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The Stimulus Effects of 8-OH-DPAT: Evidence for a 5-HT_{2A} Receptor-Mediated Component

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Abstract

A previous investigation in our laboratory found that the stimulus effects of the 5-HT_{2A} agonist, LSD, are potentiated by 5-HT_{1A} receptor agonists including the prototypic agonist, 8-OH-DPAT. Also suggestive of behaviorally relevant interactions between 5-HT_{1A} and 5-HT_{2A} receptors are behavioral analyses of locomotor activity, head twitch response, forepaw treading and production of the serotonin syndrome; in some instances effects are augmented, in other, diminished. These observations led us in the present investigation to test the hypothesis that stimulus control by 8-OH-DPAT [0.2 mg/kg; 15 min pretreatment time] is modulated by 5-HT_{2A} ligands. Stimulus control was established with 8-OH-DPAT in a group of 10 rats. A two-lever, fixed ratio 10, positively reinforced task with saline controls was employed. As shown previously, stimulus control by 8-OH-DPAT and the generalization of 8-OH-DPAT to the 5-HT_{1A} partial agonist, buspirone, was completely blocked by the selective 5-HT_{1A} antagonist, WAY-100635. In contrast, antagonism by the selective 5-HT_{2A} antagonist, M100907 [0.1 mg/kg; 30 min pretreatment time], of 8-OH-DPAT and of the generalization of 8-OH-DPAT to buspirone was statistically significant but less than complete. In light of our previous conclusions regarding the interactions of 5-HT_{1A} agonists with LSD-induced stimulus control, the present data suggest that the interaction between 5-HT_{1A} and 5-HT_{2A} receptors is bidirectional in drug discrimination studies.

Keywords

8-OH-DPAT; 5-HT_{2A} receptor; stimulus control; M100907; 5-HT_{1A}

1. Introduction

The 5-HT_{1A} receptor may be the best characterized of the fourteen serotonergic receptor subtypes (Pucadyil et al., 2005). 5-HT_{1A} receptors have been implicated in psychiatric disorders such as depression (Celada et al., 2004) and schizophrenia (Millan, 2000; Yasuno et al., 2004) as well as the formation of memory (Winter and Petti, 1987) and neural development (del Olmo et al., 1998; Pazos et al., 1998). The 5-HT_{1A} receptor has been proposed as the pharmacological target of the azapirone anxiolytics (Cunningham et al., 1987) and may contribute to the therapeutic effects of the novel antipsychotic aripiprazole (Marona-Lewicka

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and Nichols, 2004). Thus, insight concerning 5-HT_{1A} function will offer knowledge applicable across a wide spectrum of research interests.

Dysfunction of a second serotonergic receptor subtype, 5-HT_{2A}, may also underlie a variety of central nervous system disorders including impulsive behavior (Nomura et al., 2006), Alzheimer's disease (Lorke et al., 2006), schizophrenia (Dean, 2003), and depression (de Angelis, 2002). Although selective 5-HT_{2A} antagonists have yielded disappointing results in the treatment of schizophrenia (de Paulis, 2001), 5-HT_{2A} antagonism may contribute to the lower side effect profile and increased efficacy of atypical antipsychotic drugs (Meltzer, 1999; Meltzer et al., 2003) and improve the efficacy of selective serotonin reuptake inhibitors (SSRI's) (Boothman et al., 2006). In light of these observations, manipulation of 5-HT_{2A} receptor function and the resultant behavioral effects have considerable therapeutic potential.

There is ample evidence supporting functional interactions between 5-HT_{1A} and 5-HT_{2A} receptors. *In vivo* analyses have examined these interactions using a variety of behavioral paradigms including the head twitch response (Arnt and Hyttel, 1989; Yocca et al., 1990), forepaw treading (Arnt and Hyttel, 1989; Backus et al., 1990), production of the serotonin syndrome (Backus et al., 1990), and locomotor activity (Krebs-Thomson and Geyer, 1998). However, conflicting results have emerged as some of these studies have shown additive or potentiating interactions between 5-HT_{1A} and 5-HT_{2A} receptors (Arnt and Hyttel, 1989; Backus et al., 1990), while others have shown functional opposition or antagonistic interactions (Krebs-Thomson and Geyer, 1998; Yocca et al., 1990).

As many of the aforementioned psychiatric disorders manifest themselves as alterations of cognitive function, similarly complex behavioral measures must be employed toward their investigation. To this end, drug discrimination has proven useful in determining the neuropharmacological mechanism underlying a diverse array of psychoactive substances (Koek et al., 1992; Winter, 1974, 1994). Of particular interest are drug discrimination studies showing that hallucinogens whose stimulus effects are mediated primarily by 5-HT_{2A} receptors (Fiorella et al., 1995a; Fiorella et al., 1995b; Winter et al., 2004) are potentiated by 5-HT_{1A} agonists (Reissig et al., 2005). This finding suggests that 5-HT_{1A} receptor stimulation enhances 5-HT_{2A} receptor function in the drug discrimination paradigm.

Because drug discrimination studies have found that 5-HT_{1A} receptor agonists potentiate the stimulus effects of hallucinogens whose effects are mediated by actions at 5-HT_{2A} receptors (Reissig et al., 2005), we hypothesized that 5-HT_{2A} receptors may have a modulatory effect on the stimulus effects of 8-OH-DPAT. Thus, in the present study, the 5-HT_{2A} antagonist M100907 was evaluated for its ability to modulate the stimulus effects of 8-OH-DPAT. This will further characterize functional interactions between 5-HT_{1A} and 5-HT_{2A} receptors using drug discrimination, a technique able to model the subjective effects of drug-receptor interactions.

2. Materials and Methods

2.1 Subjects

Ten male Fischer 344 rats were obtained at an age of approximately 6 weeks from Harlan Sprague-Dawley Inc. [Indianapolis, IN, U.S.A.], housed in pairs under a 12-h light-dark cycle beginning at 6:00 a.m., and allowed free access to water in their home cages. All training and testing took place during the light cycle. Subjects were fed standard rat chow. Caloric restriction was used to maintain a body weight of approximately 275 g. Caloric restriction has been shown to lengthen the life span and decrease the incidence of pathologies in Fischer 344 rats (Keenan et al., 1994). Based on a recent sample of 25 rats, the average life span under these conditions is 34.3 months [S.E.M.=1.1]. Animals used in these studies were maintained in accordance

with U.S. Public Health Service Policy on Humane Care and Use of Laboratory Animals as amended August 2002. All experimental protocols were approved by the Institutional Animal Care Unit.

2.2 Drug Discrimination training

Six small animal test chambers (MED Associates ENV-008) were used for 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 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 (MED-PC State Notation, Version IV). Subjects were trained to discriminate 8-OH-DPAT from saline (0.2 mg/kg, 15-min pretreatment time, intraperitoneal injection). A fixed ratio 10 (FR10) schedule of reinforcement was employed. 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. After stimulus control was established, 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 of the three previous training sessions. The 8-OH-DPAT training dose produced 99.3% drug-appropriate responding during training sessions conducted throughout the course of this study. In contrast, less than 3% drug-appropriate responding was observed in training sessions that were preceded by the injection of saline.

2.3 Test Procedures

After stimulus control with 8-OH-DPAT was established, combination and substitution tests were conducted once per week in each animal if the criterion for drug-induced stimulus control were met. Tests were balanced between subjects trained on the previous day with saline and 8-OH-DPAT, 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. Data for any subjects failing to emit 10 responses within the constraints of the 10-min test session were not considered in the calculation of the percent drug-appropriate responding but were included in analysis of response rates.

For purposes of discussion of these data, definitions were according to Winter et al. (2000). Complete generalization of the 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 significant difference between the response distributions of the training drug and the test drug; and (c) there is a statistically difference between the response distributions of the test drug and saline control sessions. Partial generalization or antagonism is defined as being present when the mean response distribution after a test drug or combination of drugs is less than 80% drug-appropriate responding and is statistically significantly different from both training conditions. Finally, when the response distribution after a test drug is not different from that in saline 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 an antagonist.

Substitution tests were performed with buspirone [1.0 mg/kg] given 15 min before testing. The effects of antagonists on 8-OH-DPAT-induced stimulus control were assessed by co-administration of either M100907 [0.1 mg/kg] or WAY-100,635 [0.3 mg/kg] 30 min before testing and an agonist (buspirone) 15 min before testing.

2.4. Drugs

8-hydroxy-2-(di-*N*-propylamino)tetralin, WAY-100,635, and buspirone were purchased from Tocris [Ellisville, MO, USA]. M100907 was synthesized at the Laboratory of Medicinal Chemistry, National Institute of Diabetes, Digestive and Kidney Disorders at the National Institutes of Health [Bethesda, MD, USA]. A stock solution of M100907 [0.5 mg/ml] was made by dissolving M100907 in a minimal volume of 0.2% w/v tartaric acid and diluting with water. All other drugs were dissolved in 0.9% saline. Doses are expressed as mg/kg of the salts. The IP route was employed for all drugs with the exception of WAY-100,635 which was administered SC. An injection volume of 0.25 ml was employed for all drugs.

2.5. Statistical analysis

The statistical significance of tests of antagonism with M100907 and 8-OH-DPAT were determined using two-way ANOVA with dose of 8-OH-DPAT and pretreatment with M100907 as factors. Other behavioral data were assessed for statistical significance using one-way analysis of variance [ANOVA] followed by pair-wise comparisons using the Student-Newman-Keuls method. Differences were considered statistically significant if the probability of their having arisen by chance was ≤ 0.05 . All analyses were conducted using SigmaStat for WindowsTM (Jandel Scientific Software, San Rafael, CA).

3. Results

3.1 8-OH-DPAT Dose Effect Relationship

Fig. 1 shows an orderly, dose-related increase in 8-OH-DPAT-appropriate responding in rats trained and tested with 8-OH-DPAT. When the training dose of 8-OH-DPAT (0.2mg/kg) was tested in rats pretreated with WAY-100,635 (0.3 mg/kg), 8-OH-DPAT appropriate responding was completely blocked. Pretreatment with WAY-100,635 caused a significant decrease in drug appropriate responding ($p < 0.001$), although response rate was not altered.

3.2 Substitution and Combination tests with buspirone, M100907 and WAY-100,635

Fig. 2 shows the results of substitution tests with buspirone and combination tests using the selective 5-HT_{2A} antagonist M100907 (Marek and Aghajanian, 1994; Sorensen et al., 1993) and the 5-HT_{1A} antagonist WAY-100,635. It is seen that M100907 attenuates the stimulus effects of the training dose (0.2 mg/kg), and an intermediate dose (0.1 mg/kg), but not the lowest dose (0.05 mg/kg) of 8-OH-DPAT tested. Two-way ANOVA revealed that the overall level of 8-OH-DPAT appropriate responding was decreased by pretreatment with M100907 ($F_{2,118}=9.006; p=0.003$). Pretreatment with M100907 also produced a significant increase in subject's rate of responding ($F_{2,118}=5.534; p=0.003$).

A 1.0 mg/kg dose of buspirone substituted completely for 8-OH-DPAT. This substitution was significantly decreased by pretreatment with M100907 and WAY-100,635 as revealed by one-way ANOVA ($F_{2,46}=99.743; p < 0.001$).

Discussion

The data in Fig. 1 demonstrate that the stimulus effects of 8-OH-DPAT are completely blocked by the selective 5-HT_{1A} antagonist WAY-100,635 (Fletcher et al., 1993; Fletcher et al., 1996; Forster et al., 1995). These results are in agreement with previous reports suggesting that

5-HT_{1A} stimulation is the primary component of the 8-OH-DPAT stimulus cue (Celada et al., 2004; Cunningham et al., 1987; Sanger and Schoemaker, 1992; Tricklebank et al., 1987).

Fig. 2 shows that antagonism of 5-HT_{2A} receptors attenuates the stimulus effects of the training dose (0.2 mg/kg) and an intermediate dose (0.1 mg/kg), but not the lowest dose (0.05 mg/kg) of 8-OH-DPAT tested. These results are interesting in light of a previous investigation which failed to attenuate the 8-OH-DPAT stimulus cue using the 5-HT₂ antagonist ketanserin (Cunningham et al., 1987). However, the latter study used a higher dose of the training agent (0.4 mg/kg), different strain of rat (Sprague Dawley), and different FR schedule (FR=20). Additionally, ketanserin may exhibit affinity for other brain receptors including 5-HT_{2C} receptors, α 1 receptors, and dopamine receptors (Leysen et al., 1985). The present study employed M100907, a more selective 5-HT_{2A} antagonist which has a > 100-fold higher affinity for 5-HT_{2A} versus 5-HT_{2C} receptors (Johnson et al., 1996; Kehne et al., 1996). Our finding that 8-OH-DPAT generalizes completely to the 5-HT_{1A} agonist buspirone (Peroutka, 1985; Riblet et al., 1982) and that this substitution is blocked by WAY-100,635 demonstrates that this is not an idiosyncratic event unique to 8-OH-DPAT.

Previous behavioral studies have yielded inconclusive results regarding the complex interaction between 5-HT_{2A} and 5-HT_{1A} receptor subtypes. For example, the head-twitch response, a behavior typically associated with 5-HT_{2A} receptor stimulation (Green et al. 1983; Schreiber et al. 1995b) is variably affected by 5-HT_{1A} agonists. While quipazine-induced head twitches are increased by administration of the 5-HT_{1A} agonist gepirone (Eison et al. 1986; Yocca et al. 1991), DOI-mediated head twitches (Darmani et al. 1989) are decreased by 8-OH-DPAT. Further complicating matters is a report demonstrating the ability of 8-OH-DPAT to increase 5-MeO-DMT-induced, but not 5-hydroxytryptophan-induced, head-twitches in rats (Goodwin and Green, 1985). Thus, it appears that the interaction between 5-HT_{1A} and 5-HT_{2A} receptors on the head-twitch response is dependent upon the compounds used to investigate this interaction.

In vitro evidence also suggests an interaction between 5-HT_{1A} and 5-HT_{2A} receptors. Electrophysiological studies have shown that 5-HT_{1A} and 5-HT_{2A} receptors mediate opposite responses on pyramidal neuron membrane excitability (Araneda and Andrade, 1991; Ashby et al., 1994). This antagonistic interaction can be extended to include 5-HT release, where stimulation of 5-HT_{2A} receptors causes 5-HT release in mice (Bortolozzi et al., 2003) and rats (Martin-Ruiz et al., 2001), an effect that is reversed by 5-HT_{1A} agonism.

Other behavioral analyses have yielded similar, contradictory results regarding 5-HT_{2A} and 5-HT_{1A} receptor interactions. Isobolographic analysis suggests that 5-HT_{1A} and 5-HT_{2A} receptors act antagonistically with regards to their locomotor suppressing effects (Krebs-Thompson and Geyer 1998). An antagonistic 5-HT_{1A}/5-HT_{2A} interaction is also seen in the regulation of body temperature in rats (Gudelsky et al., 1986). However, 8-OH-DPAT-induced forepaw treading is increased by the 5-HT_{2A} agonist 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI) suggesting additive effects between 5-HT_{1A} and 5-HT_{2A} receptors (Arnt and Hyttel 1989). It may be argued however, that all of these behavioral measures are components of the serotonin syndrome, a condition thought to be caused by excessive serotonin at 5-HT_{1A} (Darmani and Ahmad, 1999) and 5-HT₂ receptors (Pranzatelli and Pluchino, 1991).

Considering the above data, our discrimination results do not lend themselves to easy interpretation. Our results showing that M100907 attenuates the stimulus effects of 5-HT_{1A} receptor agonists suggests the engagement of a complex synaptic circuit in the stimulus effects of 5-HT_{1A} agonists. It would appear that 5-HT_{2A} receptors are involved in producing this cue, but their exact role remains to be determined. In light of the previous report demonstrating the

potentiating effects of 5-HT_{1A} agonists on LSD-induced stimulus control (Reissig et al., 2005); it appears that 5-HT_{2A} and 5-HT_{1A} agonists have a bidirectional, modulatory influence upon one another in the drug discrimination paradigm. As it has been shown recently that M100907 can function as a discriminative stimulus (Dekeyne et al., 2002) it would be interesting to determine the effects of 8-OH-DPAT and WAY-100,635 on this stimulus cue.

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Figure 1.

Dose-response relationship for 8-OH-DPAT alone and in combination with WAY-100,635. Circles represent the effects of 8-OH-DPAT alone in rats trained with 8-OH-DPAT as a discriminative stimulus (0.2 mg/kg; 15 min pretreatment time). Each point represents the mean of two determinations in each of 10 rats, with the exception of WAY-100,635 where a single determination is shown. The open hexagon represents the effects of WAY-100,635 (0.3 mg/kg 30 min. pretreatment) in combination with the training dose 8-OH-DPAT. The point at V is for vehicle controls.

Figure 2.

Dose-response relationship for 8-OH-DPAT alone and in combination with M100907.

Circles represent the effects of 8-OH-DPAT alone in rats trained with 8-OH-DPAT as a discriminative stimulus (0.2 mg/kg; 15 min pretreatment time). Each point represents the mean of two determinations in each of 10 rats, unless otherwise noted. *Triangles* represent the effects of M100907 (0.1 mg/kg 30 min. pretreatment) in combination with 8-OH-DPAT. The points at V are for either vehicle controls [*circle*] or M100907 alone [*triangle*]. The *closed square* represents the effects of buspirone (1.0 mg/kg 15 min pretreatment). The *open square* represents the effects of buspirone given in combination with M100907. The *hexagon* represents the effects of buspirone in combination with WAY-100,635. An asterisk indicates a statistically significant difference from 8-OH-DPAT given alone.