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The effects of acute and subchronic treatment with fluoxetine and citalopram on stimulus control by DOM

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Abstract

Previous reports from our laboratory have provided evidence that acute, i.e., concurrent, treatment with selective serotonin reuptake inhibitors (SSRIs) augments the stimulus effects of indoleamine and phenethylamine hallucinogens in the rat. In the present investigation, the acute effects of fluoxetine and citalopram on stimulus control induced by (−)-2,5-dimethoxy-4-methylamphetamine (DOM) were compared with those following subchronic, i.e., 10-day treatment with the SSRIs. Stimulus control was established using DOM (0.56 mg/kg; 75-min pretreatment time) in a group of 11 rats. A two-lever, fixed ratio 10, positively reinforced task with saline controls was employed. The effects of a range of doses of DOM when given alone were compared with those following both acute and subchronic pretreatment with fluoxetine and citalopram in combination with DOM. It was found that acute administration of fluoxetine and citalopram potentiated the stimulus effects of DOM. Furthermore, it was observed that the degree of potentiation was not diminished by treatment with either fluoxetine or citalopram for a period of 10 days. It is concluded that whatever adaptive changes may take place in response to a 10-day period of treatment with either citalopram or fluoxetine, these adaptations are independent of the mechanisms responsible for the potentiation of the stimulus effects of DOM by the SSRIs.
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Keywords: Drug discrimination; Rat; SSRIs; Hallucinogens; DOM; Fluoxetine; Citalopram

1. Introduction

Previous reports from our laboratory have provided evidence that selective serotonin reuptake inhibitors (SSRIs) including fluoxetine, fluvoxamine and venlafaxine augment the stimulus effects of indoleamine and phenethylamine hallucinogens in the rat (Fiorella et al., 1996; Winter et al., 1999a). Mechanistic interpretations of these observations are made difficult by the fact that to varying degrees SSRIs (a) may inhibit the activity of drug-metabolizing enzymes (Greenblatt et al., 1999; Preskorn, 1997; Richelson, 1997) and (b) partially substitute for the phenethylamine hallucinogen, 2,5-dimethoxy-4-methylamphetamine (Winter et al., 1999b). The latter effect appears to be a consequence of activity at serotonergic receptors of the 5-HT_{2A} and 5-HT_{2C} subtypes (Winter et al., 1999c), the same receptors believed to mediate DOM-induced stimulus control (Fiorella et al., 1995a; Glennon et al., 1984; Winter et al., 1999c). Furthermore, and despite their name, SSRIs as a class tend to be nonselective in blocking monoamine reuptake. Indeed, it has been proposed that the therapeutic actions of fluoxetine, the prototypic SSRI, are due to combined actions at the serotonin, norepinephrine and dopamine transporters (Stanford, 1996), and the antidepressant effects of venlafaxine are explicitly attributed to combined actions at the serotonin and norepinephrine transporters (Briley, 1998; Burnett and Dinan, 1998; Harvey et al., 2000). However, citalopram is a clinically effective reuptake inhibitor whose direct actions appear to be confined to the serotonin transporter (Christensen et al., 1977; Hyttel, 1982; Millan et al., 1999a, 2000) and which, in comparison with fluoxetine, interacts minimally with metabolic enzymes (Richelson, 1997; Jeppesen et al., 1996; Hiemke and Hartter, 2000). Furthermore, studies in our laboratory indicate that citalopram (a) is without DOM-like stimulus effects, (b) does not alter brain levels of DOM and

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(c) produces true potentiation of the stimulus effects of DOM (Eckler et al., 2002).

It is generally assumed that SSRIs exert their antidepressant effects by producing an increase in serotonergic neurotransmission (Popik, 1999). However, following the observation in microdialysis studies that serotonin release following SSRIs is increased in animals treated with an antagonist at 5-HT_{1A} receptors (Invernizzi et al., 1992), it was suggested that the commonly observed delay in onset of their antidepressant effects (Baumann, 1992) is due to activation of somatodendritic 5-HT_{1A} autoreceptors, which decrease postsynaptic release of 5-HT (Artigas, 1993; Artigas et al., 1994; Hjorth, 1993). According to this formulation, it is only after desensitization of the somatodendritic 5-HT_{1A} autoreceptors occurs that the antidepressant effect emerges. Clinical support for this idea comes from studies in which an accelerated therapeutic effect was observed following the combination of an SSRI with pindolol, a drug that antagonizes 5-HT_{1A} receptors (Artigas et al., 1994, 1996; Blier and Bergeron, 1995). In addition, consideration must be given to adaptive changes involving other serotonergic receptors especially that of the 5-HT_{2C} receptor subtype (Fiorella et al., 1995b).

If adaptive mechanisms similar to those observed for the 5-HT_{1A} receptor and other serotonergic receptor subtypes are active in the interaction between SSRIs and the stimulus effects of DOM, we would predict a difference in the interaction following subchronic as compared with acute treatment. In the present investigation, we have tested the hypothesis that augmentation of the stimulus effects of DOM by fluoxetine and citalopram is diminished following 10-day treatment with the latter drugs.

2. Methods

2.1. Animals

A group of 11 male Fischer-344 rats was obtained from Charles River Breeding Laboratories (Wilmington, MA) at an age of approximately 6 weeks. They were housed in pairs and allowed free access to water in the home cage. Room lighting was on a 12-h light–dark cycle beginning at 6 a.m. All handling and testing occurred during the light phase. Standard rat chow was provided immediately following training sessions. Caloric intake was controlled so as to maintain adult body weights of approximately 250 g. Caloric control has been shown to lengthen life span and decrease the incidence of a variety of pathologies in Fischer 344 rats (Keenan et al., 1994). All animals used were maintained in accordance with the National Institutes of Health Guide for Care and Use of Laboratory Animals (Publication No. 85-23, revised 1985). All experimental protocols were approved by the Institutional Animal Care and Use Committee of the University at Buffalo.

2.2. Apparatus

Three small animal test chambers (Coulbourn Instruments model E 10-10) were used for all experiments. These were housed in larger light-proof, sound-insulated boxes, which 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, which delivered 0.1 ml of sweetened condensed milk diluted, 2:1 with tap water. Sessions were managed by a microcomputer using operant control software (Coulbourn Instruments D91-12, version 4.0).

2.3. 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. Seventy-five minutes before each 10-min training session, subjects were injected intraperitoneally with either saline or DOM (0.6 mg/kg). Following the administration of DOM, every 10th response on the DOM-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 DOM-appropriate lever. During discrimination training, DOM and saline were alternated on a daily basis. DOM-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.

After stimulus control with DOM was well established, tests of generalization were conducted once per week in each animal. Tests were balanced between subjects trained on the previous day with saline and DOM, 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 DOM-appropriate lever. Response rate was calculated for each session by dividing total number of responses emitted prior to lever selection, that is, prior to the emission of 10 responses on either lever, by elapsed time.

Tests of the interaction between DOM and the acute administration of either fluoxetine or citalopram were conducted as previously described (Fiorella et al., 1996; Winter et al., 1999a). The dose–effect relationship for DOM alone was established with doses in descending order, i.e., 0.3 and 0.1 mg/kg of DOM, and the results of training days at a dose of 0.6 mg/kg established the point at that dose. The dose–effect relationship for DOM alone was determined four times, i.e., prior to each series of tests in which DOM was

tested in combination with an SSRI. For acute interactions, the SSRI was administered 15 min before a range of doses of DOM and stimulus control was measured 75 min later. As was noted above, tests were conducted once per week with doses in descending order, i.e., 0.6, 0.3 and 0.1 mg/kg of DOM. Tests of the effects of subchronic treatment with either fluoxetine or citalopram on stimulus control by DOM were conducted in an identical fashion with the exception that, during a 10-day period of SSRI administration, no discrimination training took place and each subject received either fluoxetine (2.5 mg/kg/day) or citalopram (3.0 mg/kg/day). On the 11th day, all subjects were tested with either fluoxetine (2.5 mg/kg) or citalopram (1.0 mg/kg) followed by DOM. The order of experiments was as follows: acute fluoxetine, acute citalopram, subchronic fluoxetine and subchronic citalopram. A 1-week wash-out period followed each series with acute fluoxetine or citalopram and a 2-week period without any SSRI treatment followed subchronic administration of fluoxetine. Following training to criterion performance with DOM, a total of 40 weeks was devoted to the tests described. Control performance remained stable during that period and, for purposes of clarity of presentation, the two dose–effect relationships obtained prior to treatment with fluoxetine were combined as were those prior to treatment with citalopram.

2.4. Statistical analysis

The statistical significance of the interaction between a range of doses of DOM and either fluoxetine or citalopram was determined using repeated measures ANOVA with dose of DOM and SSRI treatment as factors. Subsequent multiple comparisons were made by the method of Student–Newman–Keuls. Differences were considered to be statistically

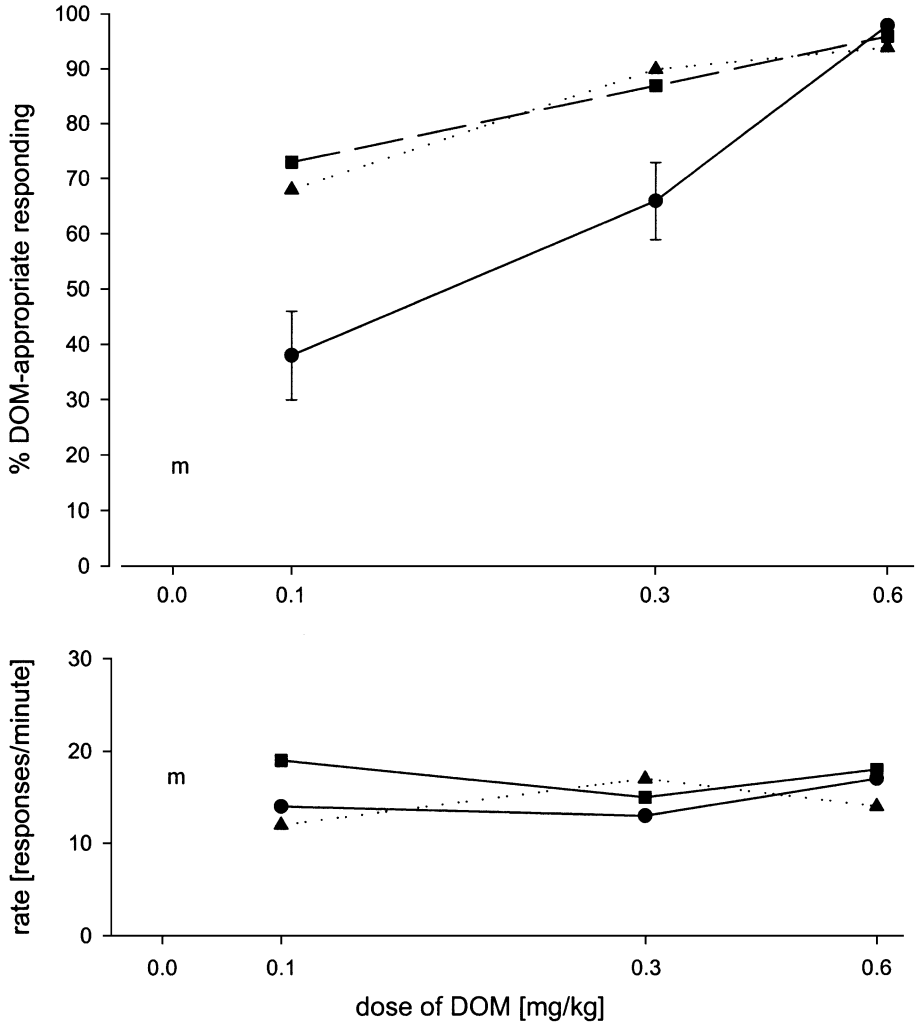

Fig. 1. Dose–response relationship for DOM alone and in combination with fluoxetine. Circles represent the effects of DOM alone in rats trained with DOM as a discriminative stimulus (0.6 mg/kg). Squares represent the effects of DOM in combination with fluoxetine (2.5 mg/kg). Triangles represent the effects of DOM in combination with fluoxetine (2.5 mg/kg) following treatment with fluoxetine for 10 days at a dose of 2.5 mg/kg. With the exception of the training dose of DOM, all points represent the mean of one determination in each of 11 rats. Standard errors of the mean are indicated for DOM alone. The point at a dose of 0.0 is for fluoxetine alone. Ordinate: upper panel: percent DOM-appropriate responding; lower panel: rate expressed as responses per minute; abscissa: dose plotted on a log scale.

significant if the probability of their having arisen by chance was $<.05$. All analyses were conducted using SigmaStat for Windows (Jandel Scientific Software, San Rafael, CA). Control data for the three treatment conditions (none, acute and subchronic) 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.

2.5. Drugs

The following drugs were generously provided by the organizations indicated: (−)-DOM HCl (National Institute on Drug Abuse, Rockville, MD, USA), (±)-fluoxetine HCl (Lilly Research Laboratories, Indianapolis, IN, USA), citalopram hydrobromide (H. Lundbeck, Copenhagen, Denmark). All drugs were dissolved in 0.9% saline solution and injected in a volume of 1 ml/kg body weight. The intraperitoneal route was employed for all drugs.

3. Results

It was previously reported that acute treatment with fluoxetine enhances the stimulus effects of DOM (Winter et al., 1999a). The data shown in Fig. 1 replicate that finding. Also presented in Fig. 1 is the observation that the effects of fluoxetine on DOM-induced stimulus control are not diminished following a 10-day period of treatment with fluoxetine. When applied to doses of DOM of 0.1 and 0.3 mg/kg, ANOVA revealed a difference in DOM-appropriate responding in the three treatment groups [$F(10,2)=12.72$, $P<.001$]. Subsequent pairwise multiple comparisons indicated a significant difference ($P<.05$) between the effects of DOM

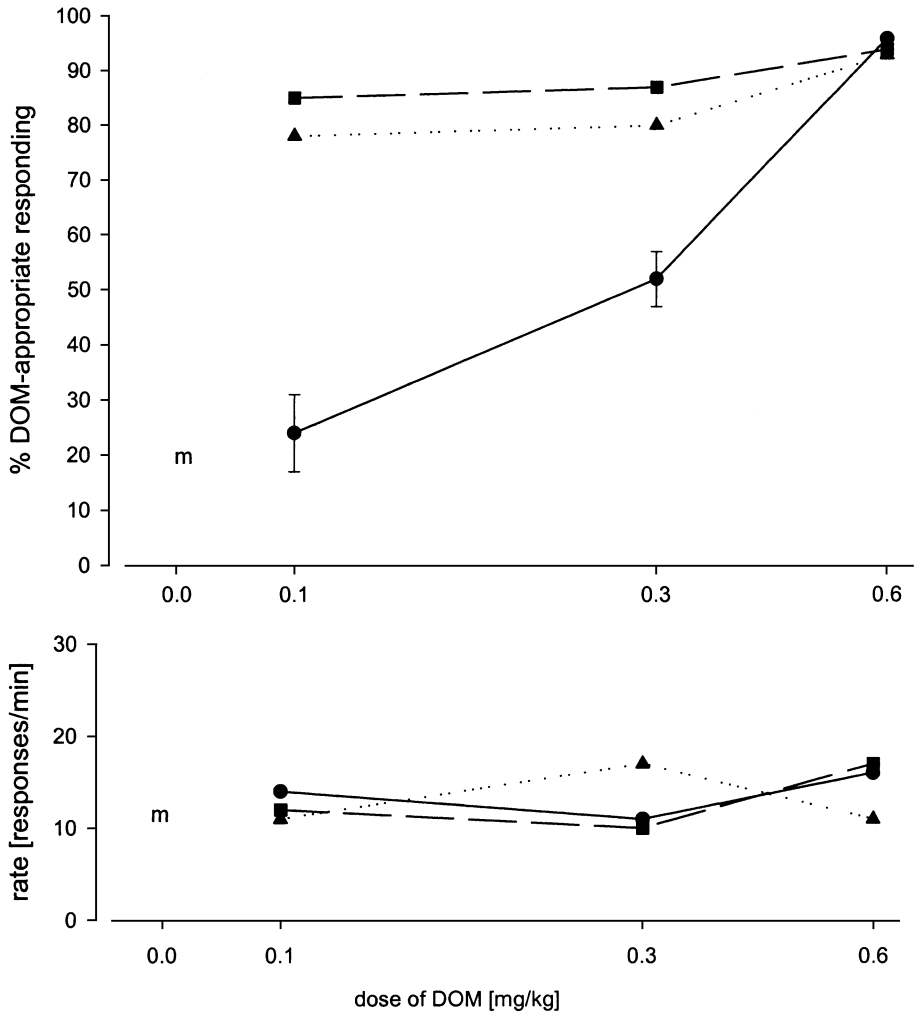

Fig. 2. Dose–response relationship for DOM alone and in combination with citalopram. Circles represent the effects of DOM alone in rats trained with DOM as a discriminative stimulus (0.6 mg/kg). Squares represent the effects of DOM in combination with citalopram (1.0 mg/kg). Triangles represent the effects of DOM in combination with citalopram (1.0 mg/kg) following treatment with citalopram for 10 days at a dose of 3.0 mg/kg/day. With the exception of the training dose of DOM, all points represent the mean of one determination in each of 11 rats. Standard errors of the mean are indicated for DOM alone. The point at a dose of 0.0 is for citalopram alone. Ordinate: upper panel: percent DOM-appropriate responding; lower panel: rate expressed as responses per minute; abscissa: dose plotted on a log scale.

alone and following treatment with fluoxetine given either acutely or subchronically. However, there was no significant difference between the effects of acute and subchronic treatment with fluoxetine on stimulus control by DOM. In addition, there was no significant interaction between dose of DOM and treatment with fluoxetine.

In acute studies of citalopram, we earlier reported potentiation of the stimulus effects of DOM (Eckler et al., 2002) and that finding is replicated in Fig. 2. In addition, the data of Fig. 2 indicate that a 10-day period of treatment with citalopram does not diminish the interaction of DOM with citalopram. Application of ANOVA to doses of DOM of 0.1 and 0.3 mg/kg yielded a significant difference in the three treatment groups [$F(10,2)=36.863$, $P<.001$]. However, as was the case for fluoxetine, subsequent pairwise multiple comparisons indicate that the results of acute and subchronic treatment with citalopram do not differ from one another but that each is significantly different from DOM alone ($P<.05$). No significant interaction was observed between treatment with citalopram and dose of DOM.

4. Discussion

The data shown in Figs. 1 and 2 do not support the hypothesis that augmentation of the stimulus effects of DOM by SSRIs, which is seen after acute treatment is diminished or absent following 10-day treatment. This observation is not without precedent. Thus, Lee and Kornetsky (1998) found no tolerance to the effects of fluoxetine on rewarding brain stimulation following 21 days of treatment with the drug. Furthermore, while substantial evidence indicates that diminished sensitivity of 5-HT_{1A} receptors occurs following repeated administration of SSRIs (Blier et al., 1987; Le Poul et al., 1995), these adaptive changes may be less than complete (Auerbach and Hjorth, 1995; Hjorth and Auerbach, 1999; Dremencov et al., 2000), differential effects may be seen depending upon brain region (Kreiss and Lucki, 1997) and pre- or postsynaptic localization (Davidson and Stamford, 1998; de Montigny et al., 1990; Haddjeri et al., 1999) and contemporaneous compensatory changes may occur at other serotonergic receptor subtypes (Massou et al., 1997; Laakso et al., 1996; Li et al., 1993) or at receptors for other neurotransmitters (Maj and Rogoz, 1999). Of particular interest in this regard are the observations by Cremers et al. (2000) following continuous administration of citalopram to rats via osmotic minipumps for 15 days. At the end of that period, they observed a decreased response to challenge by 8-OH-DPAT thus indicating a desensitization of the 5-HT_{1A} autoreceptor, but there was no augmentation of the effect of citalopram on 5-HT levels.

In any assessment of the chronic effects of drugs, the duration of treatment is an important variable. With respect to 5-HT_{1A} autoreceptors, previous studies have found that functional desensitization is electrophysiologically demonstrable within 3 days (Blier et al., 1987; Le Poul et al., 1995) and treatment for 10–14 days is adequate to induce adaptive changes in brain levels of serotonin as measured by in vivo microdialysis (Invernizzi et al., 1992; Dawson et al., 2000). Of particular relevance to the present investigation, de Montigny et al. (1990) observed a reduced effect of LSD on firing rate of neurons of the nucleus raphe dorsalis following 14-day treatment with citalopram. Nonetheless, it may be argued that administration of fluoxetine and citalopram for 10 days in the present investigation is of too short a duration to permit complete adaptation to their effects and that a longer period of treatment would have revealed a diminished effect of these drugs on stimulus control by DOM. In this regard, it is customary in assessing the effects of chronic treatment upon drug-induced stimulus control to suspend training during the period of treatment (Young, 1990). In this way, one eliminates the possibility that, during the period of drug administration, an altered discrimination based upon a modified property of the drug is learned. While the 10-day period employed in the present study should be adequate to reveal adaptive changes, still longer periods appear feasible. Thus, for example, suspension of training with morphine for 14 days does not alter dose–response functions relative to those established during sustained training (Sannerud and Young, 1987; Young et al., 1992) and, in our laboratory, stimulus control by DOM was found to be stable for 21 days without concomitant training (Doat et al., 2002). An additional potential confounder relates to the duration of action of fluoxetine and citalopram. The former drug and its active metabolite, norfluoxetine, in particular, are characterized by very long half-lives in human subjects (Rosenbaum et al., 1998). However, in the rat, the half-lives are 5–8 and 10–16 h for fluoxetine and norfluoxetine, respectively (Marona-Lewicka and Nichols, 1998). Relative to fluoxetine, citalopram is short-acting with a half-life in humans of about 35 h, while, in the rat, all effects on serotonin levels in the brain are absent 20 h after either acute or chronic (14-day) treatment with the drug (Arborelius et al., 1996). Thus, it would appear that the washout periods employed in the present investigation are adequate to allow for elimination of the SSRIs between individual tests.

In seeking the mechanisms by which SSRIs, administered either acutely or chronically, potentiate the stimulus effects of DOM, guidance may be sought in a consideration of the stimulus properties of the SSRIs themselves. As a class, antidepressant drugs have proved difficult to train but recent successes have been reported with the SSRIs, sertraline and citalopram (Marona-Lewicka and Nichols, 1998) and LY233708 (Wolf and Leander, 1999). With respect to citalopram, Millan et al. (1999a) found that stimulus control was selectively correlated with elevated extracellular levels of serotonin. Subsequent investigations suggested that stimulus control by citalopram is mediated in large measure by 5-HT_{2C} receptors (Millan et al., 1999b) and that its stimulus effects are perhaps unrelated to its antidepressant properties

(Dekeyne et al., 2001). It is of interest that subchronic treatment with fluoxetine has been shown to augment neuroendocrine responses believed to be mediated by 5-HT_{2C} receptors (Li et al., 1993) and both fluoxetine and citalopram upregulate 5-HT_{2C} receptors in rat choroid plexus (Laakso et al., 1996). We have earlier presented evidence that the stimulus effects of DOM are modulated by activity at 5-HT_{2C} receptors (Fiorella et al., 1996). Reports of the effects of chronic treatment with SSRIs on the serotonin transporter and upon the 5-HT_{2A} receptor are inconsistent (for reviews, see Durand et al., 1999; Zanardi et al., 2001).

The clinical significance of the present data is uncertain. To the extent that drug-induced stimulus control in the rat reflects human subjective effects (Brauer et al., 1997; Sanger et al., 1994; Schuster and Johanson, 1988), we would predict an augmentation of the actions of DOM in individuals who concurrently ingest an SSRI either acutely or chronically. Although we are unaware of any studies which have explicitly examined this phenomenon in human subjects, anecdotal reports obtained by Bonson and Murphy (1996) indicate an enhancement of the subjective effects of LSD in persons chronically treated with tricyclic antidepressants and Bonson et al. (1996) describe a person who experienced an enhanced response to LSD following the ingestion of fluoxetine for 1 week. On the other hand, the latter study found that the majority of those surveyed (28 of 32) experienced a diminution of the effects of LSD after the ingestion of an SSRI for more than 3 weeks.

In summary, the present data confirm our previous reports of the augmentation of the stimulus effects of DOM by the acute co-administration of fluoxetine and citalopram. Furthermore, we observe no diminution of the effects of the SSRIs on DOM-induced stimulus control following a 10-day period of treatment with either fluoxetine or citalopram. The mechanisms by which these interactions arise and the possible consequences of even longer periods of treatment remain to be established.

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