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Nisoxetine and Amphetamine Share Discriminative Stimulus Properties in Mice[1,2]

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SNODDY, A. M. AND R. E. TESSEL. *Nisoxetine and amphetamine share discriminative stimulus properties in mice.* PHARMACOL BIOCHEM BEHAV **19**(2) 205–210, 1983.—The interaction of amphetamine with noradrenergic neurons could mediate a portion of the drug's discriminative stimulus properties. To test this hypothesis, mice were trained to discriminate 1.0 or 3.2 mg/kg amphetamine, 32 mg/kg of the selective norepinephrine uptake inhibitor, nisoxetine, or 32 mg/kg nisoxetine + 1.0 mg/kg amphetamine from saline. Differential drug- or saline-appropriate responding was determined using a two photocell-beam procedure with beam interruption as the operant. Reinforcement (5-sec access to evaporated milk) was presented on a fixed-ratio 20 (FR-20) schedule. Mice trained to discriminate 1.0 mg/kg amphetamine from saline generalized to nisoxetine (32 mg/kg) alone and to doses of 0.56 mg/kg amphetamine and above but not to lower doses unless pretreated with nisoxetine (20 or 32 mg/kg). Mice trained to discriminate nisoxetine (32 mg/kg) from saline generalized to 0.56, 1.0 and 3.2 mg/kg amphetamine and generalized to all amphetamine doses when pretreated with nisoxetine (32 mg/kg). Mice trained to discriminate the drug combination from saline generalized to nisoxetine (32 mg/kg) alone, and to 3.2 mg/kg amphetamine tested alone, to 0.56 mg/kg of amphetamine or above when the lower dose of nisoxetine (20 mg/kg) was used, and to all test doses of amphetamine with nisoxetine (32 mg/kg) pretreatment. Mice trained to discriminate 3.2 mg/kg amphetamine from saline generalized to no test dose of amphetamine following either saline or nisoxetine (32 mg/kg) pretreatment. Testing with several doses of pentobarbital (1.0, 3.0, 10.0 and 18.0 mg/kg) resulted in saline-appropriate responding regardless of training group. These observations indicate that the mouse may be a useful subject for drug discrimination experiments and are consistent with the notion that the discriminative stimulus properties of a low dose of amphetamine are at least partially noradrenergically mediated.

Drug discrimination *d*-Amphetamine Nisoxetine Mice

LIKE a number of other drugs, amphetamine possesses reinforcing and discriminative stimulus properties as well as the capacity to elicit changes in gross motor activity and schedule-controlled responding [3, 15, 17, 29]. It is generally held that these effects are dopaminergically mediated since they can be antagonized by dopaminergic receptor antagonists [19], and are at least to some extent mimicked by reputedly direct and indirect dopamine agonists [11, 19, 20], and the dopamine reuptake inhibitors bupropion and nomifensine [2, 11, 24].

However, data from our laboratory suggest the involvement of central noradrenergic neurons in some of the behavioral effects of amphetamine. Nisoxetine, a potent inhibitor of central norepinephrine but not dopamine uptake [12, 25, 26, 27, 34, 35], at doses which have no consistent effects on behavior per se, but inhibit amphetamine-induced norepinephrine release in the mouse cerebral cortex *in vivo* [27], abolishes the locomotor stimulation and increases in fixed-interval responding in mice induced by amphetamine [6, 26, 27]. In contrast, such pretreatment potentiates amphetamine-induced decreases in fixed- ratio responding [6, 26, 27] and amphetamine-induced stereotypy in mice (an action presumed to be due to amphetamine-induced striatal dopamine release [32]).

The purpose of the present experiment was to extend these findings in the mouse to the discriminative stimulus (cue) properties of amphetamine, an action that appears to depend on central and not peripheral catecholamines [10]. It was hypothesized that if the discriminative-stimulus complex elicited by amphetamine importantly involved amphetamine-induced norepinephrine release then nisoxetine might antagonize this effect. Alternatively, since nisoxetine can potentiate the stereotypy elicited by amphetamine [6, 26, 27], it might be that the cues associated with nisoxetine plus amphetamine are mediated primarily by central dopamine and thus are qualitatively different from those of either drug alone.

Finally, since inhibitors of norepinephrine reuptake, like amphetamine, can increase the net efflux of this transmitter from at least some brain regions [27], nisoxetine might share discriminative stimulus properties with amphetamine. The results support the final hypothesis.

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[2]A preliminary abstract of this study appears in the *Fed Proc* **41**: 1072, 1982.
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METHOD

Subjects

Male ICR mice (30–35 g) were purchased from Harlan Sprague-Dawley (Indianapolis, IN). At the start of the study the mice were food deprived to 80% of their free feeding weights. The animals were given ad lib access to food approximately every three months and their 80% weights adjusted to this new ad lib weight to allow for growth throughout the lifetime of the animals. Mice were housed individually under a 12-hr light/dark cycle. Sessions were conducted between 0800 and 1700 hours five days per week. Each of four training groups contained two animals.

Apparatus

Animals were trained and tested in a modified rodent test chamber (BRS/LVE RTC-020) housed in a sound attentuated cubicle with a ventilating fan. The chamber was modified to contain two photocell corridors of the type described by Wenger and Dews [30]. Each reinforcer consisted of 5-sec access to 0.01 ml of evaporated mild. Milk was delivered by operation of a small liquid dipper (BRS/LVD SLD-002) located between the two corridors (Fig. 1). All programming and recording was done by electromechanical control equipment in an adjoining room.

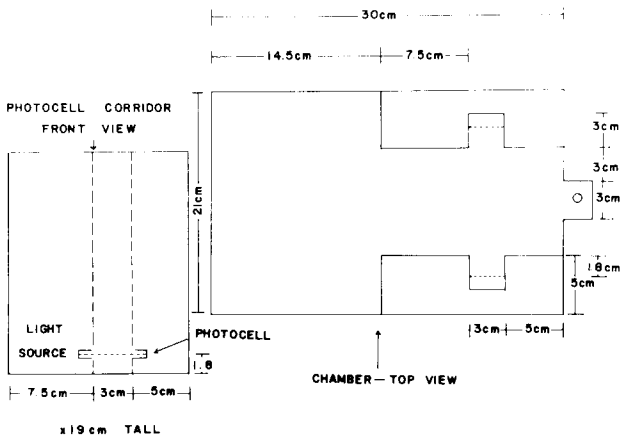

FIG. 1. Diagram of the experimental chamber as viewed from above and facing one photocell corridor.

Discrimination Training and Testing

Discrimination training was begun with the first operant training session. Animals were trained to discriminate one of four drug conditions from saline starting with continuous reinforcement (fixed-ratio 1; (FR-1)]. Training was continued until the terminal schedule was reached, a fixed-ratio 20 (FR-20). Forty minutes prior to a drug training session animals were injected intraperitoneally (IP: 0.01 ml/g body weight) with either 32 mg/kg nisoxetine or saline (0.9% NaCl). Ten minutes prior to the start of the session, animals were injected with saline, 1 mg/kg amphetamine, or 3.2 mg/kg amphetamine. The times of pretreatment and treatment were chosen such that the maximal effect of the drugs would occur within the operant session [26,36]. On saline training days, two saline injections were given at the above times prior to the session. Thus mice were trained to discriminate saline plus 1.0 mg/kg amphetamine from saline plus saline (i.e., the 1.0 mg/kg amphetamine group), saline plus 3.2 mg/kg amphetamine from saline plus saline (i.e., the 3.2 mg/kg amphetamine group), 32 mg/kg nisoxetine plus saline from saline plus saline (i.e., 32 mg/kg nisoxetine group), or 32 mg/kg nisoxetine plus 1.0 mg/kg amphetamine from saline plus saline (i.e., the combination group). For one-half of the animals, breaking a photocell beam only on the left side of the chamber was reinforced on drug days; responses on the right side were reinforced only on saline training days. For the other half of the animals the situation was reversed such that the right side was drug-appropriate and the left side saline-appropriate. All responses activated a feedback relay but responses emitted on the injection-inappropriate side had no other programmed consequences. Following reinforcement there was a 45-sec time-out during which responses had no programmed consequences. Sessions were terminated after 20 reinforcers had been presented or after 30 min, and a random schedule of drug and saline training sessions was used with the added contingency that no more than two saline or drug training sessions occurred on consecutive days. This random schedule allowed for the occurrence of a nearly equal number of drug and saline sessions during each two-week period. Once animals responded on the terminal schedule such that at least 90% of the completed ratios during a two-week period occurred on the injection-appropriate side, test sessions were begun.

Test Sessions

Test sessions differed from training sessions only in that during test sessions reinforcement could be obtained by completing the response requirement using either photocell corridor. Test sessions with pentobarbital utilized saline pretreatment with pentobarbital as the treatment. Drugs and doses were tested in a nonsystematic order.

Drugs

The drugs used in the study were *d*-amphetamine sulfate (Smith, Kline and French, Philadlphia, PA), nisoxetine-HCl (Eli Lilly, Indianapolis, IN), and sodium pentobarbital (Merck, Sharpe and Dohme, West Point, PA). All drugs were dissolved in saline (0.9% NaCl) solution and doses expressed as the salt.

Data Analysis

Generalization data were analyzed by the Kruskal-Wallis test. The decreases in operant responding were analyzed using Dunnett's test.

RESULTS

Mice trained to discriminate 32 mg/kg nisoxetine from saline took longer (mean=40 sessions) to meet the discrimination criterion than mice trained to discriminate 1.0 mg/kg amphetamine, 32 mg/kg nisoxetine + 1.0 mg/kg amphetamine or 3.2 mg/kg amphetamine from saline (mean =30 sessions). Once the discrimination was established in each group, responding was nearly 100% accurate on both saline and drug training days.

As illustrated in Fig. 2, animals received 100% of the session's reinforcers using the drug-appropriate photocell corridor on drug days and 0% on saline days regardless of training condition. When various doses of amphetamine were substituted for the training condition, mice trained to dis-

criminate 1.0 mg/kg amphetamine from saline (Fig. 2a) generalized only to 0.56 through 3.2 mg/kg amphetamine (i.e., during test sessions, a mean of at least 80% of the fixed-ratio trials were completed using the drug-appropriate corridor). However, pretreatment with nisoxetine (32 mg/kg) combined with either saline or amphetamine (0.10, 0.32, 0.56, 1.0 and 3.2 mg/kg) treatment resulted in complete generalization to the training condition in these animals. Generalization to all test doses of amphetamine was also achieved when a lower dose of nisoxetine (20 mg/kg) was used as the pretreatment. However, this dose of nisoxetine when combined with saline showed only a partial generalization to the 1 mg/kg amphetamine cue (approximately 63% drug-appropriate responding). Thus the percent of drug-appropriate trials completed in animals pretreated with either 20 or 32 mg/kg nisoxetine was significantly greater ($p<0.05$) than that associated with saline pretreatment when the treatment consisted of saline, 0.10, 0.32 or 0.56 mg/kg amphetamine (Fig. 2a).

Similarly, mice trained to discriminate 32 mg/kg nisoxetine from saline generalized only to the three highest doses of amphetamine tested (0.56, 1.0 and 3.2 mg/kg) when saline pretreatment replaced nisoxetine (Fig. 2b). However, all doses of amphetamine substituted for the training condition when combined with 32 mg/kg nisoxetine pretreatment. Thus, there were significant reductions ($p<0.01$) in the percentage of drug-appropriate trials when saline replaced 32 mg/kg nisoxetine as the pretreatment for animals treated with amphetamine doses of 0.10 or 0.32 mg/kg. The ability of 1.0 mg/kg amphetamine to substitute for the training condition of this group (32 mg/kg nisoxetine + saline) and the ability of 32 mg/kg nisoxetine to substitute in animals trained to discriminate saline + 1.0 mg/kg amphetamine from saline (Fig. 2a), indicates that there was a marked cross-generalization between nisoxetine and amphetamine.

Mice trained to discriminate 32 mg/kg nisoxetine plus 1.0 mg/kg amphetamine from saline (Fig 2c) generalized to 32 mg/kg nisoxetine alone and to 3.2 mg/kg amphetamine alone. Generalization to all test doses of amphetamine occurred when 32 mg/kg nisoxetine was the pretreatment. Generalization to the lower dose of nisoxetine (20 mg/kg) alone did not occur. However, the combination of nisoxetine with various amphetamine doses resulted in a shift to the left in the amphetamine generalization curve as compared to the curve associated with saline pretreatment.

In contrast to the above, no dose of amphetamine below 3.2 mg/kg substituted in mice trained to discriminate 3.2 mg/kg amphetamine from saline (Fig. 2d) and pretreatment with 32 mg/kg nisoxetine instead of saline had no effect on the amphetamine dose-generalization curve. There were no significant differences between the pretreatments at any of the amphetamine doses. The pharmacological specificity of the cross-generalization between nisoxetine and amphetamine is supported by the failure of behaviorally active doses of pentobartial (1, 3, 10, or 18 mg/kg; Ganousis and Tessel, unpublished observations, [29]) to generalize to the drug-training condition of any group tested (data not presented).

Table 1 presents the amphetamine dose-generalization data obtained for each of the drug-training conditions so that the potency of amphetamine can be compared directly (see also saline pretreatment, Fig. 2). The data suggest that the potency of amphetamine as a discriminative stimulus depended markedly on the training condition, with the order of potency being: saline plus 1.0 mg/kg amphetamine> 32 mg/kg nisoxetine plus saline > 32 mg/kg nisoxetine plus 1.0 mg/kg amphetamine > saline plus 3.2 mg/kg amphetamine.

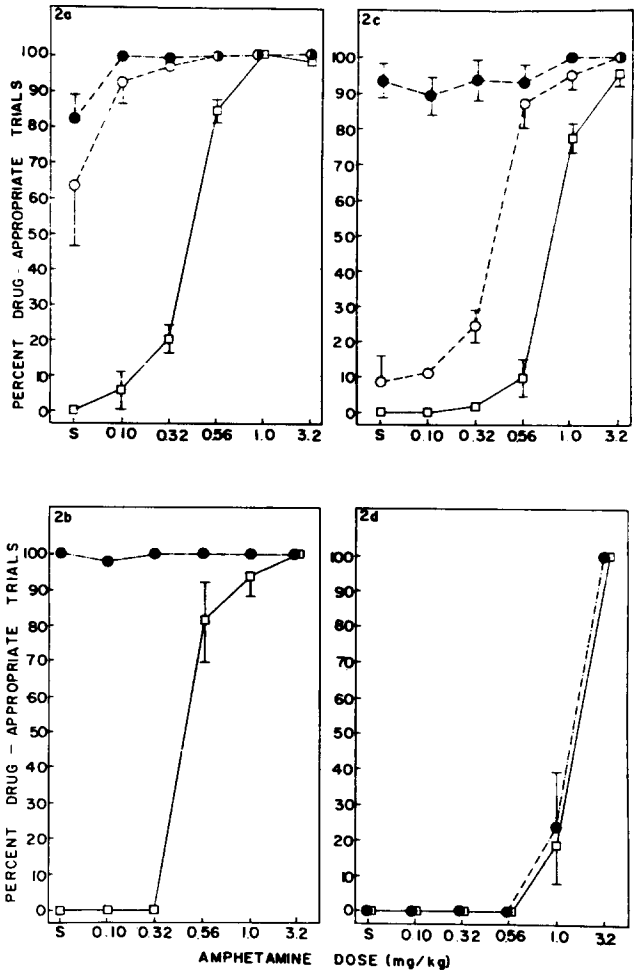

FIG. 2. Discrimination of various doses of amphetamine following pretreatment with saline (□—□), 20 mg/kg nisoxetine (○- - -○), and 32 mg/kg nisoxetine (●— · —●) in mice trained to discriminate 1.0 mg/kg amphetamine (2a), 32 mg/kg nisoxetine (2b), 32 mg/kg nisoxetine + 1.0 mg/kg amphetamine (2c) or 3.2 mg/kg amphetamine (2d) from saline. The dependent variable was the number of trials completed using the drug-appropriate photocell corridor divided by the total number of trials completed in a given session. Each point represents the mean±SEM of two to three observations in each of two mice.

Evidence for behavioral toxicity in the saline plus 3.2 mg/kg amphetamine group and the 32 mg/kg nisoxetine plus saline training group was also obtained (Tables 2A and 2B, respectively). The proportion of the total available reinforcers obtained by animals in both groups decreased over the course of the experiment, with the reductions beginning eleven weeks after the study was initiated (first two-week block indicated in Table 2). In the amphetamine group, this proportion decreased only during drug-training sessions. In the nisoxetine group, however, the decline in total available reinforcers obtained was associated with a reduction in responding under both injection conditions (drug and saline). In neither group was the degree of discrimination affected. There was no clear pattern of reduction in either of the other two training groups (saline + 1.0 mg/kg amphetamine and 32 mg/kg nisoxetine + 1.0 mg/kg amphetamine; data not shown).

TABLE 1

PROPORTION OF TOTAL TRIALS THAT WERE COMPLETED USING THE DRUG-APPROPRIATE CORRIDOR AS A FUNCTION OF TRAINING CONDITION

Training Conditions*		Amphetamine Dose (mg/kg) Combined with Saline Pretreatment					
Pretreatment	Treatment	0.00	0.10	0.32	0.56	1.00	3.20
Saline	1.0 Amphetamine	0.00±0.00	5.50±5.50	19.50±4.01†	85.17± 3.38†	100.00±0.00‡	98.75±1.25
32 Nisoxetine	Saline	0.00±0.00	0.00±0.00	0.00±0.00	81.25±11.97†	94.00±6.00‡	100.00±0.00
32 Nisoxetine	1.0 Amphetamine	0.00±0.00	0.00±0.00	2.00±2.00	8.40± 5.28	74.29±4.52§	97.71±3.25
Saline	3.2 Amphetamine	0.00±0.00	0.00±0.00	0.00±0.00	0.00± 0.00	18.75±3.75	100.00±0.00

Data are expressed as a percentage of the total number of trials that were completed on the drug-appropriate side.
Each value represents the mean (±S.E.M.) of four to six observations.
*Numbers in the column indicate dose in mg/kg.
†Significantly greater than other training groups—$p<0.01$.
‡Significantly greater than 32 mg/kg nisoxetine + 1.0 mg/kg amphetamine and saline + 3.2 mg/kg amphetamine animals—$p<0.05$.
§Significantly greater than saline + 3.2 mg/kg amphetamine—$p<0.05$.

TABLE 2

EFFECTS OF LONG-TERM AMPHETAMINE (A) OR NISOXETINE (B) TRAINING ON THEIR DISCRIMINATION FROM SALINE, AND ON TRIAL COMPLETION

Two-week Period	Proportion of Trials Completed on the Injection-Appropriate Side	Proportion of Total Available Reinforcers Obtained During Saline Sessions	Proportion of Total Available Reinforcers Obtained During Drug Sessions
(A) Mice Trained to Discriminate 3.2 mg/kg Amphetamine from Saline			
(1)	100.00 ± 0.00	92.50 ± 4.33	90.00 ± 4.08
(2)	94.71 ± 5.29	100.00 ± 0.00	71.66 ± 6.00
(3)	94.67 ± 4.14	92.00 ± 3.72	36.25 ± 7.47*
(4)	100.00 ± 0.00	95.00 ± 3.87	42.50 ± 11.09*
(5)	99.44 ± 0.55	97.50 ± 2.50	23.00 ± 6.04*
(6)	100.00 ± 0.00	97.50 ± 2.50	23.33 ± 8.82*
(B) Mice Trained to Discriminate 32 mg/kg Nisoxetine from Saline			
(1)	96.70 ± 2.40	83.00 ± 10.17	90.83 ± 5.23
(2)	95.50 ± 3.00	69.00 ± 14.18	89.00 ± 6.00
(3)	94.00 ± 3.93	71.25 ± 8.26	60.00 ± 5.40*
(4)	94.00 ± 2.64	47.50 ± 12.65*	51.67 ± 8.03*
(5)	94.25 ± 3.43	65.00 ± 12.08	57.50 ± 12.99
(6)	100.00 ± 0.00	78.33 ± 6.01	76.25 ± 10.08

Mean ± SEM of data obtained from 3 to 5 sessions in each of two mice.
*$p<0.01$ Compared to value of Two-Week Period number one.

DISCUSSION

The present study has demonstrated that amphetamine and nisoxetine share discriminative stimulus properties, an effect that contrasts with previous behavioral studies using nisoxetine and amphetamine [6, 26, 27]. Amphetamine has previously been shown to possess discriminative stimulus properties in both the rat [8,9] and pigeon [33]. The present paper has extended this species generality to include a species not previously used in drug discrimination studies, the mouse.

Amphetamine releases both norepinephrine and dopamine in brain [1]. Yet it is generally believed that the cues produced by amphetamine depend predominantly if not exclusively on the drug's ability to release central dopamine, since they can be antagonized by dopamine receptor blockade [19]. On the other hand, administration of nisoxetine *in vitro* has little effect on dopamine uptake, spontaneous dopamine efflux or amphetamine-induced dopamine release in brain tissue at concentrations that markedly affect similar parameters of noradrenergic function [12, 25, 26, 27, 34, 35]. *In vivo*, nisoxetine antagonizes α-methyl-*m*-tyrosine-induced central norepinephrine, but not dopamine, depletion [5]. Therefore the most parsimonious explanation to account for

the present findings is that the shared discriminative stimulus properties of amphetamine and nisoxetine depend on synaptic concentrations of norepinephrine.

It has been shown in previous studies that the training dose has marked effect on the dose-generalization curves obtained such that the curve is shifted to the right as training dose increases [31]. The present study was no exception (Table 1 and Fig. 2). In addition, it is important to note that animals trained to discriminate 3.2 mg/kg amphetamine from saline failed to generalize to any other test condition. This disparity from the other generalization curves may be attributable to either of two possibilities. It may be that 3.2 mg/kg amphetamine is associated with a qualitatively similar but quantitatively more intense stimulus complex than that produced by the other doses tested. Alternatively, the large amphetamine dose may elicit a stimulus complex that is qualitatively different from that produced by nisoxetine or lower amphetamine doses.

For example, the cue associated with 1.0 mg/kg amphetamine could be dependent upon the release of norepinephrine whereas that associated with 3.2 mg/kg amphetamine could be dependent upon the release of norepinephrine plus the release of dopamine (a qualitatively different cue). If this were the case, 3.2 mg/kg amphetamine could substitute in mice trained to discriminate 1.0 mg/kg amphetamine from saline because the "dopamine" portion of the cue is not attended to (i.e., is masked [33]; see [14] for discussion of cue masking). However, in animals trained to attend to this "dopamine" cue (3.2 mg/kg amphetamine versus saline), its absence in the effects of lower amphetamine doses and of nisoxetine results in no generalization to these lower doses. Neither possibility can be eliminated entirely. However, it was observed that 3.2 mg/kg amphetamine substituted for the training condition in animals trained to discriminate 1.0 mg/kg amphetamine from saline. In addition, a drug previously shown to be associated with cues that are qualitatively different from those produced by amphetamine, pentobarbital [13,33], in the present study did not substitute for the 1.0 mg/kg amphetamine cue at any dose tested. These findings suggest that if qualitative differences existed between the stimuli elicited by the two amphetamine doses, they do not appear to have been of overwhelming importance in determining dose-generalization.

Long-term administration of 3.2 mg/kg of amphetamine or 3.2 mg/kg of nisoxetine was found to disrupt operant responding. The reasons for these effects are unclear but, in the case of long-term amphetamine administration, could be attributable to the elicitation of a motor behavior, probably stereotypy, that is incompatable with performance of the operant response. Certainly, daily injections of amphetamine, combined with daily measurements of the drug's ability to stimulate locomotion and stereotyped grooming, licking and chewing result in shifts to the left in the drug's dose-response curves [21]. In addition, chronic amphetamine administration may have neurotoxic properties [4, 16, 18]. Data concerning the behavioral effects of long-term norepinephrine uptake inhibitor administration have been infrequently reported. However, a behavioral disruption similar to those obtained in the present study using nisoxetine, were reported by Shearman *et al.* [22] in rats when desmethylimipramine was used. Regardless, it is interesting to note the apparent ability of amphetamine (1.0 mg/kg) to antagonize the disruptive effect of 32 mg/kg nisoxetine (see Results).

Previous research suggests that amphetamine only partially substitutes for desmethylimipramine (DMI) in rats trained to discriminate the norepinephrine uptake inhibitor from saline [22]. In the present study, however, a specific and selective norepinephrine reuptake inhibitor completely generalized to amphetamine and vice versa. This disparity may be due to the multiple neurochemical actions produced by DMI at higher doses (e.g., α-adrenergic, histaminergic and muscarinic receptor antagonism) [7, 23, 28], such that the cues produced by higher DMI but not nisoxetine doses are qualitatively different from those produced at lower doses. Preliminary studies from our laboratory have shown that DMI (20 mg/kg) at least partially substitutes in animals trained to discriminate 1.0 mg/kg amphetamine from saline.

In conclusion, bidirectional similarity between the discriminative stimuli associated with the administration of amphetamine and the norepinephrine uptake inhibitor, nisoxetine, has been demonstrated in a species not previously used for operant drug discrimination studies, the mouse. The present data therefore suggest that norepinephrine may mediate the discriminative stimulus properties of at least low doses of amphetamine. More definitive statements await additional research.

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