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The 5-HT₇ receptor influences stereotypic behavior in a model of obsessive-compulsive disorder

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Abstract

The 5-HT₇ receptor has been suggested as a new putative target for the treatment of neuropsychiatric disorders, especially depression. This hypothesis is based on the finding that antidepressant drugs have relatively high affinity for the 5-HT₇ receptor, and that inactivation or blockade of the receptor leads to an antidepressant-like profile in behavioral models and sleep parameters. Obsessive-compulsive disorder is also believed to involve the serotonergic system and is treated using antidepressants, thus it is of interest to study the possible role of the 5-HT₇ receptor in this disorder. We have evaluated the effect of inactivation or pharmacological blockade of the 5-HT₇ receptor in three mouse behavioral models that are believed to mimic some of the stereotypic aspects of obsessive-compulsive disorder. In the most well established behavioral model, marble burying, both inactivation and blockade of the 5-HT₇ receptor reduced stereotypic behavior in that the number of marbles buried decreased. In two newer, less well characterized models, head dipping and plastic-mesh screen chewing, there was no difference between wild-type mice and mice lacking the 5-HT₇ receptor. Taken together the data confirms and expands on previous findings that the 5-HT₇ receptor is of importance for behaviors affected by antidepressants, and suggests that the 5-HT₇ receptor might be of relevance as a target for the treatment of obsessive-compulsive disorder.

Keywords

serotonin; marble burying; head dipping; screen chewing; SB-269970

The 5-HT₇ receptor, one of the most recently discovered receptors for serotonin [12], has been found to modulate behaviors affected by antidepressant drugs. In both the forced swim test and the tail suspension test, inactivation or blockade of the 5-HT₇ receptor lead to antidepressant-like behavior [7,13,35]. Furthermore, inactivation or pharmacological blockade of the 5-HT₇ receptor lead to changes in rapid eye movement sleep that are opposite to those seen in depression [8,13]. In addition, it has been shown that certain antidepressants might exert some of their effects by acting directly at the 5-HT₇ receptor [26].

Obsessive-compulsive disorder (OCD) is a debilitating disease with an overall prevalence of close to 1 % [15]. There is strong evidence in support of a significant role for 5-HT in OCD and antidepressant drugs, mainly selective serotonin reuptake inhibitors (SSRIs), are the pharmacological treatment of choice for OCD [4,15]. However, as many as 40 % of patients do not respond to currently available treatment options [15], so continued research is necessary.

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Establishing good animal models for OCD has proved to be exceedingly difficult, most clearly demonstrated by the large number of models tried [21,23]. Marble burying is one of the more well-established models for OCD [19,27,28]. New models of supposedly stereotypic behavior, such as the screen chewing and head dipping tests used along with marble burying in the present study, are also continuously being developed and tested [2].

Even though SSRIs supposedly act by blocking the 5-HT transporter, and polymorphisms in the gene for this protein might be related to OCD [5,24], several 5-HT receptor subtypes have also been implicated in OCD. A recent study showed that mice lacking the 5-HT_{2C} receptor show increased compulsive behavior in several behavioral tests [2]. However, the involvement of the 5-HT_{2C} receptor is controversial as both agonists and antagonists have induced or worsened symptoms of OCD [18,20,31,37]. Studies have also suggested that 5-HT_{2A} receptor agonism might have beneficial anti-OCD effects [25,29]. Other evidence suggest an involvement of the 5-HT_{1A} receptor, since agonists at this receptor, specifically, 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT) have been shown to reduce OCD-like behavior [19,23].

As 8-OH-DPAT is also an agonist at 5-HT₇ receptors, and since 5-HT₇ receptors influence behaviors modified by antidepressants, it is of interest to study the possible involvement of this receptor in models of OCD. We have investigated the effects of inactivation or blockade of the 5-HT₇ receptor on marble burying, screen chewing, and head dipping behavior.

Ten-to-twelve week old male 5-HT₇^{-/-} mice and their male 5-HT₇^{+/+} sibling controls were used. The generation of the 5-HT₇^{-/-} mouse strain has been described previously [10]. The mice used in this study had been back-crossed on a C57BL/6J background for at least 16 generations.

Marble-burying behavior was studied as previously described [19,36]. Twenty-four glass marbles (1.5 cm in diameter) were placed on 5 cm of sawdust bedding along the perimeter of a clear plastic box (44 × 22 × 20 cm). An individual mouse was placed in the box for 30 min. and the number of marbles buried at least two-thirds deep were counted. The effect of (R)-3-(2-(2-(4-methylpiperidin-1-yl)-ethyl)pyrrolidine-1-sulfonyl)phenol (SB-269970; 10 mg/kg) given as a single intraperitoneal injection 30 min. prior to the test was also evaluated. This dose was chosen based on its effectiveness in other behavioral and thermoregulation experiments [11,13]. SB-269970 was dissolved in 0.9% NaCl, which was also used as vehicle control.

Plastic mesh screen chewing and head dipping behavior was tested with minor modifications as previously described [2]. For screen chewing mice were individually housed with free access to food and water. A plastic circular grid-style mat (screen) with a diameter of 7 cm was placed in the cage during a ten-day period. The screen was weighed before and after the experiment. Differences in appearance of the screens indicating different chewing patterns were determined at the end of the experiment. A “spoke” was defined as a freed piece of screen (1.5 – 3.0 mm in length) that radiated from the center of the circular screen. A “spoke site” was defined as a location where a spoke was present or the mouse had chewed a radial segment to less than 1.5 mm.

For head-dipping habituation, mice were individually housed and weighed before testing and on each day of testing. Food intake was assessed by weighing available food. Food was removed before the first trial of a day and returned after the last trial, making food available for 21 h each day. The head dipping was studied using a 30 × 30 cm platform with a single 3.5 cm hole in the center placed on a 20 cm high bucket. The platform was screened from the rest of the room except for a small space where the investigator could observe the behavior. On three consecutive days, each mouse was given a 10-min trial repeated three times at 1-h intervals. The number of head dips was scored. A dip was defined as submerging the head into

the hole with both eyes below the surface of the platform. The platform was wiped down with ethanol between individual mice.

All values are expressed as means $\pm$ standard errors of mean (S.E.M.). Student's t-test was used to compare non-paired groups for a single independent variable and two-way ANOVA was used to compare data sets with two independent variables. $p < 0.05$ was considered significant.

In the marble burying test, in untreated animals there was a 55% reduction in the number of marbles buried by 5-HT₇^{-/-} mice compared to 5-HT₇^{+/+} mice (Fig. 1A). A two-way ANOVA showed significant effect for genotype ($F(1, 28) = 8.53, p < 0.01$), treatment (SB-269970) ($F(1, 28) = 12.62, p < 0.01$), and for an interaction between the two ($F(1, 28) = 5.24, p < 0.05$). Thus, 5-HT₇^{-/-} mice buried fewer marbles than 5-HT₇^{+/+} mice, and 5-HT₇^{+/+} mice treated with SB-269970 buried fewer marbles than vehicle-treated 5-HT₇^{+/+} mice (Fig. 1B). In other words, inactivation or blockade of the 5-HT₇ receptor induced a similar reduction in the number of marbles buried.

The results from the screen chewing test are summarized in Table 1. There were no differences that reached significance in the amount chewed or in the chewing pattern between 5-HT₇^{+/+} and 5-HT₇^{-/-} mice.

A two-way ANOVA of the head dipping data showed a significant effect for session ($F(8,240) = 19.55, p < 0.0001$), but no effect for genotype ($F(1,240) = 1.33, p = 0.26$) and no significant interaction between the two ($F(8,240) = 1.11, p = 0.35$). Thus, there was a significant habituation seen in the behavior that was similar in both 5-HT₇^{+/+} and 5-HT₇^{-/-} mice (Fig. 2). The habituation was most pronounced during the first day of testing.

The major finding of the present study was that inactivation or blockade of the 5-HT₇ receptor reduced marble burying behavior, a mouse behavioral model linked to OCD and anxiety. A similar reduction in the number of marbles buried was observed in mice lacking the 5-HT₇ receptor as in wild-type mice given a single injection of the selective 5-HT₇ receptor antagonist SB-269970 (10 mg/kg). The similarity in effect seen between inactivation and blockade is in line with previous studies evaluating models of depression [7,13,35]. In both the forced swim test and the tail suspension test an antidepressant-like effect has been observed after inactivation of the 5-HT₇ receptor [7,13] and also after treatment with a selective antagonist [13,35].

It has previously been found that agonism at the 5-HT_{1A} receptor also reduces marble burying behavior [19,23]. This is of interest in relation to previously described relationships between 5-HT_{1A} and 5-HT₇ receptors. As 5-HT_{1A} receptors inhibit adenylyl cyclase [3] and 5-HT₇ receptors activate it [22], it could easily be hypothesized that agonism at the 5-HT_{1A} receptor and antagonism at the 5-HT₇ receptor produced the same effect. Indeed, the present results would support such a hypothesis. However, several previous studies found that antagonism or inactivation of both receptor subtypes produce the same result. This has been the case in thermoregulation where blocking or inactivating 5-HT_{1A} or 5-HT₇ receptors inhibit the hypothermic effect induced by 5-HT [6,11,17]. A similar relationship is also seen in models of depression in which mice lacking the 5-HT_{1A} receptor and mice lacking the 5-HT₇ receptor both show decreased immobility in the tail suspension test and the forced swim test [7,13,14, 30,32]. Further studies are required to fully describe the functional relationship between 5-HT_{1A} and 5-HT₇ receptors and their effects on second messengers at the systems level.

The 5-HT₇ receptor has previously been suggested as a putative target for the treatment of depression as blockade or inactivation of the receptor leads to an anti-depressant like profile in animal models of depression and in sleep parameters [7,8,13]. The present results support

that notion as antidepressants have been shown to reduce marble burying [16,29]. The mechanism behind such an antidepressant-like profile remains unclear, but might include the localization of the receptors to areas such as the hippocampus and amygdala [12], and/or their possible regulation of the activity of serotonergic neurons by interactions with glutamatergic [9] or GABAergic [34] neurons in the raphe nuclei.

Marble burying has also been used as a model for anxiety as anxiolytic agents such as diazepam have been shown to reduce burying behavior [28]. Indeed, antidepressants, particularly SSRIs, are effective in the treatment of anxiety [1]. The degree of reduction in the number of marbles buried observed in the present study is similar to that observed with benzodiazepines in C57BL/6J mice [27]. Even greater reduction in the number of marbles buried can be achieved with other anxiolytics, e. g. buspirone [27]. However, the possible role of 5-HT₇ receptors in anxiety is not clearly understood. One study found no change in mice lacking the 5-HT₇ receptor in the light-dark transfer test, a model of anxiety [33], and another study saw no change in the elevated plus maze in such mice [7]. In contrast, a third study found that the selective 5-HT₇ receptor antagonist SB-269970 had an anxiolytic effect in rats in the elevated plus maze, although with an inverted U-shaped dose-response curve and with an effect smaller than observed with diazepam in the same study [35]. Further studies are needed to more clearly define the role, if any, of 5-HT₇ receptors in anxiety.

Certain drugs, however not the most commonly used anxiolytics or antidepressants, will reduce marble burying behavior at least partly by reducing spontaneous locomotor activity [27]. It is unlikely that this is the case in the present study, as it has been previously shown that locomotor activity is not altered in 5-HT₇^{-/-} mice [33] and that SB-269970 at any dose tested, including the one used in the present study, does not alter locomotor activity in C57BL/6J mice [35].

The lack of effect observed in the present study in the screen chewing and head dipping tests is currently difficult to interpret. These tests have to our knowledge only been used in one previous study [2] and it is therefore difficult to design a positive control. Their correlation, if any, to the marble burying test has never been evaluated. In view of the lack of difference between 5-HT₇^{+/+} and 5-HT₇^{-/-} mice in screen chewing and head dipping we did not evaluate the possible modulation by SB-269970 of these behaviors, as there in our hands has always been a correlation between effects observed after inactivation and blockade of the 5-HT₇ receptor. Nevertheless, the tests have been suggested as models for compulsive-like behavior, especially in view of the distinct chewing pattern observed in mice lacking the 5-HT_{2C} receptor in the screen chewing test [2]. A definitive conclusion on the possible relevance of these tests for animal behavior in general and OCD in particular awaits future studies.

In conclusion, the present study show that inactivation of the 5-HT₇ receptor leads to decreased burying behavior in the marble burying test, a model linked to OCD and anxiety, a finding that is also mimicked in wild-type mice after treatment with a selective 5-HT₇ receptor antagonist. The results strengthen and extend the hypothesis that antagonism of the 5-HT₇ receptor might be a valuable approach for the treatment of disorders, such as major depression and OCD, currently treated with antidepressants.

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Fig. 1.

In the marble burying test (A) 5-HT₇^{-/-} mice buried fewer marbles than 5-HT₇^{+/+} mice. A similar reduction in burying behavior (B) could be induced in 5-HT₇^{+/+} mice by a single injection of the selective 5-HT₇ receptor antagonist SB-269970 (10 mg/kg) given intraperitoneally 30 min. before the test. The antagonist had no effect in 5-HT₇^{-/-} mice. Data is presented as mean $\pm$ S.E.M. $n = 8$ animals per group. ** $p < 0.01$, student's t -test (A) or two-way ANOVA followed by Newman-Keuls post-hoc analysis (B).

Fig. 2.

There was no difference between 5-HT₇^{+/+} mice (open symbols) and 5-HT₇^{-/-} mice (filled symbols) in the head dipping test. (A) shows data for each of the three daily sessions and (B) shows the daily average for the three consecutive days of testing. Both genotypes show a similar habituation, which was most marked during the first day of testing. Data is presented as mean $\pm$ S.E.M. $n = 16$ animals per genotype.

Table 1

There was no difference between 5-HT₇^{+/+} mice and 5-HT₇^{-/-} mice in any of the parameters measured in the screen chewing test.

Genotype	n	Amount chewed (g)	Spoke sites	Spokes	Remaining spokes (%)
5-HT ₇ ^{+/+}	16	0.16 ± 0.05	10.25 ± 5.39	2.31 ± 1.85	96.45 ± 1.87
5-HT ₇ ^{-/-}	16	0.10 ± 0.06	8.38 ± 5.98	3.44 ± 2.99	97.09 ± 2.08

Data is presented as mean ± S.E.M.