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ARTICLE

Partial generalization of (−)DOM to fluvoxamine in the rat: implications for SSRI-induced mania and psychosis

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Abstract

Recent reports have implicated selective serotonin-reuptake inhibitors in the induction of psychosis and mania when SSRIs are given in combination with neuroleptics. We hypothesize that the partial substitution of fluvoxamine for the hallucinogen, (−)DOM, in the rat provides evidence for a 5-HT_2-mediated effect of fluvoxamine which may in turn account for the adverse effects observed in humans. Male Fischer-344 rats were trained with (−)DOM (0.56 mg/kg) as a discriminative stimulus using standard operant procedures. Tests of generalization were then conducted with fluvoxamine either alone or in combination with the 5-HT_{1A} antagonist, WAY-100635, the 5-HT_2 antagonist, pirenperone, and the neuroleptics, fluphenazine, chlorpromazine, thioridazine, loxapine, risperidone, and clozapine. In rats trained with (−)DOM, fluvoxamine at a dose of 20 mg/kg yielded a maximum 58% (−)DOM-appropriate response. This partial generalization was potentiated by treatment with WAY-100635 and antagonized by pirenperone, loxapine, risperidone, and clozapine. The present data are compatible with a 5-HT_2-mediated effect of fluvoxamine which may play a role in SSRI-induced mania and psychosis. It is predicted by the results of this study that the probability of these adverse effects will be increased by the concurrent use of antagonists at 5-HT_{1A} receptors and decreased by neuroleptics with antagonistic activity at 5-HT_2 receptors.

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Introduction

It has long been recognized that monamine oxidase inhibitors and heterocyclic antidepressants are sometimes associated with the induction of mania and cycle acceleration in patients with bipolar disorder (for review, see Altshuler et al., 1995). In part because of a more favourable profile of adverse effects, fluoxetine, the prototypic selective serotonin-reuptake inhibitor (SSRI), and the drugs which followed it into clinical use have revolutionized the treatment of depression (Anderson and Tomenson, 1994; Andreason and Black, 1995; Pincus et al., 1998). However, reports of fluoxetine-induced mania have appeared from time to time (see Feder, 1990; Howland, 1996; and references therein) and, in a recent double-blind, placebo-controlled study of fluoxetine in children and adolescents, manic symptoms developed in 6% of the fluoxetine-treated patients (Emslie et al., 1997). Furthermore, Bowers and his colleagues (1998a, b) have recently drawn attention to the fact that a similar phenomenon may occur in persons treated with SSRIs in combination with neuroleptics. In a group of patients previously diagnosed as having a psychotic disorder, they found that 23 of 207 consecutive psychiatric admissions were due to antidepressant-induced psychosis and mania. In 19 of the 23 patients, an SSRI was the sole antidepressant in use at the time of admission (Bowers M, personal communication: August 1998).

Because of the extensive evidence which indicates that indoleamine and phenethylamine hallucinogens act via serotonergic systems (for review, see Winter et al., In Press c) and the high probability that SSRIs will be used concurrently with hallucinogens (Bonson and Murphy, 1996; Bonson et al., 1996), we earlier examined the interaction of fluoxetine with the stimulus effects of lysergic acid diethylamide (LSD) in the rat. Potentiation of LSD-induced stimulus control was observed (Fiorella et

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al., 1996). We later extended this finding to include the antidepressants fluvoxamine and venlafaxine in combination with other hallucinogens including the phenethylamine, (−)DOM (2,5-dimethoxy-4-methylamphetamine; Winter et al., In Press a). In the course of these investigations, we observed that, when given alone, fluoxetine, venlafaxine, and fluvoxamine partially substituted for (−)DOM; fluvoxamine was the most active in this regard and for this reason was chosen for further investigation.

In the present investigation, we tested the hypothesis that the partial substitution of fluvoxamine for (−)DOM in rats trained with the latter drug is due to agonistic effects at serotonergic receptors of the 5-HT_2 type. Serotonergic receptors have long been implicated in actions of hallucinogens such as LSD and DOM (Glennon, 1990; Jakab and Goldman-Rakic, 1998; Winter, 1978; Wooley and Shaw, 1954) and the stimulus effects of both drugs are blocked by the 5-HT_2 antagonist, pirenperone (Colpaert et al., 1982; Glennon et al., 1983). For these reasons, we examined in the present study the antagonistic efficacies vs. fluvoxamine of pirenperone and of several antipsychotic drugs which we previously had shown to have varying abilities to block (−)DOM-induced stimulus control (Fiorella et al., 1995c).

Methods

Animals

Male Fischer-344 rats were obtained from Charles River Breeding Laboratories, Inc. (Wilmington, MA, USA) at an age of approx. 6 wk. They were housed in pairs, subjected to a 12 h light–dark cycle, and allowed free access to water in the home cage. All handling and testing occurred during daytime hours. Standard rat feed was provided immediately following training sessions. Caloric intake was controlled so as to maintain adult body weights of approx. 300 g. Animals used in these studies were maintained in accordance with the 'Guide for Care and Use of Laboratory Animals' of the Institute of Laboratory Animals Resources, National Research Council.

Apparatus

Six small animal test chambers (Coulbourne Instruments model E10–10) 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. Centred 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 (Coulbourne Instruments D91-12, version 4.0).

Procedure

Thirty rats were trained to discriminate (−)DOM (0.56 mg/kg; i.p. injection) from saline in a two-lever choice task. We used a 75 min pretreatment time on the basis of our previous study of the time-course of (−)DOM (Fiorella et al., 1995a). A fixed-ratio 10 (FR10) schedule of reinforcement was used. Stimulus control with (−)DOM was assumed to be present when, in five consecutive sessions, response choice was at least 83% correct, i.e. no more than two incorrect responses were emitted prior to completion of 10 responses on the correct lever. All animals trained reached criterion performance after a mean of 36 sessions (range = 27–56). Tests of generalization and of antagonism were then conducted once per week for each animal as long as the performance during the remainder of the week did not fall below the criterion level of an 83% correct response. Stimulus control was maintained over the course of the experiments with the training conditions yielding a mean of 98% (DOM) and 3% (saline) drug-appropriate response, 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% DOM-appropriate and is significantly different from both training conditions. Due to variations in weekly performance, not all animals received the same number of treatments. However, all data-points shown in the figures represent independent measurements, i.e. a given test was not repeated in any of the subjects.

Data analysis

The degree of generalization of (−)DOM to fluvoxamine was assessed by individual applications of a repeated measures analysis of variance (ANOVA) of the results following fluvoxamine and both training conditions. Subsequent multiple comparisons were made by the method of Student–Newman–Keuls for each dose of fluvoxamine tested. The statistical significance of the interactions between fluvoxamine and either pirenperone

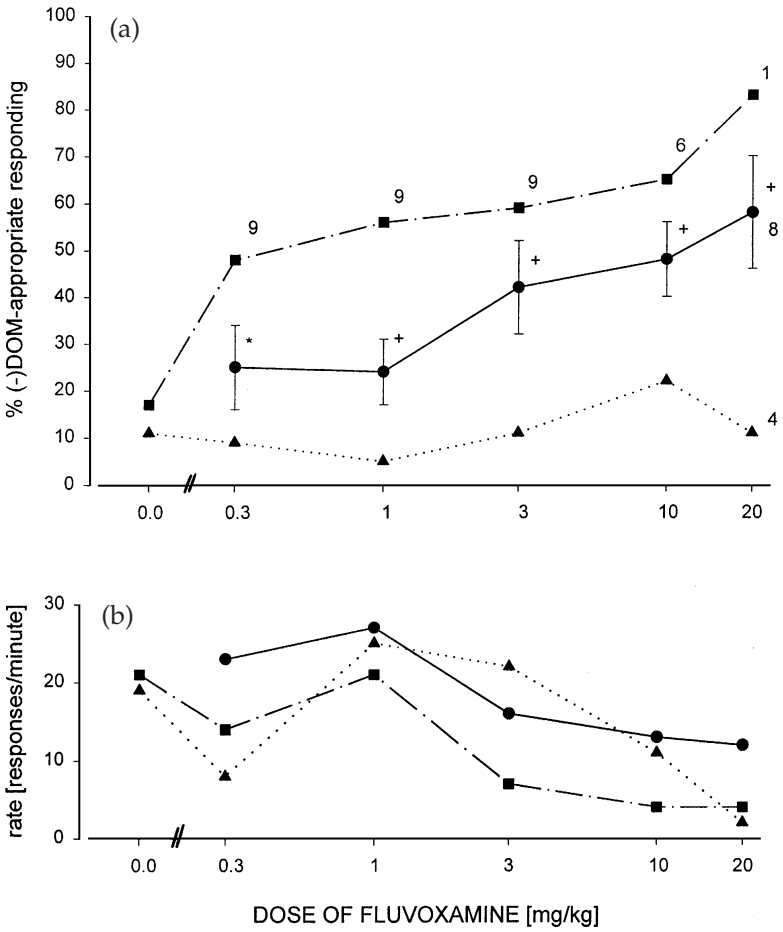

Figure 1. The effects of fluvoxamine alone (●; ±S.E.M.; 90 min pretreatment time) and in combination with WAY-100635 (■; 0.3 mg/kg; 30 min pretreatment time) and with pirenperone (▲; 0.16 mg/kg; 60 min pretreatment time) in rats trained with (−)DOM (0.56 mg/kg; 75 min pretreatment time) as a discriminative stimulus. For the dose–response relationship for fluvoxamine alone, comparisons are with the training dose of (−)DOM; *, significantly different from (−)DOM; +, significantly different from both training conditions. The values given at the zero dose-point are for WAY-100635 and pirenperone when given alone. For fluvoxamine alone, each point represents the mean of two determinations in each of 10 subjects. For the combination of fluvoxamine with either pirenperone or WAY-100635, each point represents the mean of one determination in each of 10 subjects. If all subjects did not complete the test session, a number adjacent to a data-point indicates those which did complete the session. (a) Mean percentage of responses on the (−)DOM-appropriate lever. (b) Response rate expressed as responses per minute.

or WAY-100635 was determined using two-way ANOVA with treatment and dose level as factors. In tests of antagonism of the stimulus effects of fluvoxamine by antipsychotic drugs, significance was assessed by individual applications of Student's *t* test for each dose of antagonist tested. 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, USA). 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

Risperidone, clozapine, loxapine succinate, thioridazine HCl, and fluphenazine 2 HCl were purchased from Research Biochemicals International (Natick, MA, USA). The following drugs were generously provided by the organizations indicated: (−)DOM HCl (National Institute on Drug Abuse, USA), fluvoxamine maleate (Solvay Duphar BV, Weesp, The Netherlands), WAY-100635 (Wyeth-Ayerst Research, Princeton, NJ, USA), and

pirenperone (Janssen Pharmaceutica, Beerse, Belgium). Risperidone and clozapine were dissolved in a few drops of an 8.5% solution of lactic acid and diluted with water. All other drugs were dissolved in 0.9% saline solution. Injection volumes were 1 ml/kg body weight. The i.p. route was employed for all drugs with the exception of WAY-100635 which was injected s.c. (Forster et al., 1995).

Results

(−)DOM elicited a greater than 98% drug-appropriate response during training sessions conducted throughout the course of this study. In contrast, less than 3% drug-appropriate response was observed in training sessions which were preceded by saline treatment. Response rates were not significantly different under the two training conditions with rates of 28.4 and 29.8 responses per minute in (−)DOM and saline training sessions, respectively.

When rats were tested with a range of doses of fluvoxamine (Figure 1), a rather flat dose–response relationship resulted. A maximum 58% (−)DOM-appropriate response was observed at the highest dose tested (20 mg/kg) but at this dose the response rate decreased to 52% of control values and not all subjects completed the test sessions. At doses of 1, 3, 10 and 20 mg/kg of fluvoxamine, an intermediate degree of generalization of (−)DOM to fluvoxamine was observed, i.e. the percentage of DOM-appropriate response was significantly different from both training conditions. At all doses of fluvoxamine tested, the combination of pirenperone and fluvoxamine yielded less (−)DOM-appropriate response than did fluvoxamine alone. The results of a two-way ANOVA for the comparison of fluvoxamine alone with the combination of fluvoxamine and pirenperone indicate that pirenperone diminishes the percentage of (−)DOM-appropriate response induced by fluvoxamine [$F(1,90) = 11.54$; $p < 0.002$]. In contrast with the antagonism of the stimulus effects of fluvoxamine by pirenperone, the rate of suppression by fluvoxamine

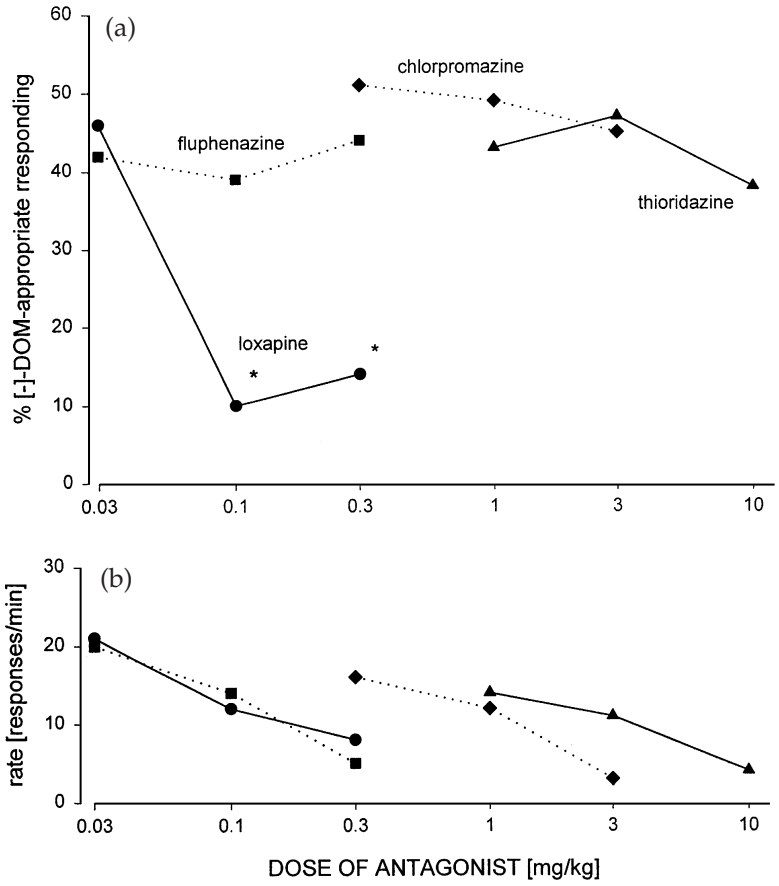

Figure 2. The dose–response relationships for fluphenazine (■), loxapine (●), chlorpromazine (◆), and thioridazine (▲) in combination with a dose of 3 mg/kg of fluvoxamine (90 min pretreatment time) in rats trained with (−)DOM as a discriminative stimulus. A pretreatment time of 60 min was used for all of the antipsychotic drugs. Statistical comparisons are between fluvoxamine alone and in combination with an antipsychotic drug; $^{*}p < 0.05$. Other details are as in Figure 1.

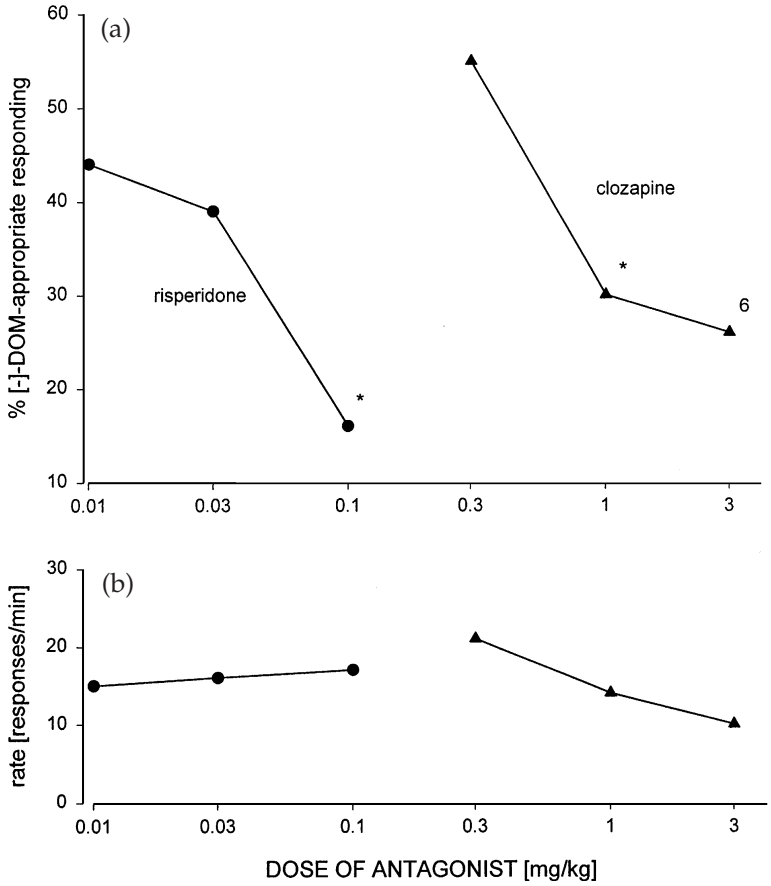

Figure 3. The dose–response relationships for risperidone (●) and for clozapine (▲) administered in combination with a dose of 3 mg/kg of fluvoxamine (90 min pretreatment time) in rats trained with (−)DOM as a discriminative stimulus. Other details are as in Figures 1 and 2.

was not diminished; indeed, at the highest dose of fluvoxamine tested, the response rate was further suppressed by the addition of pirenperone.

In contrast with the effects of pirenperone on fluvoxamine, it is seen in Figure 1 that WAY-100635 in combination with fluvoxamine results in an increase in (−)DOM-appropriate response. Across all doses, a two-way ANOVA revealed a significant increase in (−)DOM-appropriate response following the combination of fluvoxamine and WAY-100635 compared with fluvoxamine alone [$F(1,80) = 4.16$; $p < 0.05$]. For doses of fluvoxamine of 3 mg/kg and higher, response rates were further suppressed by WAY-100635 and the number of subjects able to complete the test sessions declined in a dose-related fashion.

To test the possible antagonistic effects of neuroleptics, a range of doses of each was given in combination with a fixed dose (3 mg/kg) of fluvoxamine. This dose was chosen because it produced a significant degree of substitution when given alone while permitting all of the animals to complete the test sessions (Figure 1). Of the neuroleptics tested, significant antagonism of fluvoxamine-induced (−)DOM-appropriate response was seen with loxapine (Figure 2), risperidone, and clozapine (Figure 3). Response rates were diminished by all of the neuroleptics with the exception of loxapine.

Discussion

The results of the present study provide further evidence that fluvoxamine may partially substitute for the stimulus effects of (−)DOM in rats trained with the latter drug (Winter et al., In Press a). Furthermore, the fact that fluvoxamine's partial substitution for (−)DOM is antagonized by pirenperone indicates that fluvoxamine is acting via a mechanism mediated by 5-HT_2 receptors. While it is true that pirenperone has significant affinity for dopaminergic, adrenergic, and serotonergic receptors (Kennis et al., 1986), it is quite selective for the 5-HT_2 type within the family of serotonergic receptors (Hoyer et al., 1985). In addition, previous studies have shown that pirenperone is an effective antagonist of (−)DOM-

induced stimulus control (Fiorella et al., 1995b; Winter et al., In Press a) and that the stimulus effects of DOM and its congener, DOI, are mediated by agonistic effects at 5-HT_{2A} receptors (Fiorella et al., 1995b; Ismaiel et al., 1993; Schrieber et al., 1994) with the 5-HT_{2C} receptor playing a significant modulatory role (Fiorella et al., 1995d).

In contrast with the effects of pirenperone, the interactions of WAY-100635 with fluvoxamine, as seen in Figure 1, cannot be explained by direct effects upon 5-HT_2 receptors because WAY-100635 has negligible affinity for those receptors (Forster et al., 1995). A more likely mechanism for potentiation of fluvoxamine by WAY-100635 is via blockade of presynaptic 5-HT_{1A} autoreceptors. In this regard, it is widely assumed that SSRIs exert their antidepressant effects by producing an increase in serotonergic neurotransmission. Following the observation in microdialysis studies that serotonin release following SSRIs is increased in animals treated with an antagonist at 5-HT_{1A} receptors, it was suggested that the commonly observed delay in onset of their antidepressant effects is due to activation of somatodendritic 5-HT_{1A} autoreceptors which decrease postsynaptic release of 5-HT (Artigas, 1993; Hjorth, 1993). According to this formulation it is only after the desensitization of the somatodendritic 5-HT_{1A} autoreceptors occurs with chronic treatment, that the antidepressant effect emerges. (−)Pindolol, an antagonist at both 5-HT_{1A} and β-adrenergic receptors, has been used as a pharmacological means to mimic desensitization. Following positive results in depressed patients in open studies (Artigas et al., 1994; Blier and Bergeron, 1995), this hypothesis was tested in placebo-controlled double-blind investigations. These investigations have yielded both positive (Perez et al., 1997; Tome et al., 1997; Zanardi et al., 1997) and negative (Bermann et al., 1977; Moreno et al., 1997) findings. Nonetheless, whatever the clinical consequences of the interaction between 5-HT_{1A} receptor blockade and SSRIs, the data shown in Figure 1 indicate that WAY-100635, a highly selective, pure antagonist at 5-HT_{1A} receptors, potentiates the (−)DOM-like effects of fluvoxamine.

If the partial generalization of (−)DOM to fluvoxamine is mediated by 5-HT_2 receptors, we would predict that antagonists of the 5-HT_2 receptor other than pirenperone would likewise block fluoxetine. Instead of testing this hypothesis with anti-serotonergic drugs for which minimal or no clinical data are available, we chose to examine a series of proven antipsychotic drugs with varying abilities to produce a functional in vivo blockade of 5-HT_2 receptors. Earlier we examined such a series in terms of their ability to antagonize (−)DOM-induced stimulus control (Fiorella et al., 1995c). The results seen in Figures 2 and 3 indicate that the partial generalization of (−)DOM to fluvoxamine is not antagonized by chlorpromazine, fluphenazine, or thioridazine but is blocked by loxapine, risperidone, and clozapine. This pattern is identical to that previously observed with (−)DOM (Fiorella et al., 1995c). It should be noted that functional in vivo blockade of 5-HT_2 receptors as indicated by antagonism of stimulus control by (−)DOM is not well correlated with in vitro receptor-binding affinities. Thus, for example, chlorpromazine and fluphenazine have higher affinities for the 5-HT_2 receptor than does clozapine (Meltzer et al., 1989). A plausible explanation of the data of Figures 2 and 3, as well as those seen with pirenperone (Figure 1) is that the partial mimicry of (−)DOM by fluvoxamine is mediated by 5-HT_2 receptors. However, in view of the negligible affinity of fluvoxamine for the 5-HT_{2A} receptor as seen in radioligand-binding studies (Olivier et al., In Press; Rabin and Winter, unpublished observations), it is unlikely that fluvoxamine is acting directly upon these receptors. Also arguing for an indirect action is the fact that while antagonism of 5-HT_{1A} receptors potentiates the DOM-like effects of fluvoxamine, as seen in Figure 1, WAY-100635 does not potentiate DOM-induced stimulus control (Winter et al., In Press b).

Soon after LSD came into widespread non-medical use, reports appeared linking its ingestion with psychotic episodes (Cohen and Ditman, 1963; Glass and Bowers, 1970; Kleber, 1967) and it was proposed that serotonergic systems might be involved (Bowers, 1972, 1975). To the extent that LSD and DOM share a common 5-HT_2-mediated mechanism of action, the conclusion of the present study that fluvoxamine partially mimics (−)DOM in rats by acting, perhaps indirectly, upon 5-HT_2 receptors leads to the prediction that fluvoxamine and other SSRIs might exacerbate psychosis and that this effect would be diminished by blockade of 5-HT_2 receptors. The fact that many antipsychotic drugs have significant affinity for 5-HT_2 receptors (Meltzer et al., 1989) and some exhibit functionally significant antagonism at those receptors (Fiorella et al., 1995c; Meltzer and Nash, 1991) provides a potential means for testing these predictions. In this regard it may be asked why, if fluvoxamine partially mimics (−)DOM, the incidence of SSRI-induced mania and psychosis is not higher. Emslie et al. (1997) observed that for fluoxetine in children and adolescents the phenomenon is only 6%. No definitive answer is at hand but it may be suggested that fluvoxamine perhaps is atypical in mimicking (−)DOM; it appeared to be the most active of the three SSRIs examined previously (Winter et al., In press a). Alternatively, it may be that some segments of the population are more vulnerable than others. For example, in case reports by Omar et al. (1995), the use of fluoxetine was

associated with visual hallucinations in two elderly demented women.

As was previously noted, there is evidence that the adjunctive use of an antagonist of somatodendritic 5-HT_{1A} autoreceptors may shorten the latency of the antidepressants effects of SSRIs. In addition, it has been reported that the combination of SSRIs with antipsychotic drugs may increase the efficacy of the latter drugs particularly with respect to negative symptoms of schizophrenia (Goff et al., 1995). Both sets of observations increase the probability that SSRIs will be used together with either neuroleptics or antagonists at 5-HT_{1A} receptors. To the extent that one can extrapolate from rat to man, the present data suggest that the combination of fluvoxamine, and possibly other SSRIs, with 5-HT_{1A} receptor antagonists or with neuroleptics lacking antagonistic activity at 5-HT_2 receptors may present an increased risk of adverse effects in the form of exacerbation of psychosis, mania, or both.

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