phenomenon reflects an unmasking by xylamine of a separate effect of LSD on stimulus sampling or habituation [2].

In any case, the present results are consistent with the hypothesis that central noradrenergic neurons contribute to the behavioral effects of LSD. Given the widespread depletions of brain NE produced by intraventricular xylamine, the present study does not help to clarify the anatomic locus of this interaction. Additional studies using regionally specific depletions of NE will be needed to determine whether this interaction is dependent upon some particular brain region or is due to a distributed influence of NE. While hallucinogens such as LSD may act directly upon noradrenergic neurons, it is also possible that these neurons only play a role in the expression of the effects of LSD. For example, LSD is known to indirectly potentiate the responses of LC cells and facial motoneurons to afferent stimuli [5,28], phenomena which may provide a basis for the augmented responsiveness to sensory stimuli produced by hallucinogens. Thus, further experiments will also be required to define the direct or indirect nature of the mechanism underlying the interaction between NE depletions and the behavioral effects of LSD.

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