

# Nefazodone in the rat: mimicry and antagonism of [–]-DOM-induced stimulus control

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## Abstract

Nefazodone is presently marketed as an antidepressant that inhibits both serotonin (5-hydroxytryptamine, 5-HT) and norepinephrine reuptake while antagonizing pirenpirone (5-HT<sub>2</sub>) receptors. This 5-HT receptor type is believed to play a prominent role in the underlying mechanism of action of serotonergic hallucinogens. Antidepressant medications now represent the most commonly prescribed psychoactive medications in the world and are likely to be ingested in the presence of hallucinogens with increased frequency; the consequences are largely unknown. The present investigation examined the interaction between the serotonergic phenethylamine hallucinogen [–]-2,5-dimethoxy-4-methylamphetamine ([–]-DOM), and nefazodone, in rats trained with [–]-DOM [0.6 mg/kg; 75 min pretreatment time] as a discriminative stimulus. The data indicate that maximal substitution of nefazodone for the [–]-DOM stimulus was present using a 45-min pretreatment time before testing. Using this pretreatment time, a dose of nefazodone of 12.0 mg/kg administered alone resulted in 76% DOM-appropriate responding. When a range of doses of nefazodone was combined with the training dose of [–]-DOM, a pattern of responding compatible with partial agonism was observed. The intermediate degree of [–]-DOM generalization to nefazodone was significantly antagonized by the 5-HT antagonists, 5-HT<sub>2</sub>, SR 46349B (5HT<sub>2A/2C</sub>), and M100907 (5-HT<sub>2A</sub>). Taken together, the present data suggest that (a) nefazodone acts as a partial agonist and (b) these effects are mediated by the 5-HT<sub>2A</sub> receptor.

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## 1. Introduction

Late in 1994, nefazodone was approved for the treatment of depression in the United States (Von Moltke et al., 1999). This drug was developed to improve the side-effect profile of the phenylpiperazine antidepressant, trazodone, which caused excessive sedation and postural hypotension (Kent, 2000). Nefazodone was initially identified as a potential antidepressant by its activity in a classic antidepressant screen, reversal of reserpine-induced ptosis (Taylor et al., 1982). A subsequent investigation indicated that nefazodone possessed affinity for the 5-HT<sub>2A</sub> receptor in vitro (Taylor et al., 1995). Nefazodone is said to be a unique antidepressant in that it inhibits serotonin (5-HT) uptake both in vivo and in vitro while antagonizing the 5-HT<sub>2A</sub> receptor (Stahl,

1998; Fontaine, 1993; Kent, 2000). The latter activity was assessed using the head-shake response in rodents. These head shakes are believed to be mediated by 5-HT<sub>2A</sub> receptors (Handley and Singh, 1986; Kennett and Curzon, 1991; Handley and Dursun, 1992). Thus, for example, the 5-HT<sub>3</sub> agonist, quipazine, induces head shakes and is antagonized by nefazodone (Eison et al., 1990; Nacca et al., 1998). Biochemical effects of quipazine have also been shown to be inhibited by nefazodone (Hemrick-Luecke et al., 1994). Meyer et al. (1999) assessed the acute effects of nefazodone on 5-HT<sub>2A</sub> receptor binding using [<sup>18</sup>F]setoperone PET. Nefazodone induced a significant change in 5-HT<sub>2A</sub> affinity in vivo, further supporting the idea that nefazodone is a 5-HT<sub>2A</sub> receptor antagonist. However, no studies have examined the possibility that nefazodone might act as a partial agonist.

Extensive evidence indicates that the stimulus properties of both indoleamine and phenethylamine hallucinogens are mediated by serotonergic systems (Glennon, 1994; Winter, 1994). The phenethylamine hallucinogen, 2,5-dimethoxy-4-

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methylamphetamine ([–]-DOM), in comparison to lysergic acid diethylamide (LSD), binds with selectivity for 5-HT<sub>2A</sub> and 5-HT<sub>2C</sub> receptors, possessing approximately two orders of magnitude lower affinity for other serotonergic and nonserotonergic receptors (Leysen et al., 1989) and therefore was chosen for use in the present study (for a review, see Glennon, 1990). In previous studies in our laboratories using hallucinogen-induced stimulus control it was observed in the rat that acute pretreatment with [–]-fluoxetine, a selective serotonin reuptake inhibitor (SSRI), potentiates the stimulus effects of the indoleamine hallucinogen LSD (Fiorella et al., 1996). Subsequent investigations extended that finding to include other SSRIs and [–]-DOM (Winter et al., 1999a, 2002; Eckler et al., 2002). In the course of those studies it was observed that racemic fluoxetine, fluvoxamine, and venlafaxine all mimicked to varying degrees the stimulus effects of [–]-DOM; fluvoxamine was the most active of the group (Winter et al., 1999b) while citalopram failed to significantly substitute for the [–]-DOM stimulus at any dose tested (Eckler et al., 2002).

The continued widespread illicit use of hallucinogens (Johnston, 1997; Leshner, 1999) coupled with the fact that the SSRIs are the most widely prescribed psychoactive drugs in the world (Gram, 1994; Pincus et al., 1998) makes it likely that co-ingestion of these agents represents a common phenomenon, the consequences of which are largely unknown. The present study was undertaken to test the hypothesis that nefazodone, despite its activity as an antagonist at 5-HT<sub>2</sub> receptor, potentiates the stimulus effects of [–]-DOM as do the other SSRIs that we have examined.

## 2. Materials and methods

### 2.1. Materials

[–]-DOM hydrochloride was supplied by the National Institute on Drug Abuse (Rockville, MD, USA). Nefazodone hydrochloride was kindly provided by Bristol-Myers Squibb (USA) and SR 46349B by Sanofi Recherche (France). Pirenpirone was purchased from Research Biochemicals International (Natick, MA, USA). All drugs used in the behavioral experiments were dissolved in 0.9% NaCl and solutions were intraperitoneally injected in a volume of 1.0 ml/kg bodyweight.

### 2.2. Animals

Male Fischer-344 rats were obtained from Harlan Sprague–Dawley (Indianapolis, IN, USA) at an age of approximately 6 weeks. They were housed in pairs with free access to food and water in a temperature-controlled room under a constant 12:12 h light–dark cycle. All experiments were conducted during the light phase. Subjects were fed standard rat chow following experimental sessions.

Caloric intake was controlled to yield a mean body weight of about 250 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 Animal Resources, National Research Council. The present study was approved by the Institutional Animal Care and Use Committee of the University at Buffalo.

### 2.3. Drug-induced stimulus control

Six small animal test chambers (Med-Associates Model ENV-008) housed in larger lightproof Malaguard sound-attenuating cubicles (Med-Associates Model ENV-022M), were used for all experiments. Each box had a house light and exhaust fan. The chamber contained two levers mounted on 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.

Ten subjects were trained to discriminate [–]-DOM (0.6 mg/kg, 75 min pretreatment time, intraperitoneal injection) from saline as described previously (Fiorella et al., 1995a). A nonresetting fixed ratio 10 (FR10) schedule of reinforcement was employed using the MED-PC version IV behavioral programming application. Drug-induced stimulus control was assumed to be present when, in five consecutive sessions, 83% or more of all responses before the delivery of the first reinforcer were on the appropriate lever. [–]-DOM-induced stimulus control was established after 25–30 training sessions. The [–]-DOM training dose (0.6 mg/kg 75 min pretreatment time) produced 99.3% drug-appropriate responding. After stimulus control was established with [–]-DOM, tests were conducted once per week in each animal so long as performance did not fall below the criterion level of 83% correct responding in any one of the previous three training sessions. Half of the test sessions were conducted the day after saline training sessions with the remainder following [–]-DOM training sessions. 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 a percentage of total responses emitted on the drug-appropriate lever. For purposes of discussion of these data, complete generalization of a training drug to a test drug is said to be present when (a) a mean of 80% or more of all test responses occurs on the drug-appropriate lever; (b) there is no statistically significant difference between the response distributions of the training drug and the test drug; and (c) there is a statistically significant difference between the response distributions of the test drug and saline control sessions. An intermediate degree of generalization is defined as being present when response distributions after a test drug are less than 80% drug appropriate, and are significantly different from both training conditions. Finally, when the response distribution after a test drug is not statistically significantly different from that in saline

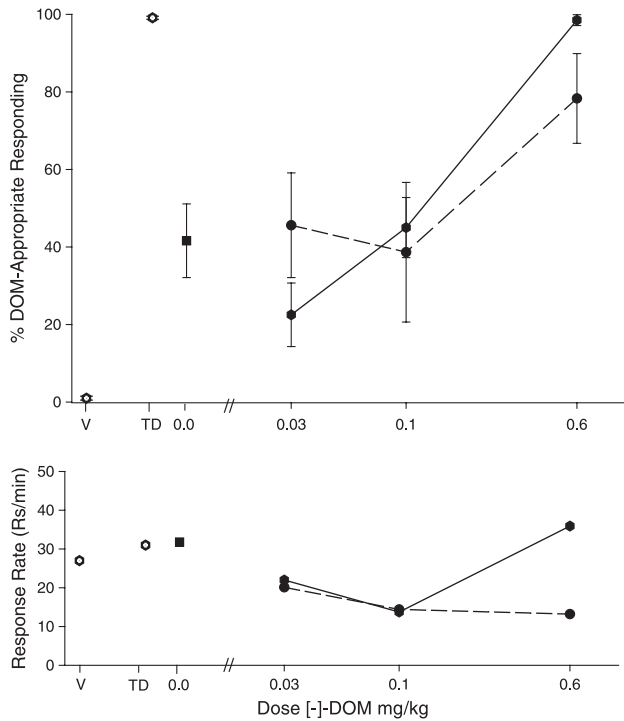


Fig. 1. Stimulus effects of  $[-]$ -DOM alone (solid line with hexagons) and in combination with a fixed dose of nefazodone (6.0 mg/kg; broken line with circles) in rats trained with  $[-]$ -DOM (0.6 mg/kg) as a discriminative stimulus. The data points shown at a dose of 0.0 is for nefazodone administered alone (circle), while the V and TD on the abscissa (open hexagons) are means ( $\pm$ S.E.M.) for the vehicle (saline) and training drug sessions, respectively. Ordinate, top panel: percent  $[-]$ -DOM-appropriate responding. Ordinate, bottom panel: response rate. Abscissa: dose of  $[-]$ -DOM. Data are expressed as mean  $\pm$  S.E.M. [ $N=10$ ].

control sessions, an absence of generalization of the training drug to the test drug is assumed. Similar criteria are applied to the definitions of full, partial, and no antagonism. Thus, full antagonism is assumed to be present when (a) less than 20% of all test responses are on the training drug-appropriate lever; (b) there is no significant difference between the response distributions in the test of antagonism and the saline control; and (c) there is a statistically significant difference between the response distributions of the test drug alone and in combination with the antagonist. Response rate was calculated for each session by dividing the total number of responses emitted on both levers by the elapsed time before 10 responses on either lever. Pretreatment times were 75 min for  $[-]$ -DOM, 30 min for M100907, 30 min for SR 46349B, 60 min for pirenpirone, and from 15 to 90 min for nefazodone.

#### 2.4. Statistics

The degree of generalization of  $[-]$ -DOM to nefazodone at various pretreatment times was assessed by one-way analysis of variance (ANOVA) with the Tukey test used for pairwise multiple comparisons. All other behavioral data were assessed for statistical significance using individual

applications of Student's  $t$  test. Differences were considered statistically 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, USA). Data from test sessions were compared to data from immediately preceding training sessions. However, for purposes of clarity, mean values for control data are shown in all figures.

### 3. Results

When a fixed dose of nefazodone (6.0 mg/kg, 90 min) was administered in combination with a range of doses of  $[-]$ -DOM (Fig. 1), no statistically significant change in the dose–response curve for  $[-]$ -DOM was observed. Taken together, however, the overall pattern is suggestive of partial agonist activity, i.e., enhancement of  $[-]$ -DOM effects at low doses and diminution of its effects at higher doses. The same dose of nefazodone was administered alone to address its agonistic activity in terms of its ability to mimic the stimulus effects of  $[-]$ -DOM. Consistent with our previous observations with fluoxetine, fluvoxamine, and venlafaxine (Winter et al., 1999a,b), nefazodone alone resulted in 42%  $[-]$ -DOM appropriate responding indicating significant partial mimicry of  $[-]$ -DOM.

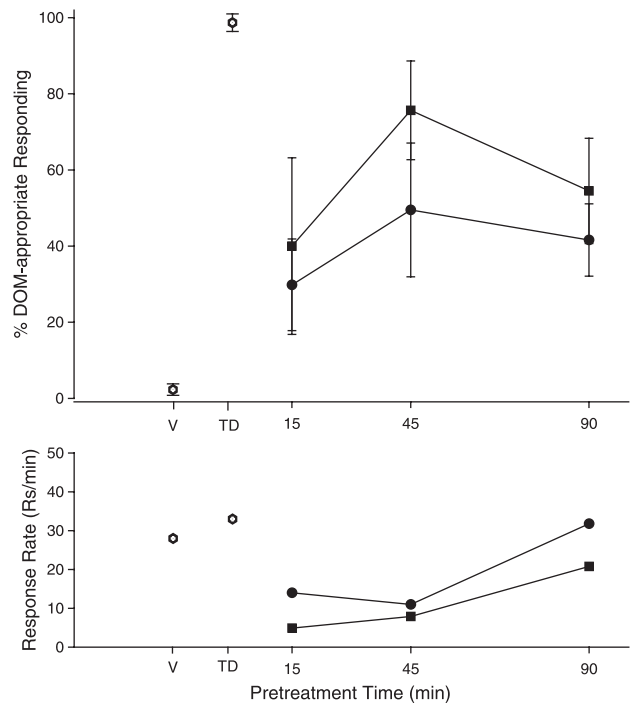


Fig. 2. Time course of 6.0 mg/kg (circles) and 12.0 mg/kg (squares) nefazodone in  $[-]$ -DOM-trained animals. Data shown at points V and TD on the abscissa (open hexagons) are means ( $\pm$ S.E.M.) for the vehicle (saline) and training drug sessions. Ordinate, top panel: percent  $[-]$ -DOM-appropriate responding. Ordinate, bottom panel: response rate (responses per minute). Abscissa: pretreatment time. Data are expressed as mean  $\pm$  S.E.M. [ $N=10$ ].

The temporal relationship for mimicry by nefazodone of [–]-DOM-induced stimulus control was next examined (Fig. 2). Results for doses of 6.0 and 12.0 mg/kg of nefazodone suggest that maximal [–]-DOM substitution occurs using a 45-min pretreatment time. All data points were found to be significantly different from both saline and [–]-DOM training conditions. Thus, the stimulus effects of nefazodone, independent of dose and pretreatment time, result in an intermediate degree of generalization.

Using the 45-min pretreatment time established by the data of Fig. 2, a range of doses of nefazodone was administered either in the presence or absence of the training dose of [–]-DOM (Fig. 3). Nefazodone alone resulted in a dose-related increase in [–]-DOM-appropriate responding, with a maximum of 76%. When a range of doses of nefazodone was administered in the presence of the training dose of [–]-DOM, a dose-related decrease in [–]-DOM-appropriate responding was observed. A dose of 12.0 mg/kg of nefazodone alone was significantly antagonized by piren-

enirone (5-HT<sub>2</sub>), SR 46349B (5-HT<sub>2A/2C</sub>), and M100907 (5-HT<sub>2A</sub>).

#### 4. Discussion

The present data indicate that the stimulus effects of the phenethylamine hallucinogen, [–]-DOM, are differentially altered, relative to dose, by pretreatment with the monoamine reuptake inhibitor, nefazodone. Similar to (±) fluoxetine, fluvoxamine, and venlafaxine (Winter et al., 1999a), the enhancement of [–]-DOM-induced stimulus control occurs in the presence of significant partial substitution by nefazodone. However, unlike (±) fluoxetine, fluvoxamine, venlafaxine, and citalopram, higher doses of nefazodone appear to reduce [–]-DOM appropriate responding (Fig. 1). This biphasic effect of nefazodone was not predictable based on reports of nefazodone being a potent 5-HT<sub>2A</sub> antagonist (Taylor et al., 1995; Davis et al., 1997). More specifically, as the dose of nefazodone administered intraperitoneally is increased, we observe an elevation in [–]-DOM appropriate responding.

The interaction of a drug with its receptors may be characterized by the affinity of the drug for the receptors and its intrinsic activity at the receptors (Ariens, 1964). The former term refers to the probability that a drug molecule will interact with its receptor to form the drug–receptor complex. Intrinsic activity refers to the pharmacological effectiveness of the drug–receptor complex. Thus, both agonists and antagonists have affinity for a given receptor but a fully effective agonist has an intrinsic activity of 1.0 whereas an antagonist possesses an intrinsic activity of 0.0. Drugs with affinity for the receptor which are neither full agonists nor pure antagonists, i.e., their intrinsic activity is less than 1.0 but greater than 0.0, are referred to as partial agonists or mixed agonist/antagonists. The latter term emphasizes that a partial agonist in the presence of a full agonist may function as an antagonist (Winter, 1995). Thus, for example, a person physically dependent upon morphine may undergo the opioid withdrawal syndrome when treated with an opioid partial agonist such as pentazocine. A classic behavioral demonstration using drug-induced stimulus control in the rat was provided by Holtzman (1983) in animals trained with morphine and tested with nalorphine, an opioid partial agonist.

In the present study (Fig. 3), when a range of doses of nefazodone is given, an intermediate degree of generalization is evident. The fact that the stimulus properties of nefazodone are fully antagonized by pirenirone indicates that nefazodone is acting via a mechanism mediated by 5-HT<sub>2</sub> receptors. Although pirenirone has significant affinity for dopaminergic, adrenergic, and serotonergic receptors (Kennis et al., 1986), it is quite selective for the 5-HT<sub>2</sub> type within the serotonergic receptor family (Hoyer et al., 1985). While the propenone-oxine derivative SR 46349B has been described as a selective 5-HT<sub>2A/2C</sub> receptor antagonist

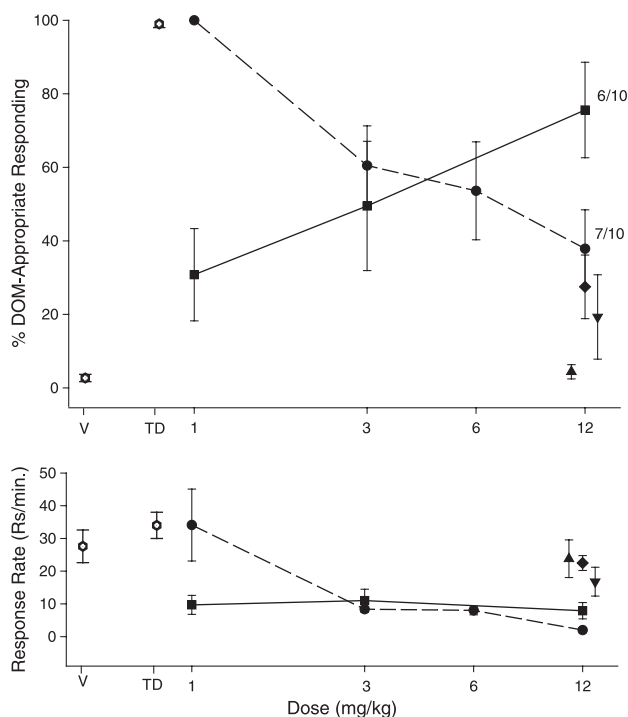


Fig. 3. Dose–response for nefazodone administered alone (45-min pretreatment time) in [–]-DOM-trained animals (squares) and in the presence of 0.6 mg/kg [–]-DOM (circles: 75 min pretreatment). In addition, the results of the combination of nefazodone alone (12.0 mg/kg) with pirenirone (triangle up: 60-min pretreatment time, 0.16 mg/kg), SR 46349B (diamond: 30-min pretreatment time, 1.0 mg/kg), and M100907 (triangle down: 30-min pretreatment time, 0.05 mg/kg) are shown. Ordinate, top panel: percent [–]-DOM-appropriate responding. Ordinate, bottom panel: response rate (responses per minute). Abscissa: dose of nefazodone. Data shown at points V and TD on the abscissa (open hexagons) are means ( $\pm$ S.E.M.) for the vehicle (saline) and training drug sessions, respectively. Data are expressed as mean  $\pm$  S.E.M. [ $N=10$ ]. When subjects tested were unable to complete the test session a fraction is present on the figure [number of animals completing/number of animals tested].

(Darmani, 2001) it has been reported to possess a 30-fold higher affinity for 5-HT<sub>2A</sub> than 5-HT<sub>2C</sub> (Rinaldi-Carmona et al., 1992, 1993a,b). In contrast, M100907 displays almost 200-fold higher affinity for 5-HT<sub>2A</sub> than 5-HT<sub>2C</sub> (Sorensen et al., 1993; Kehne et al., 1996; Schmidt et al., 1997). More specifically, nefazodone is antagonized by both SR 46349B and M100907, indicating the involvement of 5-HT<sub>2A</sub> receptors in mediating the stimulus effects of nefazodone. However, when nefazodone is administered in combination with a fully effective dose of [–]-DOM, antagonism of [–]-DOM is observed. In a similar manner, our data depicted in Fig. 3 would suggest that nefazodone, which is marketed as an antidepressant that possesses 5-HT<sub>2</sub> antagonistic effects, might in fact represent a partial agonist at this receptor.

Research conducted by Nacca et al. (1998) not only quantitated nefazodone in the brain, but also identified metabolites. The researchers called for a thorough investigation into the possibility of active metabolites, specifically the contribution of 1-(*m*)-chlorophenylpiperazine (mCPP) in the overall clinical effects of nefazodone (Nacca et al., 1998). Of all psychoactive substances studied to date, there is a wealth of information concerning mCPP, fueled by use of mCPP in evaluating the serotonergic function of humans. In general, mCPP has been thought of as a centrally acting serotonergic agonist (Hamik and Peroutka, 1989) while acting as an antagonist within the vasculature (Cohen and Fuller, 1983). Drug-discrimination procedures have previously been conducted in our laboratory, using mCPP as the training agent, and have shown that both LSD and DOM partially generalize to the stimulus effects of mCPP (Fiorella et al., 1995b). A significant role for mCPP in the overall stimulus effects of nefazodone is plausible but is not addressed by present experiments.

It appears unlikely that 5-HT itself is mediating the observed behavioral effect. Multiple reports indicate that nefazodone is a weak reuptake inhibitor while possessing potent antagonism at 5-HT<sub>2A</sub> receptors (Davis et al., 1997; Hemrick-Luecke et al., 1994). In addition, citalopram, which is one of the more selective and potent 5-HT transport inhibitors, fails to mimic the [–]-DOM stimulus at a comparable dose (Eckler et al., 2002). It is probable that nefazodone itself and/or its primary metabolite(s) are directly mediating the observed behavioral effect.

Functionally, a partial agonist and an antagonist will both decrease overall stimulation while in the presence of a full agonist. Thus, in the rat, coadministration of nefazodone and serotonergic hallucinogens may diminish the subjective effects of the hallucinogen. However, nefazodone has been said to be a unique antidepressant in that it weakly inhibits 5-HT transport while acting as an antagonist at 5-HT<sub>2A</sub> receptors. Taken alone, a range of doses of nefazodone (3.0–12.0; 45 min) appear to antagonize the stimulus effects of [–]-DOM, which is consistent with 5-HT<sub>2A</sub> receptor antagonism. In contrast with the attributed property of possessing 5-HT<sub>2A</sub> antagonism, the data indicate that (a)

the identical dose of nefazodone administered using the same pretreatment time (45 min) resulted in greater than 75% [–]-DOM-appropriate responding and (b) the stimulus effects of nefazodone are blocked by the 5-HT antagonists pirenpirone (5-HT<sub>2</sub>), SR 46349B (5-HT<sub>2A/2C</sub>), and M100907 (5-HT<sub>2A</sub>).

The ability of SSRIs to partially substitute for the stimulus effects of [–]-DOM in the rat (Winter et al., 1999a) led to the suggestion (Winter et al., 1999b) that agonist activity by SSRIs at 5-HT<sub>2</sub> receptors might account for the exacerbation of psychosis sometimes observed in patients treated with SSRIs (Bowers et al., 1998a,b). Similar exacerbation of psychosis by nefazodone would not be expected based upon the reported efficacy of nefazodone as an antagonist at 5-HT<sub>2</sub> receptors (Taylor et al., 1982, 1995; Eison et al., 1990). Although acute and chronic effects of a given drug may have distinct cellular bases, nefazodone has been associated with visual disturbances and hallucinations in patients (Schwartz, 1997; Shuster, 1999; Mosberian et al., 1999). The clinical significance of the present investigation is uncertain. The present data indicate that nefazodone acts as a partial agonist in rats trained with [–]-DOM as a discriminative stimulus and that this partial agonist activity is mediated by 5-HT<sub>2</sub> receptors.

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