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5-HT_{1A} receptor activity disrupts spontaneous alternation behavior in rats

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Abstract

Agonists selective for three different serotonin (5-HT) receptor subtypes were tested for the ability to disrupt spontaneous alternation behavior (SAB) in the CD strain of rats. Rats were scored for alternation or repetition in their choice of arms of a T-maze equally baited with chocolate milk. Compared with vehicle controls, the 5-HT_{1A} agonist 8-hydroxy-dipropylaminotetraline (8-OH-DPAT; 2 mg/kg) significantly ($P < .0001$) increased repetitive choices (disrupted SAB). In contrast, intraperitoneal injections with the 5-HT_2 agonist *R*-(−)-dimethoxyiodophenylaminoethane (DOI; 1 mg/kg) or the 5-HT_3 agonist *N*-methyl quipazine (NMQ; 3 mg/kg) had no significant effect on SAB in CD rats. Onset of vicarious trial and error (VTE) behavior prolonged the time required for each rat to select an arm of the T-maze when injected with either 8-OH-DPAT ($P < .0001$) or buspirone (1–2 mg/kg), a 5-HT_{1A} partial agonist. The disruption of SAB and the induction of VTE behavior were reversible with behavioral scores returning to preinjection levels within 48 h after injections. The disruption of SAB by 8-OH-DPAT was also seen with the Long–Evans rat strain. The results extend the use of the SAB model and point to a specific role of 5-HT_{1A} receptors in the induction of repetitive behavioral patterns.

Keywords: Serotonin; 5-HT receptor subtypes; Spontaneous alternation behavior; Vicarious trial and error; Obsessive–compulsive disorder

1. Introduction

The efficacy of selective serotonin (5-HT) reuptake inhibitors (SSRI) in treatment of obsessive–compulsive disorder (OCD) (Pigott et al., 1990; Greist et al., 1995; Ravizza et al., 1996) has focused attention on the role of serotonin in brain pathways controlling repetitive thoughts and behaviors. In contrast to long-term administration of SSRI, acute administration of serotonin agonists can exacerbate or even generate new symptoms in humans with OCD (Zohar et al., 1987; Pigott et al., 1991; Stern et al., 1998). Among a group of 12 OCD patients, symptoms of the disorder were significantly greater following administration of *meta*-chlorophenylpiperzine (mCPP), a 5-HT agonist that has an affinity for the 5-HT_{1A}, 5-HT_{1D}, and 5-HT_{2C} receptor subtypes, when compared with placebo administration (Zohar et al., 1987). The duration of worsened symptoms ranged from 1 to 2 days following mCPP administration. Half of those tested developed entirely new obsessions. Both OCD patients and control individuals who received mCPP had significantly greater levels of generalized anxiety than did those who received placebo (Zohar et al., 1987). Pigott et al. (1991) showed that metergoline, a 5-HT antagonist that has an affinity for the 5-$HT_{1/2}$ receptor subtypes, protected against the OCD-eliciting effects of mCPP when administered prior to mCPP.

The SSRI fluoxetine is also effective in treating repetitive behavioral disorders in animals. This has been shown with the naturally occurring canine acral lick dermatitis (Rapoport et al., 1992) and with food restriction-induced running in female Sprague–Dawley rats (Altemus et al., 1993). As in humans, serotonin agonists can elicit abnormal repetitive behavioral patterns in animals (Yadin et al., 1991). Specifically, Yadin et al. (1991) monitored disruption of spontaneous alternation behavior (SAB) as a means of developing an animal model that includes a repetitive pattern of behavior. In this behavioral paradigm, rats normally tend to alternate in their choice of sides of a T-maze on successive trials, when both arms of the maze are baited with an equal amount of an attractant such as chocolate milk. Sprague–Dawley rats were exposed acutely to serotonin

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agonists by injection with either a selective 5-HT_{1A} agonist, 8-hydroxy-dipropylaminotetraline (8-OH-DPAT; 2 mg/kg), or a less selective 5-HT agonist, 5-methoxy-*N*,*N*-dimethyltryptamine (5-MeODMT;1.25 mg/kg). After receiving either of these agonists, rats tended to repeatedly choose one arm over the other. Thus, serotonin agonists disrupted SAB providing a possible animal model for OCD (Yadin et al., 1991). Administration of fluoxetine (5 mg/kg, two times a day for 21 days) protected against the acute effects of these agonists. This is consistent with evidence that chronic administration of an SSRI results in desensitization of one or more components of serotonin transmission, including 5-HT_{1A} autoreceptors (Lesch et al., 1991; Blier and Bouchard, 1994; Blier and De Montigny, 1994; Li et al., 1997; Lerer et al., 1999; Kantor et al., 2001).

Given the ability of 5-HT agonists to elicit repetitive behavioral patterns in both animals (Yadin et al., 1991) and humans (Zohar et al., 1987; Pigott et al., 1991; Stern et al., 1998), the present study set out to extend the use of disrupting SAB in an animal model of OCD (Yadin et al., 1991) by testing additional rat strains and other serotonin agonists. Although 8-OH-DPAT, a specific 5-HT_{1A} agonist, disrupted SAB, it appeared to do so no more effectively than a nonspecific 5-HT agonist (Yadin et al., 1991). Thus, it was essential to begin testing additional agonists with selectivity for other 5-HT receptor subtypes. This could strengthen the hypothesis that 5-HT_{1A} receptors play a specific role in the induction of repetitive behavioral patterns. It is relevant to clinical studies (cited above) because mCPP, which consistently exacerbated obsessive–compulsive symptoms in humans with OCD, is a serotonin agonist perhaps best characterized for effects at 5-HT_{2C} receptors (Kennett et al., 1994).

As suggested by Yadin et al. (1991), it was also of interest to extend their model by testing the 5-HT_{1A} agonist buspirone and by attempting to quantify the amount of time animals spent performing vicarious trial and error (VTE) type behavior at the T-maze decision point. Buspirone is a nonbenzodiazepine anxiolytic and partial agonist at 5-HT_{1A} receptors that has been used in the long-term clinical treatment of OCD (Hoyer et al., 1994). VTE is characteristic of the inability to make a choice when faced with two more alternatives. It was hypothesized that specific activation of the 5-HT_{1A} receptor would induce repetitive behavioral patterns and increase time spent performing VTE behavior. Our goal was to test the selectivity of this hypothesis by comparing 8-OH-DPAT with buspirone and with agonists of 5-HT_2 and 5-HT_3 receptors.

2. Materials and methods

2.1. Animals

Juvenile male CD and Long–Evans rats were obtained from Charles River Breeding Labs (MD). The animals weighed an average of 70 g at the start and 90 g at the end of the experiment period. They were housed in groups of two or three rats and were given free access to food and water. Additional Long–Evans rats weighed up to 400 g at the time of testing. These were housed individually with free access to food and water. The environment was climate controlled and included a 12-h light–dark cycle. Prior to testing, animals were deprived of food for 24 h. All animals were treated in accordance with the ethical standards set forth by the American Psychological Association (1992) and all protocols were approved by the Institutional Review Board (Monmouth University).

2.2. Materials

A black Plexiglas T-maze was built according to published specifications (Yadin et al., 1991) for testing SAB. All arms of the maze measured 50 × 10 cm, and the height of all arms was 30 cm. A black guillotine door created a start box separate from the main alley of the maze. The maze was marked at intervals 15 cm equidistant from the center of the point where the three arms of the maze interconnected. These marks were used to designate the decision area within which a choice of baited arms was being made. Chocolate milk (3 ml) was used as a reward in both arms of the T-maze. Selective serotonergic agents (obtained from Sigma-Aldrich, St. Louis, MO) were the 5-HT_{1A} agonist 8-OH-DPAT and partial agonist buspirone HCl, the 5-HT_2 agonist DOI, and the 5-HT_3 agonist *N*-methyl quipazine (NMQ). All agents were dissolved in 0.3 ml isotonic saline and injected intraperitoneally with a 1-cm^3 syringe.

2.3. Methods

Before any testing, rats were acclimated to the maze for 15 min on each of five separate days. In general, Long–Evans rats required a somewhat longer acclimation period (up to 10 days) before consistent baseline measures could be obtained. During the acclimation period, the animals freely explored all aspects of the maze, and chocolate milk was replaced as needed. Each rat was then confined in the start box for 5 min.

Spontaneous alternation behavior was tested and scored using procedures based on those of Yadin et al. (1991). An individual rat was placed in the start box and the guillotine door was raised. The animal passed through the decision point and made a choice of goal arm often consuming some portion of the chocolate milk reward. The time the rat took to make a decision was recorded by starting the timing when an animal first crossed the line indicating entrance into the decision area. The timing ended when an animal crossed one of the two lines in the baited arms indicating a choice had been made. The animal was then returned to the start box, the chocolate milk was replaced as needed, and the procedure was repeated. While the rat was within the decision area, the

appearance of any VTE behavior was noted. To be designated as a VTE behavior, an animal must give some clear behavioral indication that all possible choices at a decision point are being considered (Tolman, 1939).

During a series of seven trials, a SAB score was assigned to each rat based on the number of repetitions that occurred before an alternation. A right–left or left–right alternation was scored a 1. Repetition in the choice of one arm was scored according to the number of repetitions before an alternation. With this scoring system, the higher the SAB score, the greater the disruption of the normal SAB. Baseline SAB scores were determined for each rat prior to drug testing.

During the drug-testing phase of the experiment, animals were injected with 8-OH-DPAT (2 mg/kg ip), buspirone (1–2 mg/kg ip), NMQ (3 mg/kg ip), DOI (1 mg/kg ip), or vehicle alone (isotonic saline). Behavior was tested 15 min after injection. The dosage for 8-OH-DPAT was identical to that of Yadin et al. (1991) so that direct comparisons could be made with their study. Doses of buspirone (Bizot et al., 1999; Rehman et al., 1999; Esteban et al., 2002), NMQ (Mok et al., 2000), and DOI (Young et al., 1993; Kaur and Ahlenius, 1997; Kurumanji et al., 2000) were selected from other behavioral studies wherein these doses were shown to be effective in rats. Thirteen CD rats were injected with 8-OH-DPAT, eight with buspirone, six with NMQ, four with DOI, and eight with saline. All Long–Evans rats ($N=8$) were injected with 8-OH-DPAT. For each measurement of VTE, a time limit of 5 min was set for a rat to make a choice of arm after reaching the decision point area. If a choice was not made within this time, VTE was recorded as 5 min and SAB was not determined.

Baseline SAB was tested on four different days. On the fourth day of baseline testing, drug testing was also performed. Two to 7 days later, the animals were tested in the maze again, without drug administration, in order to obtain recovery data. All rats were euthanized upon conclusion of the study following the guidelines of the American Veterinary Association.

3. Results

Individual average baseline SAB scores varied from 1.1 to 2.3 with a mean baseline score of 1.5 (Fig. 1). Behavioral scores ranged from 1.8 to 7.0 after administration of 8-OH-DPAT. The mean score was 4.7 for 8-OH-DPAT (Fig. 1). Animals retested at least 48 h after drug administration had SAB scores that were indistinguishable from the baseline, pre-agonist testing.

In contrast to the effects of 8-OH-DPAT, behavioral scores after agonist administration ranged from 1.2 to 2.0 for NMQ, 1.1 to 1.7 for DOI, and 1.2 to 5.4 for saline. Mean SAB scores were 1.6 for NMQ, 1.6 for DOI, and 1.9 for saline (Fig. 1). In a comparison of baseline measurements with the effects of 8-OH-DPAT (mean SAB = 4.7), a repeated-measures ANOVA yielded significant results

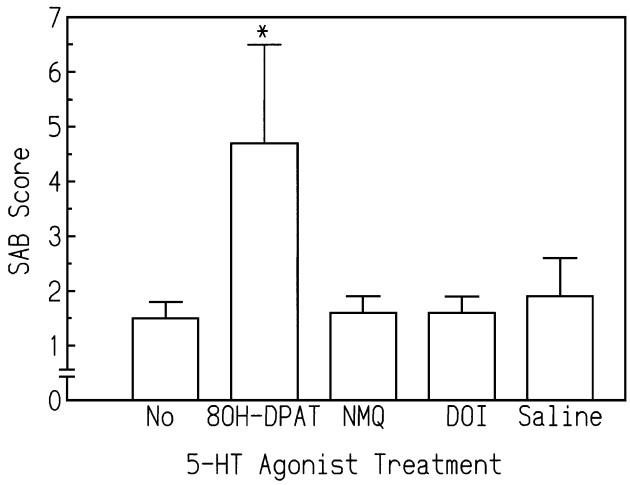

Fig. 1. Effects of 5-HT agonists on SAB. A SAB score was assigned to each rat based on the number of alternations or repetitions that occurred during each series of seven trials. Baseline SAB scores (No = no injection with agonist) were determined for each rat prior to drug testing. During the drug-testing phase of the experiment, animals were injected with 8-OH-DPAT (2 mg/kg ip), NMQ (3 mg/kg ip), DOI (1 mg/kg ip), or vehicle alone (saline) and behavior was tested 15 min after injection. Thirteen Sprague–Dawley rats were injected with 8-OH-DPAT, six with NMQ, four with DOI, and eight with saline. Values are mean ± S.E.M. * Only rats injected with 8-OH-DPAT had SAB values significantly different ($P<.001$) from baseline.

[$F(1,15)=19.6$, $P<.0001$]. Bonferroni post hoc testing illustrated that the effect of 8-OH-DPAT on SAB scores was significantly different than the effect of NMQ, DOI, or saline ($P<.0001$ in all cases).

Mean times spent performing VTE behaviors were also determined (Fig. 2) for CD rats. In this study, VTE was characterized consistently by the rat stopping at the decision point with repetitive head movements back and forth in the directions of the baited arms of the maze. In some cases, the rat would start down one arm only to stop, turn around, and return to the decision point. Overall, the time spent within the decision area ranged from 1 to 19 s with a mean of 5 s for baseline measurements. After injection with serotonin agonists, time spent within the decision area ranged from 53 to 242 s for 8-OH-DPAT with a mean of 113 s. For NMQ, the mean time spent in the decision was 9 s with a range of 2 to 50 s. For DOI, the mean time spent in the decision area was 5 s with a range of 2 to 15 s. A 3 (drug group) × 8 (baseline/drug trials) mixed-design ANOVA illustrated that VTE durations after 8-OH-DPAT injection were significantly different than baseline measurements [$F(2,7)=59.5$, $P<.0001$]. The same analysis revealed that VTE measures within a series of trials did not differ significantly [$F(1,7)=3.2$, $P>.05$]. Moreover, there was no significant Trials × Drug interaction [$F(2,7)=3.8$, $P>.05$]. Rats injected with buspirone moved into the decision area and generally to the decision point between the two baited arms. At this point, VTE behavior persisted throughout the 300-s time period. Therefore, VTE but not SAB scores were recorded for rats injected with buspirone.

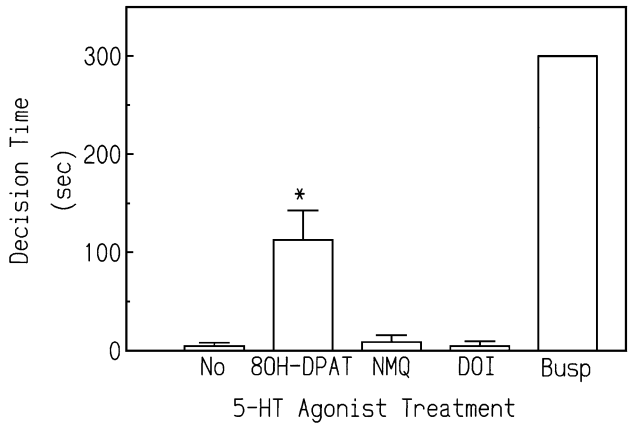

Fig. 2. Effects of 5-HT agonists on VTE. Following initial baseline measurements (No = no injection), rats were injected with 8-OH-DPAT (2 mg/kg ip), NMQ (3 mg/kg ip), DOI (1 mg/kg ip), or buspirone (Busp, 1–2 mg/kg ip) and behavior was tested 15 min after injection. The time spent by each rat in the decision area was determined. VTE data were obtained for three animals injected with 8-OH-DPAT, three injected with NMQ, four injected with DOI, and eight injected with buspirone HCl. Values are mean ± S.E.M. * Values for 8-OH-DPAT were significantly greater than baseline ($P < .001$) or than NMQ or DOI ($P < .001$). * * Rats injected with buspirone (Busp) failed to move beyond the decision point within the 5 min (300 s) limit set for the analysis.

To obtain some additional comparative results with another rat strain, SAB scores were determined before and after injecting Long–Evans rats with 8-OH-DPAT. Baseline SAB scores yielded a mean of 1.3 ± 0.2. The SAB score was approximately threefold higher (3.7 ± 0.7) after injection with 8-OH-DPAT. This effect of 8-OH-DPAT was statistically significant ($P < .01$) and comparable to the results obtained with CD rats.

4. Discussion

Based on the work of Yadin et al. (1991), it was proposed that selective activation of the 5-HT_{1A} receptor would cause a significant increase in repetitive behavior as measured by high scores in the SAB paradigm. In the present study, rats tended to choose repetitively one arm of the maze after receiving a single injection with 8-OH-DPAT. Their SAB scores averaged approximately three times higher after receiving 8-OH-DPAT and this was observed with both the Charles River CD and Long–Evans strains of rats. These scores showing disruption of SAB were comparable to those initially reported for adult Sprague–Dawley rats injected with 8-OH-DPAT or the less selective 5-HT agonist, 5-MeODMT (Yadin et al., 1991). The acute effect of 8-OH-DPAT was eliminated when the rats were treated chronically with an SSRI (Yadin et al., 1991). In the present study, the specificity of the effects of the 5-HT_{1A} receptor agonist was demonstrated by the lack of significant effects of 5-HT_2 and 5-HT_3 agonists on SAB. Initial trials have suggested that the effect of 8-OH-DPAT can be reduced by injecting rats with the 5-HT_{1A} receptor antagonist, WAY 100635 (1 mg/kg; O'Neill and Parameswaran, 1997) 10–15 min before injecting them with 8-OH-DPAT (Palumbo, Broy, and Rhoads, unpublished observations).

Given the interpretation that the disruption in SAB can serve as a model for OCD, it was also expected that animals injected with 5-HT_{1A} receptor agonists might take longer to reach a decision and that the additional time may be spent in VTE behavior. Administration of either 8-OH-DPAT or buspirone resulted in significant increases in VTE behavior as measured by the times that animals took to choose either the right or the left arm of the T-maze. In this study, VTE was characterized consistently by the rat stopping at the decision point with repetitive head movements back and forth in the directions of the baited arms of the maze. In some cases, the rat would start down one arm only to stop, turn around, and return to the decision point. Because the animals appeared to be considering and reconsidering the two arms of the maze, these behaviors satisfy the criteria established for designating VTE behavior (Tolman, 1939). In the case of buspirone, the rats failed to make a choice within the time limits set for each trial and essentially the entire time was occupied with VTE. The hypothesis that these effects would be specific for the 5-HT_{1A} receptor was again supported, as 5-HT_2 and 5-HT_3 agonists had no significant effect on VTE.

The results with saline administration were similar to baseline SAB measures and were different from measures obtained after 8-OH-DPAT administration. Thus, any mild trauma associated with intraperitoneal injection was without measurable effect on the SAB and VTE behaviors. The effects of NMQ and DOI on SAB and VTE were statistically similar to the effects of saline. Full dose responses were not performed with any of the receptor agonists and the results, especially the negative results obtained with DOI and NMQ, must be considered accordingly. However, the dose tested for DOI was at (Young et al., 1993; Kaur and Ahlenius, 1997; Kurumanji et al., 2000) or above (Krebs-Thomson et al., 1998) the highest dose used to characterize other behavioral effects of DOI on rats. Similarly, although less behavioral work has been reported for NMQ, a dosage was selected that was within the range where NMQ has been shown to be effective in rats (Mok et al., 2000). In addition, NMQ binds to the 5-HT_3 receptor with an affinity similar to that of the less selective agonist quipazine (Glennon et al., 1989) and the dose used for NMQ is on the higher end of the range used in eliciting the behavioral effects of quipazine (e.g., Rudissaar et al., 2001). Thus, for each of the receptor agonists tested, a dosage was selected because it had been shown to be effective in other studies, and because it was within the range over which the effect (or lack of effect) of an agonist could be associated with its known receptor specificity. The latter may not be true of higher doses and so these were not tested.

While both buspirone and 8-OH-DPAT disrupted SAB, this disruption differed in that the rats injected with buspir-

one did not get beyond VTE within the limits of our analysis. In most systems, 8-OH-DPAT has full agonist activity while buspirone is considered a partial agonist (Hoyer et al., 1994). Buspirone is also an antagonist at the dopamine D2 receptor (Bridge et al., 2001; Esteban et al., 2002; Pauwels and Koek, 2002). Differences in the effects of buspirone and 8-OH-DPAT have been reported. In measures of 5-HT synthesis in rat brain, Brambilla et al. (1999) showed the two 5-HT_{1A} receptor agonists had maximal effects in different brain regions. Disruption of SAB in rats may provide a useful behavioral model with which to explore further the differences between buspirone and 8-OH-DPAT.

The results from the present study build upon the proposal that the SAB behavioral paradigm can serve as a model of human OCD. As presented initially (Yadin et al., 1991) and now extended to include the CD and Long–Evans strains and the additional 5-HT_{1A} receptor agonist buspirone, disrupted SAB is in certain respects similar to the maladaptive, repetitive motor behaviors seen among patients with OCD. Given the specificity in the effects of 5-HT_{1A} receptor agonists, it might be expected then that the reported effects of mCPP on OCD patients (Zohar et al., 1987; Pigott et al., 1991; Stern et al., 1998) are due to the affinity of mCPP for the 5-HT_{1A} receptor and that activity at synapses involving 5-HT_{1A} receptors plays a crucial role in the compulsive behavior seen among patients with OCD. However, serotonin is not the only neurotransmitter implicated in repetitive behaviors or specifically in the treatment of OCD. Dopamine may play a central role in some forms of OCD (Goodman et al., 1990). In other animal studies, quinpirole hydrochloride, a dopamine agonist, induced compulsive checking behavior in rats (Szechtman et al., 1998). Administration of clomipramine hydrochloride, a less selective 5-HT reuptake inhibitor, postponed but did not prevent the repetitive behaviors that were induced by quinpirole. Heightened levels of synaptic 5-HT, a short-term effect of SSRIs, may lead to changes in other neurotransmitter and neuromodulator systems (Greist and Jefferson, 1998). Interplay of noradrenergic and serotonergic mechanisms is central to depression (Blier, 2001) and neurotransmitter interactions would be expected to be no less important in an equally complex disorder such as OCD.

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