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The Acute Effects of Monoamine Reuptake Inhibitors on the Stimulus Effects of Hallucinogens

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WINTER, J. C., S. HELSLEY, D. FIORELLA AND R. A. RABIN. *The acute effects of monoamine reuptake inhibitors on the stimulus effects of hallucinogens.* PHARMACOL BIOCHEM BEHAV **63**(3) 507–513, 1999.—In a previous study it was observed that fluoxetine potentiates the stimulus effects of lysergic acid diethylamide (LSD). In the present investigation, stimulus control was established in groups of rats using as training drugs the hallucinogens lysergic acid diethylamide (LSD); 0.1 mg/kg), (−)-2,5-dimethoxy-4-methylamphetamine [(−)-DOM; 0.56 mg/kg], ibogaine (10 mg/kg), and 5-methoxy-*N,N*-dimethyltryptamine (5-MeO-DMT; 3 mg/kg). A two-lever, fixed-ratio 10, positively reinforced task with saline controls was employed. The hypotheses tested were that (a) monoamine uptake inhibitors other than fluoxetine potentiate the discriminative effects of LSD, and (b) hallucinogens other than LSD are potentiated by acute pretreatment with monoamine uptake inhibitors. The effects of a range of doses of each of the training drugs were determined both alone and following pretreatment with the monoamine reuptake inhibitors fluoxetine, fluvoxamine, and venlafaxine. In LSD-trained subjects, all three reuptake inhibitors caused a significant increase in LSD-appropriate responding. Similar results were observed in rats trained with (−)-DOM and with ibogaine. In 5-MeO-DMT–trained subjects, only fluoxetine resulted in an enhancement of drug-appropriate responding. The reuptake inhibitors given alone elicited varying degrees of responses appropriate for the respective training drugs. For fluoxetine in rats trained with LSD and ibogaine, for venlafaxine in LSD trained, and for fluvoxamine in (−)-DOM trained, the degree of responding met our criterion for intermediate responding, i.e., significantly different from both training conditions. Subsequent experiments in (−)-DOM–trained subjects examined a range of doses of each of the reuptake inhibitors in combination with a fixed dose of (−)-DOM (0.1 mg/kg), which alone yielded about 50% (−)-DOM–appropriate responding. With the exception of the point obtained with the highest dose of venlafaxine, all data were compatible with additivity of effects rather than true potentiation. In summary, the present data extend our previous observation of the augmentation of the stimulus effects of LSD by fluoxetine to include other hallucinogens. The mechanisms by which these interactions arise and possible differential effects of acute and chronic treatment remain to be established.

Drug discrimination Rat SSRIs Hallucinogens DOM LSD Ibogaine

IN a previous report from our laboratory (13), acute treatment with (+)-fluoxetine, a selective serotonin reuptake inhibitor [SSRI; 24,51,53)], was shown to augment LSD-induced stimulus control in the rat. The interaction appeared to be potentiation, i.e., an effect greater than would have been predicted on the basis of the effects of the two drugs given separately. Although we are unaware of any studies that have explicitly examined this phenomenon in human subjects, Bonson et al. (6), described a person who experienced an enhanced response to LSD following the ingestion of fluoxetine for 1 week. In addition, Markel et al. (25) described three individuals who experienced flashbacks, i.e., recurrent LSD-like effects in the absence of the drug, when treated for depression with fluoxetine or with the SSRIs sertraline and paroxetine. In view of survey data that indicate widespread use of the hallucinogens in the United States (21), and the fact

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that SSRIs are presently the most commonly prescribed psychoactive drugs in the world, it seems likely that SSRIs and hallucinogens will be ingested by humans, either with intent or inadvertently, with increasing frequency.

In the present investigation we sought to test the hypotheses that (a) monoamine uptake inhibitors other than fluoxetine potentiate the discriminative effects of LSD, and (b) hallucinogens other than LSD are potentiated by acute pretreatment with monoamine uptake inhibitors. Toward these ends, we have examined the interactions of the SSRI's fluoxetine and fluvoxamine (8,23), and the selective serotonin/norepinephrine reuptake inhibitor (SSNRI) venlafaxine (14,27) with the stimulus effects of ibogaine (16,38), (−)-DOM, (12,41), LSD (17,35), and 5-MeO-DMT (15,45,50).

METHOD

Animals

Male Fischer-344 rats were obtained from Charles River Breeding Laboratories, Inc. (Wilmington, MA) at an age of approximately 6 weeks. They were housed in pairs and allowed free access to water in the home cage. All handling and testing occurred during daytime hours. Standard rat chow was provided immediately following training sessions. Caloric intake was controlled so as to maintain adult body weights of approximately 300 g.

Apparatus

Six small-animal test chambers (Coulbourne Instruments model E 10-10) were used for all experiments. These were housed in larger light-proof, sound-insulated boxes that contained a house light, and an exhaust fan. Chambers contained two levers mounted at opposite ends of one wall. Centered between the levers was a dipper that delivered 0.1 ml of sweetened condensed milk diluted 2:1 with tap water. Sessions were managed by a microcomputer using operant control software (Coulbourne Instruments D91-12, version 4.0).

Procedure

After learning to drink from the dipper, rats were trained to press first one and then the other of the two levers. The number of responses for each reinforcement was gradually increased from 1 to 10. During this time, the reinforced lever was alternated on a random basis. All subsequent training and testing sessions used a fixed-ratio 10 (FR10) schedule of reinforcement. Discrimination training was then begun. Fifteen minutes before each 10-min training session, subjects were injected IP with either saline or drug. Following the administration of drug, every 10th response on the drug-appropriate lever was reinforced. Similarly, responses on the saline-appropriate lever were reinforced on a FR10 schedule following the injection of saline. For half of the subjects, the left lever was designated as the drug-appropriate lever. During discrimination training, drug and saline were alternated on a daily basis. Drug-induced stimulus control was assumed to be present when, in five consecutive sessions, 83% or more of all responses prior to the delivery of the first reinforcer were on the appropriate lever.

Groups of animals were trained as previously described using the parameters as indicated: (−)-DOM (12), 0.56 mg/kg, 75 min pretreatment, $n = 8$; ibogaine (16), 10 mg/kg, 60-min pretreatment, $n = 9$; LSD (13), 0.1 mg/kg, 15-min pretreatment, $n = 7$; 5-MeO-DMT (50), 3 mg/kg, 15-min pretreatment, $n = 12$. After stimulus control with the training drugs was well established, tests of generalization and of antagonism were conducted once per week in each animal as long as performance during the remainder of the week did not fall below a criterion level of 83% correct responding. Tests were balanced between subjects trained on the previous day with saline and drug, respectively. During test sessions, no responses were reinforced, and the session was terminated after the emission of 10 responses on either lever. The distribution of responses between the two levers was expressed as the percentage of total responses emitted on the drug-appropriate lever. Response rate was calculated for each session by dividing the total number of responses emitted prior to lever selection, that is, prior to the emission of 10 responses on either lever, by elapsed time. For purposes of discussion of these data, an intermediate degree of generalization is defined as being present when the mean response distribution after a test drug is less than 80% drug-appropriate and is significantly different from both training conditions.

Statistical Analysis

Behavioral data expressed as "percent drug-appropriate responding" were transformed by squaring each value. If the transformed data did not fail tests of normality and equal variance, statistical significance was assessed using Student's *t*-test or analysis of variance with subsequent multiple comparisons by the method of Student–Newman–Kuels. In those instances when the transformed data failed either a test of normality or a test of equal variance, the Mann–Whitney rank sum test or analysis of variance on ranks was used. Differences were considered to be statistically significant if the probability of their having arisen by chance was <0.05. All analyses were conducted using SigmaStat for Windows™ (Jandel Scientific Software, San Rafael, CA). In those instances when more than one drug was tested in combination with a training drug, control data were repeated for each comparison and statistical analyses were applied using the appropriate control sessions. However, for purposes of clarity, mean values for control data are shown in all figures.

Drugs

5-Methoxy-*N,N*-diethyltryptamine oxalate was purchased from Research Biochemicals International, Natick, MA. The following drugs were generously provided by the organizations indicated: (−)-DOM HCl, (+) lysergic acid diethylamide (+)-tartrate, and ibogaine HCl (National Institute on Drug Abuse, Rockville, MD), (±)-fluoxetine HCl (Lilly Research Laboratories, Indianapolis, IN), fluvoxamine maleate (Solvay Duphar B.V., Weesp, The Netherlands), and venlafaxine HCl (Wyeth-Ayerst Research, Princeton, NJ). All drugs were dissolved in 0.9% saline solution and injected in a volume of 1 ml/kg body weight. The IP route was employed for all drugs.

RESULTS

Figure 1 shows the effects of pretreatment with fixed doses of fluoxetine, venlafaxine, and fluvoxamine on drug-appropriate responding following administration of either of two intermediate doses of LSD. At the higher of the two doses of LSD (0.03 mg/kg), all three reuptake inhibitors caused a significant increase in LSD-appropriate responding. Likewise, at the lower test dose of LSD (0.01 mg/kg), all of the reuptake inhibitors appeared to increase LSD-appropriate responding, but only that for fluoxetine reached statistical significance. It

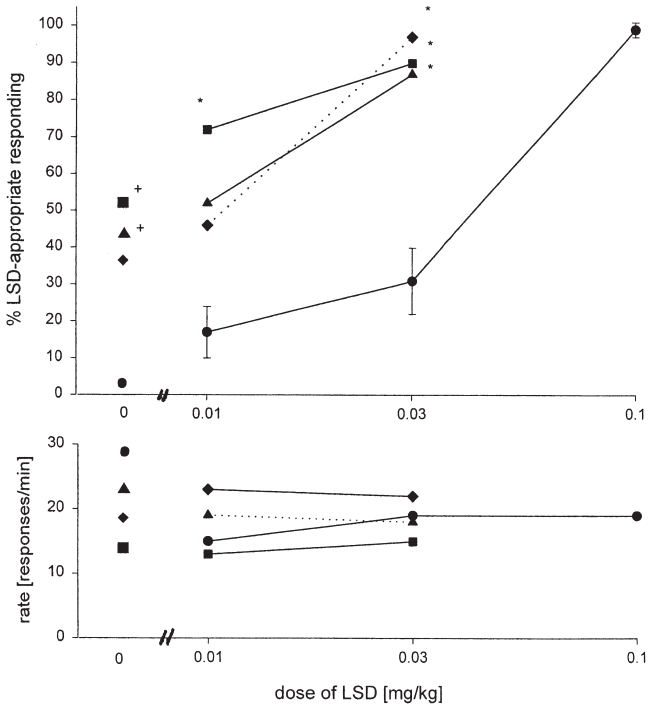

FIG. 1. The effects of LSD alone (circles; ± SEM) and in combination with fluoxetine (2.5 mg/kg; squares), venlafaxine (10 mg/kg; triangles), and fluvoxamine (10 mg/kg; diamonds) in rats trained with LSD (0.1 mg/kg) as a discriminative stimulus. The monoamine reuptake inhibitors and LSD were injected IP, 90 and 15 min, respectively, before testing. Each point represents the mean of one determination in each of seven subjects. Ordinate: upper panel—mean percentage of responses on the LSD-appropriate lever; lower panel—response rate. Abscissa: dose plotted on a log scale. Statistical comparisons are between LSD alone and in combination with the reuptake inhibitor, and significant differences are indicated by *. Data points at zero dose are for saline and the reuptake inhibitors given alone. Statistical comparisons are between saline, a reuptake inhibitor, and the training dose of LSD; a significant difference between a reuptake inhibitor and both training conditions is indicated by +.

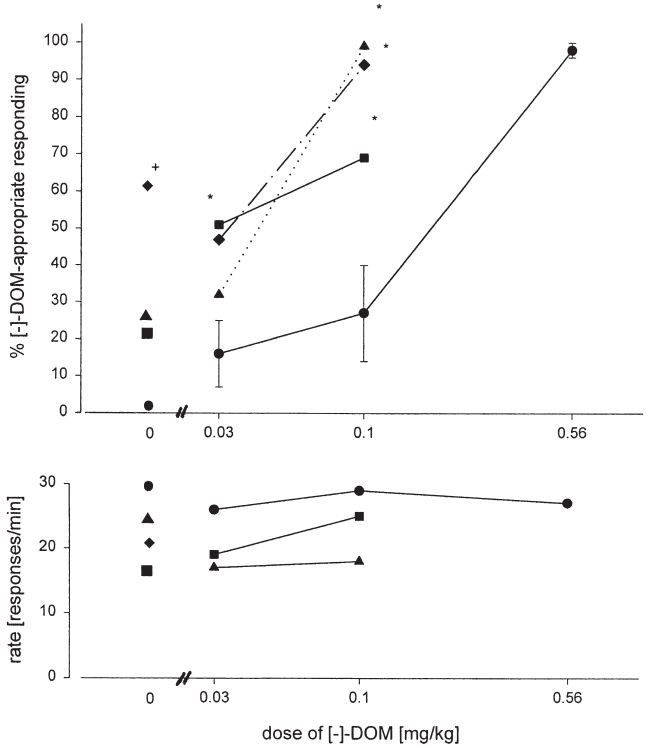

FIG. 2. The effects of (−)-DOM alone (circles; ± SEM) and in combination with fluoxetine (2.5 mg/kg; squares), venlafaxine (10 mg/kg); triangles), and fluvoxamine (10 mg/kg; diamonds) in rats trained with (−)-DOM (0.56 mg/kg) as a discriminative stimulus. The monoamine reuptake inhibitors and (−)-DOM were injected IP, 90 and 75 min, respectively, before testing. Each point represents the mean of one determination in each of eight subjects. Ordinate: upper panel—mean percentage of responses on the (−)-DOM–appropriate lever; lower panel—response rate. Abscissa: dose plotted on a log scale. Statistical comparisons are between (−)-DOM alone and in combination with the reuptake inhibitor, and significant differences are indicated by *. Data points at zero dose are for saline and the reuptake inhibitors given alone. For the zero dose data, statistical comparisons are between saline, a reuptake inhibitor, and the training dose of (−)-DOM; a significant difference between a reuptake inhibitor and both training conditions is indicated by +.

should be noted that all of the reuptake inhibitors when given alone resulted in increased levels of LSD-appropriate responding, and for fluoxetine and venlafaxine, these met our criteria for intermediate results, i.e., they were statistically significantly different from both training conditions.

In Figs. 2 and 3 it is seen that pretreatment with the reuptake inhibitors increases drug-appropriate responding in subjects trained with either (−)-DOM, a phenethylamine hallucinogen, or ibogaine, a hallucinogen of uncertain classification but that possesses certain structural and functional features in common with the indoleamines (16). As was seen in Figure 1 for LSD-trained rats, the reuptake inhibitors when given alone were not completely devoid of stimulus effects. Thus, an intermediate level of drug-appropriate responding was observed with fluvoxamine in (−)-DOM–trained subjects (Fig. 2) and with fluoxetine in rats trained with ibogaine (Fig. 3).

In contrast with the results observed in Figs. 1–3 with subjects trained with LSD, (−)-DOM, and ibogaine, respectively, rats trained with 5-MeO-DMT (Fig. 4) were only minimally influenced by the combination of the training drug with reuptake inhibitors. Indeed, of the three combinations at each of two doses of 5-MeO-DMT, only that for fluoxetine at a 5-MeO-DMT dose of 1.5 mg/kg reached statistical significance.

In light of the fact that fluvoxamine when given alone resulted in an intermediate degree of (−)-DOM–appropriate responding (Fig. 2), the question arises as to the extent to which additivity of effects rather than true potentiation might account for increased activity of (−)-DOM in combination with reuptake inhibitors. In an attempt to address that question, dose–response relationships for fluoxetine, venlafaxine, and fluvoxamine in combination with a fixed dose (0.1 mg/kg) of (−)-DOM were examined. The data of Fig. 5 for fluoxetine and of Fig. 7 for fluvoxamine are compatible with additivity of effects. In contrast, the data obtained with doses of 3 and 10 mg/kg of venlafaxine (Fig. 6) are suggestive of potentiation in that (−)-DOM–appropriate responding increased disproportionately relative to the effects of venlafaxine alone.

DISCUSSION

The data shown in Fig. 1 clearly support the hypothesis that fluoxetine is not alone among the monamine reuptake in-

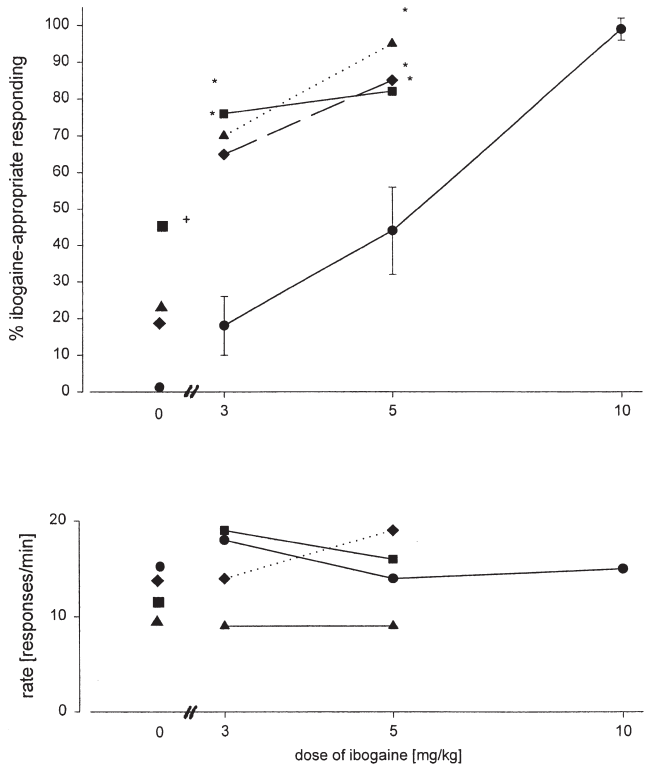

FIG. 3. The effects of ibogaine alone (circles; ± SEM) and in combination with fluoxetine (2.5 mg/kg; squares), venlafaxine (10 mg/kg; triangles), and fluvoxamine (10 mg/kg; diamonds) in rats trained with ibogaine (10 mg/kg) as a discriminative stimulus. The monoamine reuptake inhibitors and ibogaine were injected IP, 90 and 60 min, respectively, before testing. Each point represents the mean of one determination in each of nine subjects. Ordinate: upper panel—mean percentage of responses on the ibogaine-appropriate lever; lower panel—response rate. Abscissa: dose plotted on a log scale. Statistical comparisons are between ibogaine alone and in combination with the reuptake inhibitor, and significant differences are indicated by *. Data points at zero dose are for saline and the reuptake inhibitors given alone. For the zero dose data, statistical comparisons are between saline, a reuptake inhibitor, and the training dose of ibogaine; a significant difference between a reuptake inhibitor and both training conditions is indicated by +. In the interests of clarity of presentation, SEM (8.8) is omitted for the ibogaine dose of 1.5 mg/kg.

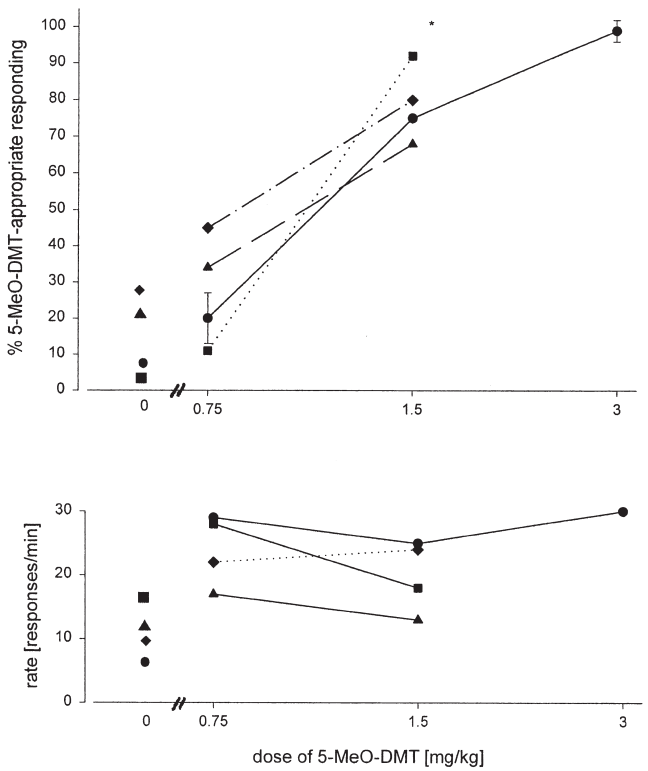

FIG. 4. The effects of 5-MeO-DMT alone (circles; ± SEM) and in combination with fluoxetine (2.5 mg/kg; squares), venlafaxine (10 mg/kg; triangles), and fluvoxamine (diamonds) in rats trained with ibogaine (10 mg/kg) as a discriminative stimulus. The monoamine reuptake inhibitors and ibogaine were injected IP, 90 and 15 min, respectively, before testing. Each point represents the mean of one determination in each of 12 subjects. Ordinate: upper panel—mean percentage of responses on the 5-MeO-DMT–appropriate lever; lower panel—response rate. Abscissa: dose plotted on a log scale. Statistical comparisons are between 5-MeO-DMT alone and in combination with the reuptake inhibitor, and significant differences are indicated by *. Data points at zero dose are for saline and the reuptake inhibitors given alone.

hibitors in its ability to enhance stimulus control by LSD. However, in view of the significant LSD-like effects seen with fluoxetine and venlafaxine when administered alone, the data do not permit a definitive conclusion as to whether the interaction represents potentiation or additivity. Although the statistically significant intermediate level of substitution by fluoxetine is explicable in terms of the relatively high affinity of fluoxetine for 5-HT_2 receptors (19,31,52), it must be noted that fluvoxamine has negligible affinity for 5-HT_2 receptors (19) and, to the extent that data obtained using human brain tissue can be extrapolated to the rat, venlafaxine would be expected to be inactive at 5-HT_2 receptors (9). We are aware of only two previous studies in which fluoxetine was administered to rats trained with LSD as a discriminative stimulus (22,42); both concluded that fluoxetine has no LSD-like effects. However, Simon and Appel (42) used a pretreatment time of 30 min for fluoxetine while maximal inhibition of serotonin reuptake occurs 1–2 h after administration (54). Kuhn et al. (22) reported mean values (n = 12) of LSD-appropriate responding for the saline training condition of 3% (SEM = 2) and for fluoxetine of 20% (SEM = 3); retrospective analysis of their data indicates a statistically significant difference (Student's t-test, $p < 0.001$).

The hypothesis that hallucinogens other than LSD are potentiated by acute pretreatment with monoamine uptake inhibitors was tested using the phenethylamine hallucinogen, (−)-DOM, ibogaine, a hallucinogen of uncertain classification but possessed of serotonergic properties (16,30,44), and the indoleamine hallucinogen, 5-MeO-DMT. The data of Figs. 2–4 suggest potentiation of (−)-DOM and of ibogaine but are equivocal with respect to 5-MeO-DMT in that only fluoxetine yielded a statistically significant enhancement, and that at only one of the two doses of 5-MeO-DMT tested. Comparison of Figs. 1, 2, and 3 with respect to the effects of the uptake inhibitors when given alone presents a picture not amenable to simple interpretation. Thus, fluoxetine yielded significant intermediate results in rats trained both with LSD (Fig. 1) and with ibogaine (Fig. 3), but fluvoxamine was most active in (−)-DOM–trained subjects (Fig. 2). The results of

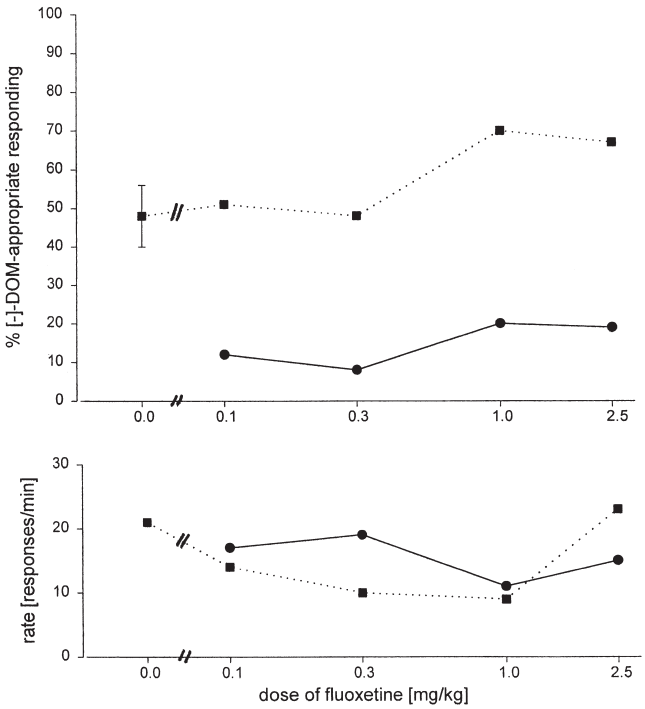

FIG. 5. Dose–response relationship for fluoxetine alone (circles) and in combination with a dose of (−)-DOM of 0.1 mg/kg (squares) in rats trained with (−)-DOM (0.56 mg/kg) as a discriminative stimulus. Each point represents the mean of one determination in each of 10 subjects. The data point at zero dose is for (−)-DOM (0.1 mg/kg) when given alone; SEM is indicated. All other details are as in Fig. 2.

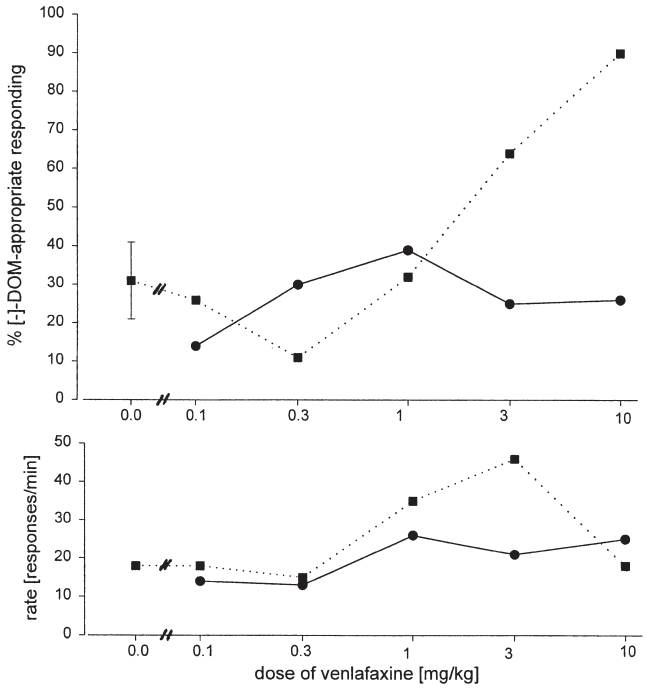

FIG. 6. Dose–response relationship for venlafaxine alone (circles) and in combination with a dose of (−)-DOM of 0.1 mg/kg (squares) in rats trained with (−)-DOM (0.56 mg/kg) as a discriminative stimulus. All other details are as in Figs. 2 and 5.

an examination of a range of doses of each of the reuptake inhibitors in rats trained with (−)-DOM (Figs. 5–7) are, with the exception of the highest dose of venlafaxine, compatible additivity of effects. In this regard, it should be noted that our previous conclusion that fluoxetine potentiates LSD (13) was based on the use of (+)-fluoxetine, a drug no longer available to us, rather than the racemic mixture employed in the present investigations. In that study, (+)-fluoxetine alone elicited no LSD-appropriate responding.

Mechanistic interpretations of the present data must consider both pharmacokinetic and pharmacodynamic factors. As a group, the monoamine reuptake inhibitors interact in a complex fashion with the cytochrome P-450 enzymes (CYPs) and are known to alter the metabolism of a wide variety of drugs (34,36,39,49). In the absence of measurements of brain concentrations of the hallucinogens, a pharmacokinetic interpretation of the observed data cannot be rejected with certainty. However, it is made less likely by two factors. The first is the distinctly different inhibitory profiles of the three reuptake inhibitors with respect to the CYPs. For example, the subtype CYP1A2 is responsible for the metabolism of many psychoactive drugs including caffeine and the tertiary amine tricyclic antidepressants. CYP1A2 is significantly inhibited in its actions by fluvoxamine as indicated by a sixfold increase in the elimination half-life of caffeine (20). In contrast, venlafaxine is devoid of inhibitory effects on CYP1A2 and fluoxetine is of intermediate inhibitory efficacy (36). The second factor that argues against a pharmacokinetic interpretation is the nature of the metabolism of LSD, (−)-DOM, ibogaine, and 5-MeO-DMT. Although we are unaware of any published accounts of the comparative metabolism of these drugs, disparate mechanisms are likely to be involved. Whereas LSD would be expected to undergo N-demethylation and glucuronidization (28), ibogaine is converted via *O*-demethylation to the active metabolite 12-hydroxyibogamine (26), 5-MeO-DMT is subject to N-oxidation (43), and (−)-DOM should be deaminated to the phenylacetone analog (37).

Speculation regarding the pharmacodynamic mechanisms by which monoamine reuptake inhibitors might potentiate the stimulus effects of hallucinogens must include possible effects upon neurotransmission mediated by serotonin, norepinephrine, and dopamine. Although fluoxetine and fluvoxamine are commonly referred to as selective serotonin reuptake inhibitors (SSRIs), animal studies using microdialysis have revealed significant effects upon all three neurotransmitters (33,46). Indeed, Stanford (46) has suggested that the clinical efficacy of fluoxetine may derive from its nonselectivity with respect to monoamine reuptake, and the effects of fluoxetine upon stimulus control by cocaine have been attributed to its actions upon dopamine reuptake (42). On the other hand, the three reuptake inhibitors chosen for the present study differ widely in their potency ratios for blockade of the reuptake of serotonin and norepinephrine. The respective in vitro values for fluvoxamine, fluoxetine, and venlafaxine are approximately 170, 35, and 4 (5,10,47,48); hence, the designation of venlafaxine as a selective serotonin/norepinephrine reuptake inhibitor [SSNRI; (27)]. These widely differing potency ratios, coupled with the data of Figs. 1, 2, and 3 showing an augmentation of the stimulus effects of LSD, (−)-DOM, and ibogaine by all three of the reuptake inhibitors, argue against an action mediated by norepinephrine.

The clinical significance of the present data is uncertain. To the extent that rat discrimination data reflect human sub-

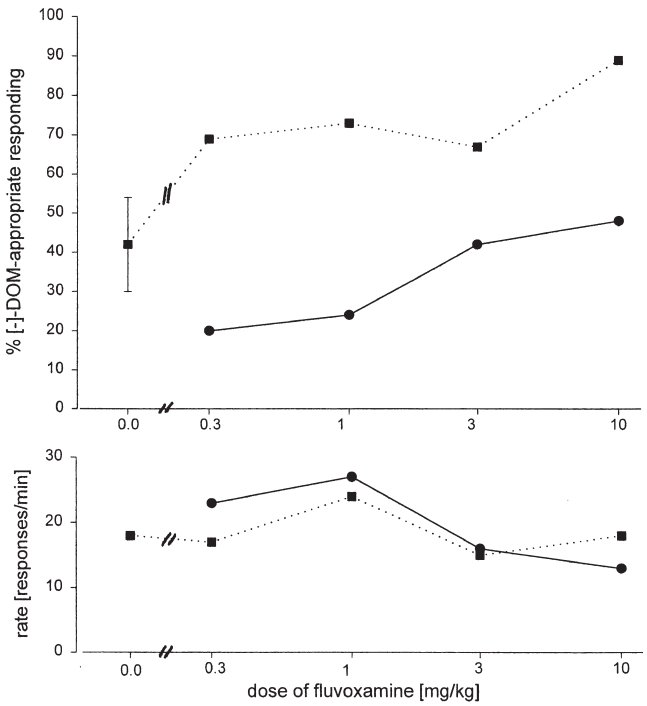

FIG. 7. Dose–response relationship for fluvoxamine alone (circles) and in combination with a dose of (−)-DOM of 0.1 mg/kg (squares) in rats trained with (−)-DOM (0.56 mg/kg) as a discriminative stimulus. All other details are as in Figs. 2 and 5.

jective effects (2,3,7), one would predict augmentation by the monoamine reuptake inhibitors of the hallucinogenic effects of LSD and DOM. This prediction is in keeping with limited human data cited earlier (6,25), and with reports of the induction of mania by SSRIs (11,18) and of fluoxetine-induced visual hallucinations in demented patients (29). In terms of the use of ibogaine as an antiaddiction medication (40), combination with a reuptake inhibitor might prove beneficial. However, in all such speculation, a clear distinction must be drawn between the acute effects of monoamine reuptake inhibitors on hallucinogens as shown in the present study, and those that might arise following chronic administration. In a survey conducted by Bonson et al. (6), 28 of 32 subjects who had taken an SSRI for 3 weeks or longer reported a decrease in the subjective effects of LSD. With respect to their antidepressant effects, a lag in onset of therapeutic effects with chronic use is generally attributed to the time required for desensitization of presynaptic autoreceptors of the 5-HT_{1A} subtype (1). This hypothesis has gained credence with the demonstration that antagonists of the 5-HT_{1A} receptor hasten the onset of the antidepressant effects of the SSRIs (4,32).

In summary, the present data confirm our previous observation of the augmentation of the stimulus effects of LSD by fluoxetine (13) and extend this observation to include other hallucinogens and other monoamine reuptake inhibitors. The mechanisms by which these interactions arise and possible differential effects of acute and chronic treatment remain to be established.

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