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The 5-HT$_7$ receptor and disorders of the nervous system: an overview

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Abstract

Rationale—The 5-HT$_7$ receptor is a more recently discovered G-protein-coupled receptor for serotonin. The functions and possible clinical relevance of this receptor are not yet fully understood.

Objective—The present paper reviews to what extent the use of animal models of human psychiatric and neurological disorders have implicated the 5-HT$_7$ receptor in such disorders. The studies have used a combination of pharmacological and genetic tools targeting the receptor to evaluate effects on behavior.

Results—Models of anxiety and schizophrenia have yielded mixed results with no clear role for the 5-HT$_7$ receptor described in these disorders. Some data are available for epilepsy, migraine, and pain but it is still very early to draw any definitive conclusions. There is a considerable amount of evidence supporting a role for the 5-HT$_7$ receptor in depression. Both blockade and inactivation of the receptor have resulted in an antidepressant-like profile in models of depression. Supporting evidence has also been obtained in sleep studies. Especially interesting are the augmented effects achieved by combining antidepressants and 5-HT$_7$ receptor antagonists. The antidepressant effect of amisulpride has been shown to most likely be mediated by the 5-HT$_7$ receptor.

Conclusions—The use of pharmacological and genetic tools in preclinical animal models strongly supports a role for the 5-HT$_7$ receptor in depression. Indirect evidence exists showing that 5-HT$_7$ receptor antagonism is clinically useful in the treatment of depression. Available data also indicate a possible involvement of the 5-HT$_7$ receptor in anxiety, epilepsy, pain, and schizophrenia.

Keywords

anxiety; depression; epilepsy; migraine; pain; schizophrenia; sleep

Introduction

Being among the most recently discovered receptors for serotonin (5-hydroxytryptamine, 5-HT), the 5-HT$_7$ receptor is also one of the least well characterized (Hedlund and Sutcliffe 2004; Shireman et al. 2008; Thomas and Hagan 2004). The initial cloning of the 5-HT$_7$ receptor was published in 1993 by several laboratories independently (Lovenberg et al. 1993; Bard et al. 1993; Ruat et al. 1993; Shen et al. 1993). Nevertheless, during the last several years a large amount of information has been collected about this receptor. A physiological role for the 5-HT$_7$ receptor within the central nervous has been clearly established in circadian rhythm regulation (Glass et al. 2003) and in thermoregulation (Hedlund et al. 2004). Interesting findings have also been made in studies focusing on learning and memory. Strong evidence supports an involvement of the 5-HT$_7$ receptor in specific aspects of hippocampus-dependent

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contextual learning and memory processing (Roberts et al. 2004; Gasbarri et al. 2008; Eriksson et al. 2008; Sarkisyan and Hedlund 2009). A role has also been suggested in neuroendocrine regulation (Jørgensen 2007). Possible functions in the periphery are mostly related to the presence of 5-HT_7 receptors on smooth muscle cells. Thus, a role for the 5-HT_7 receptor has been suggested in irritable bowel syndrome (Beattie and Smith 2008), the control of micturition (Read et al. 2003; Recio et al. 2009), and in the reproductive system (Graveleau et al. 2000). Even though of significant interest, these topics are beyond the scope of the present review.

The early finding that several antipsychotics (Roth et al. 1994) and antidepressants (Monsma et al. 1993; Mullins et al. 1999) have high affinity for the 5-HT_7 receptor, as well as its demonstrated presence in relevant regions of the brain (Bonaventure et al. 2004), has prompted several preclinical studies evaluating the possible involvement of the 5-HT_7 receptor in psychiatric disorders and other pathological processes of the nervous system. These studies have used pharmacological tools and/or mice lacking functional 5-HT_7 receptors in animal behavioral models designed to mimic, at least in part, human disorders. The pharmacological tools are mainly antagonists, with the most widely used being SB-269970 (Hagan et al. 2000) and DR4004 (Kikuchi et al. 1999). Although generally considered selective, they have been shown to also interact with other receptors (Kogan et al. 2002; Bonaventure et al. 2004). A truly selective agonist for the 5-HT_7 receptor is not available. The most frequently used candidate is AS-19, but a recent binding profile showed that it has affinity also for other receptors (Bosker et al. 2009). Several laboratories have independently created constitutive knockout mouse strains lacking the 5-HT_7 receptor (Hedlund et al. 2003; Guscott et al. 2005; Witkin et al. 2007). As seen below a considerable body of evidence supports a role for the 5-HT_7 receptor in depression. In fact, a recent study suggests that the clinically established antidepressant effect of amisulpride is due to its action at 5-HT_7 receptors (Abbas et al. 2009). Studies aimed at evaluating disorders such as anxiety and schizophrenia have also generated interesting results. The most relevant findings are summarized in alphabetical order in Table 1. The studies listed in the table together with additional supporting and sometimes contradicting evidence are discussed in the following.

Anxiety

Efforts to evaluate a possible link between the 5-HT_7 receptor and anxiety have generally been inconclusive. Behavioral characterizations of mice lacking the 5-HT_7 receptor (5-$HT_7^{-/-}$) did not detect any differences compared to 5-$HT_7^{+/+}$ mice in two anxiety models. Mice developed at The Scripps Research Institute and bred on a C57BL/6J background were evaluated in a light-dark transfer test. It was found that both genotypes spent the same amount of time in the light compartment and that they had an equal number of transitions between the light and dark compartments (Roberts et al. 2004). When a different strain of 5-$HT_7^{-/-}$ mice developed by Merck and bred on a mixed 129SvEv/C57BL/6J background were tested in an elevated plus maze there was no difference in the time spent exploring the open arms or in the number of entries onto the open arms of the maze between the two genotypes (Guscott et al. 2005). The selective 5-HT_7 receptor antagonist SB-269970 (Hagan et al. 2000) has been evaluated in both rats and mice for potential anxiolytic effect. In rats the drug induced an anxiolytic effect in the Vogel conflict drinking test and the elevated plus maze models of anxiety after both systemic (Wesolowska et al. 2006a) and intra-hippocampal (Wesolowska et al. 2006b) administration. Thus, SB-269970 increased the number of shocks tolerated in the Vogel test. In the elevated plus maze SB-269970 increased both the number of entries onto the open arms and the amount of time spent on those arms. It should be noted that SB-269970 generally had an inverted U-shaped dose-response effect and its anxiolytic effect was not as pronounced as that of diazepam, a reference anxiolytic of the benzodiazepine class (Wesolowska et al. 2006a, 2006b). SB-269970 also had a similar limited anxiolytic effect in the conflict-based four-plate test in mice as the drug increased the number of punished crossings (Wesolowska et al. 2006a). Again

the effect was smaller than seen for diazepam. Possible interpretations of the different findings are that there are species differences in anxiety-related behavior, or that compensatory mechanisms in constitutive knockouts influence the results. The narrow dose-range of SB-269970 that had an anxiolytic effect is most likely not possible to mimic in knockout mice. The overall picture becomes even more complicated when considering that the reduced marble burying behavior seen in 5-HT_7 $^{-/-}$ mice (see below) also can be considered an anxiolytic effect (Hedlund and Sutcliffe 2007).

Depression and circadian rhythm

It has been firmly established that the three closely linked physiological phenomena, circadian rhythms, sleep (see below), and mood, are all regulated by the 5-HT_7 receptor. Soon after the discovery of the receptor, it was shown that 8-OH-DPAT-induced phase resetting within the suprachiasmatic nucleus (SCN) was mediated by the 5-HT_7 receptor (Lovenberg et al. 1993). It should be noted that 8-OH-DPAT was previously considered a selective agonist for 5-HT_{1A} receptors (Hjorth et al. 1982), and the realization that it also activates 5-HT_7 receptors has prompted the reevaluation of many findings. A series of recent studies have provided additional evidence for the importance of the 5-HT_7 receptor in SCN function (Antle et al. 2003; Duncan et al. 2004; Glass et al. 2003; Sprouse et al. 2004, 2005). That the phase shifting induced by 8-OH-DPAT is mediated by the 5-HT_7 receptor is supported by the finding that the shift can be inhibited by the selective antagonists SB-269970 and DR-4004 (Ehlen et al. 2001; Sprouse et al. 2004; Kikuchi et al. 1999). However, in one study the putative 5-HT_7 receptor agonist AS-19 failed to mimic the effect of 8-OH-DPAT after systemic administration (Cuesta et al. 2009). Only one dose of AS-19 was tested and there is some uncertainty about the selectivity of AS-19 (Bosker et al. 2009).Shifting the SCN pacemaker neurons with 8-OH-DPAT is a non-photic stimulus involving serotonergic input from the dorsal and median raphe nuclei. In these nuclei 5-HT_7 receptors have been shown to modulate SCN phase resetting (Glass et al. 2003). The 5-HT_7 receptor is probably also involved in photic regulation of the SCN. It has been demonstrated using pharmacological profiling with unselective drugs (Ying and Rusak 1997) and with DR-4004 (Ehlen et al. 2001) that 5-HT-mediated reduction of photic stimulation of SCN neurons is most likely mediated by the 5-HT_7 receptor. The inhibitory effect of 8-OH-DPAT on spontaneous SCN activity is also mediated by the 5-HT_7 receptor (Yu et al. 2001). The above studies were performed in either rats or hamsters. In the mouse however, the effects of 8-OH-DPAT and hence the 5-HT_7 receptor on SCN function are not as pronounced (Antle et al. 2003).

The interaction of antidepressants with the 5-HT_7 receptor has been suggested to, at least in part, account for their function (Monsma et al. 1993; Mullins et al. 1999). Several antidepressants, both tricyclics and selective serotonin reuptake inhibitors (SSRI), induced c-*fos* expression in a way consistent with 5-HT_7 receptor activation within the SCN (Mullins et al. 1999). The effect on c-*fos* expression was attenuated after chronic treatment with antidepressants. Furthermore, chronic antidepressant drug treatment led to a downregulation of 5-HT_7 receptor binding (Mullins et al. 1999).

The forced swim test and the tail suspension test are two of the most common behavioral models for evaluating the antidepressant potential of a drug or to evaluate the phenotype of transgenic animals with respect to depression (Cryan et al. 2002; Cryan and Holmes 2005). In both of these models, pharmacological blockade of the 5-HT_7 receptor or inactivation of the receptor gene leads to an antidepressant-like behavioral profile; that is, reduced immobility (Hedlund et al. 2005; Guscott et al. 2005; Bonaventure et al. 2007; Wesolowska et al. 2006a, 2006b, 2007). It has even been shown that there is a synergistic interaction between individually ineffective doses of the selective antagonist SB-269970 and antidepressants, leading to reduced immobility in both the forced swim test and the tail suspension test (Bonaventure et al. 2007;

Wesolowska et al. 2007). Thus, concurrent administration of citalopram, an antidepressant of the SSRI type, and SB-269970 has been shown to reduce immobility in the tail suspension test in C57BL/6J mice (Bonaventure et al. 2007). At a higher dose, SB-269970 alone reduces immobility in the mouse tail suspension test (Hedlund et al. 2005; Bonaventure et al. 2007). This higher dose of SB-269970 did not alter 5-HT concentration in the rat frontal cortex, but the combination of a low dose of SB-269970 and a low dose of citalopram increased the level of 5-HT in the frontal cortex (Bonaventure et al. 2007). A similar synergistic interaction between SB-269970 and citalopram has also been demonstrated in the mouse forced swim test (Wesolowska et al. 2007). This study also reported that interactions also occur between SB-269970 and other classes of antidepressants. Thus, ineffective doses of imipramine, desipramine, and moclobemide all reduced immobility in the mouse forced swim test when given in combination with SB-269970 (Wesolowska et al. 2007). The interaction between SB-269970 and imipramine has also been shown in the forced swim test using Wistar rats in which the effect on immobility was accompanied with an increase in 5-HT levels in the prefrontal cortex (Wesolowska and Kowalska 2008). Besides the prefrontal cortex, the hippocampus has also been implicated in the effects of SB-269970 and imipramine in the rat forced swim test (Wesolowska et al. 2006b).

Chronic unpredictable mild stress is a models that attempts to induce a depression-like state in laboratory animals (Willner et al. 1992). In a recent study it was shown that 5-HT_7 receptor mRNA was upregulated in the hippocampus and hypothalamus, but not cortex in rats after exposure to such stress (Li et al. 2009). The change in mRNA levels could be inhibited by treatment with fluoxetine and curcumin, an active ingredient in turmeric extracts (Li et al. 2009).

Interestingly, a recent study has shown that the 5-HT_7 receptor is most likely clinically relevant for the treatment of depression. Amisulpride is an atypical antipsychotic that is also a proven antidepressant (Lecrubier et al. 1997; Smeraldi 1998). The antidepressant effect of amisulpride has traditionally been thought to somehow rely on its properties as a dopamine D_2/D_3 receptor antagonist, although the mechanism has never been satisfactorily explained. It has now been demonstrated that amisulpride has high affinity for the 5-HT_7 receptor and that amisulpride reduces immobility in both the tail suspension test and the forced swim test in 5-HT_7 $^{+/+}$ mice but not in 5-HT_7 $^{-/-}$ mice (Abbas et al. 2009). These findings provide at least indirect evidence that the antidepressant effect of amisulpride is mediated by the 5-HT_7 receptor. It should also be noted that aripiprazole, another atypical antipsychotic that is successfully used to augment the effect of traditional antidepressants (Berman et al. 2009), has high affinity for the 5-HT_7 receptor (Lawler et al. 1999; Shapiro et al. 2003). Taken together with findings in sleep studies (see below) there is thus a consistent body of evidence using both pharmacological and genetic tools that implicates the 5-HT_7 receptor in depression.

Epilepsy

The first study linking the 5-HT_7 receptor with seizure activity was performed before the availability of selective antagonists (Bourson et al. 1997). Instead an affinity correlation analysis was done showing that the relative affinity of seven compounds for the 5-HT_7 receptor correlated with their ability to protect against audiogenic seizures in DBA/2J mice. All of the compounds tested inhibited 5-HTstimulated cAMP formation in cells expressing the 5-HT_7 receptor and were thus antagonists at the receptor (Bourson et al. 1997). Autoradiographic mapping of 5-HT_7 receptor binding sites has revealed that the highest density of these receptors is found in the thalamus (Bonaventure et al. 2004). It has been suggested that the 5-HT_7 receptors in this region might be of importance for epilepsy, especially in the WAG/Rij rat model of absence epilepsy (Graf et al. 2004). These rats exhibit spontaneously occurring spike-wave discharges that can be exacerbated by 8-OH-DPAT. With the realization that 8-OH-

DPAT is an agonist not only for 5-HT_{1A} receptors, but also for 5-HT_7 receptors, it is likely that at least part of the potentiating effect of 8-OH-DPAT on epileptic activity is mediated by the 5-HT_7 receptor. In support of this hypothesis, it was shown that the selective 5-HT_7 receptor antagonist SB-269970 reduced spontaneous epileptic activity in WAG/Rij rats (Graf et al. 2004). In another study investigating both electrically- and chemically-induced tonic-clonic seizures it was found that the seizure threshold was lower in mice lacking the 5-HT_7 receptor (Witkin et al. 2007). This study used a 5-HT_7 $^{-/-}$ strain developed by Lilly Research Laboratories that had been bred on a CD-1 background. Using transcorneal electrical stimulation it was found that 5-HT_7 $^{-/-}$ mice had lower tonic but not clonic seizure threshold. For chemically induced seizures it was found that 5-HT_7 $^{-/-}$ mice exhibited lower thresholds for seizures induced by the GABA antagonist pentylenetetrazole, as well as for seizures induced by cocaine. It is clear that further studies are needed to sort out the role of the 5-HT_7 receptor as being either proconvulsant or anticonvulsant depending on the type of epilepsy, species, or 5-HT_7 receptor manipulation studied.

Migraine

The ability of 5-HT to induce cranial vasodilation under certain conditions has long been thought to be one of the mechanisms involved in migraine (Saxena and Ferrari 1989). Although the effect is most likely not mediated by a single receptor subtype, available evidence clearly suggest a role for the 5-HT_7 receptor. The interest in the 5-HT_7 receptor was initially driven by the observation that several migraine prophylactic drugs showed moderate to high affinity for the 5-HT_7 receptor (Bard et al. 1993; Ruat et al. 1993; Shen et al. 1993). It has been suggested that the 5-HT_7 receptor mediates 5-HT induced dilation of the carotid artery following blockade of 5-$HT_{1B/1D}$ receptors in combination with low sympathetic tone (Villalon et al. 1997). It is, however, unclear how relevant such a mechanism might be for migraine. Before the availability of selective 5-HT_7 receptor antagonists, pharmacological profiling was used to implicate the 5-HT_7 receptor as the most likely mediator of 5-HT induced vasodilation in preparations of the basilar and middle cerebral arteries (Terrón and Falcón-Neri 1999). Later it was shown that such vasodilation could be blocked *in vivo* by SB-269970 (Terrón and Martínez-García 2007). This is also true after 5-HT depletion, suggesting that the 5-HT_7 receptors involved are not sensitized by reduced availability of 5-HT (Martínez-García et al. 2009). The 5-HT_7 receptor has also been shown to mediate relaxation in a pial vein preparation (Ishine et al. 2000). Further studies are needed to determine if the 5-HT_7 receptor can be targeted for the prophylaxis or treatment of migraine.

Obsessive-compulsive disorder

As obsessive-compulsive disorder consists of both obsessive thoughts and compulsions characterized by a high degree of stereotypic behavior, this disorder has proven to be very difficult to model in laboratory animals. The pharmacological treatment of choice for obsessive-compulsive disorder is antidepressants, specifically SSRIs (Heyman et al. 2006). Thus, with the antidepressant-like effects of 5-HT_7 receptor blockade or inactivation it was hypothesized that similar manipulations could be relevant for studying obsessive-compulsive disorder. One fairly well established model for obsessive-compulsive disorder is marble burying, even though several investigators regard this mainly as a model for anxiety (Nicolas et al. 2006). Nevertheless, using marble burying it has been demonstrated that pharmacological blockade of the 5-HT_7 receptors with SB-269970 or genetic inactivation of the receptor results in a decrease in the number of marbles buried (Hedlund and Sutcliffe 2007). This result can be interpreted as a reduction of stereotypic behavior, and is similar to the effect of antidepressants. Taken together with the findings using depression models, these results provide further support for the notion that the 5-HT_7 receptor is of relevance for disorders currently treated with antidepressants.

Pain

Several studies have investigated a possible role for the 5-HT_7 receptor in pain. Pain mediation and processing at several levels of the nervous system, including peripheral, spinal, and thalamic mechanisms, have been evaluated. For peripheral pain the 5-HT_7 receptor appears to mediate a pronociceptive effect that can be inhibited by SB-269970 (Rocha-González et al. 2005). In this study flinching behavior following injection of formalin in the paw of rats was assessed. It was found that SB-269970 had a direct local peripheral antinociceptive effect when injected into the paw prior to formalin. Furthermore, SB-269970 could locally counteract the pronociceptive effect of 5-CT. When given intrathecally, SB-269970 had no direct effect on flinching, but could reverse the pronociceptive effect of 5-CT. When one considers additional studies on spinal and thalamic nociception, the interpretation becomes more complex. One study using mice lacking 5-HT_7 receptors did not see a difference in spinal pain mediation using the tail-flick test (Roberts et al. 2004). In another study using the tail-flick model in mice, it was found that intrathecally administered SB-269970 blocked the analgesic effect of morphine given subcutaneously, thus suggesting that the antinociceptive activity of descending serotonergic pathways is mediated by 5-HT_7 receptors (Dogrul and Seyrek 2009). Similar findings were made in a study assessing the effects of spinal microinjections of morphine and SB-269970 using a paw-flick model (Dogrul et al. 2009). The anatomical localization of 5-HT_7 receptors within the spinal cord supports such an interpretation (Doly et al. 2005). Similar conclusions could be drawn from another study also showing antinociceptive properties of spinal serotonergic pathways mediated by the 5-HT_7 receptor (Brenchat et al. 2009). Using both a putative selective agonist, AS-19, and the selective antagonist SB-269970, it was found that the 5-HT_7 receptor modulates capsaicin-induced mechanical hypersensitivity in mice such that the agonist had a dose-dependent antinociceptive effect that could be counteracted by the antagonist (Brenchat et al. 2009). Capsaicin was injected in the plantar surface of a paw which was then mechanically stimulated. The serotonergic compounds evaluated were administered systemically by subcutaneous injections. In rats exposed to an electric shock to the tail it was found that 8-OH-DPAT had an antinociceptive effect when injected into the medial thalamus, specifically the nucleus parafascicularis and the central lateral thalamic nucleus (Harte et al. 2005). This action could be counteracted by selective antagonists for both the 5-HT_{1A} and the 5-HT_7 receptor. The effect was observed for pain behaviors organized at the medullary and forebrain levels, but not at the spinal level, of the neuraxis (Harte et al. 2005). In a possible link between 5-HT_7 receptors, epilepsy, and pain modulation it has been suggested that 5-HT_7 receptors are involved in regulating tonic-clonic seizure-induced antinociception (Freitas et al. 2009). Taken together, available data appear to suggest differing roles for the 5-HT_7 receptor in peripheral versus central pain mediation. Further studies are most likely needed to clarify fully the relationship between the 5-HT_7 receptor and pain.

Schizophrenia

A possible role for the 5-HT_7 receptor in schizophrenia was suggested early on, as it was shown that several antipsychotics had high affinity for the 5-HT_7 receptor (Roth et al. 1994), thus opening up the possibility that some of their effect may be mediated by this receptor. Even though certain typical antipsychotics had relatively high affinity for the 5-HT_7 receptor, particularly high affinities were seen for atypical antipsychotics such as clozapine and risperidone. It was thus speculated that some of the unique properties, e.g. the lack of extrapyramidal side effects, of these drugs could be attributed to an action at the 5-HT_7 receptor (Roth et al. 1994). More recently another drug, amisulpride, with dual antipsychotic and antidepressants properties has also been shown to have high affinity for the 5-HT_7 receptor (Abbas et al. 2009). Action at the 5-HT_7 receptor is most likely relevant for the antidepressant effect of amisulpride, but might also play a role in its antipsychotic action. Several studies have attempted to test the possible relevance of 5-HT_7 receptors in schizophrenia using prepulse

inhibition (PPI). This is an attractive model as it can be used in both humans and laboratory animals. Even though PPI is not a complete model of schizophrenia, it provides a model of the sensorimotor gating deficits seen in schizophrenia patients (Geyer et al. 2001). Of particular interest for the evaluation of antipsychotics, possible new treatments, and new treatment mechanisms is the ability to pharmacologically disrupt PPI. Thus, it has been possible to identify dopaminergic, serotonergic, and glutamatergic components of PPI in which it seems that the dopaminergic mechanisms are most relevant for the action of typical antipsychotics and the glutamatergic mechanisms are most relevant for atypical antipsychotics (Geyer et al. 2001). Using the selective 5-HT_7 receptor antagonist SB-258741 (Lovell et al. 2000), it has been shown that the 5-HT_7 receptor can modulate behavior in the PPI model in Wistar rats (Pouzet et al. 2002). In this study it was found that SB-258741 did not affect amphetamine-induced disruption of PPI. However, phencyclidine (PCP)-induced disruption of PPI was counteracted by SB-258741. Thus, the conclusion was that the 5-HT_7 receptor could influence the glutamatergic, but not the dopaminergic component of PPI (Pouzet et al. 2002). Results that were for the most parts in agreement were obtained in a study using 5-HT_7 $^{-/-}$ mice (Semenova et al. 2008). Thus, the ability of the dopaminergic drugs apomorphine and amphetamine to disrupt PPI was unaltered in 5-HT_7 $^{-/-}$ mice compared to 5-HT_7 $^{+/+}$ mice, whereas the ability of PCP to disrupt PPI was diminished in the 5-HT_7 $^{-/-}$ mice. However, this study did not find any influence of SB-269970 on PCP-disrupted PPI in either C57BL/6J mice (the background strain of the 5-HT_7 $^{-/-}$ mice) or Wistar rats (Semenova et al. 2008). It should be noted that this study and another study using a different strain of 5-HT_7 $^{-/-}$ mice did not observe any inherent differences in PPI in mice lacking the 5-HT_7 receptor (Guscott et al. 2005; Semenova et al. 2008). Somewhat conflicting results were obtained in a recent study using C57BL/6J mice (Galici et al. 2008). This report presented an effect also on the dopaminergic component of PPI. Thus, SB-269970 was able to reverse amphetamine-induced disruption of PPI in C57BL/6J mice. Again, no effect of SB-269970 on the glutamatergic component of PPI was observed as evaluated using ketamine-induced disruption (Galici et al. 2008). In a human study, it has been shown that 5-HT_7 receptor mRNA is downregulated in the dorsolateral prefrontal cortex, but not the hippocampus, of schizophrenics (East et al. 2002). A study analyzing a possible correlation between single nucleotide polymorphisms in the 5-HT_7 receptor gene and schizophrenia found a positive association for two of four evaluated polymorphisms within cohorts of 383 Japanese schizophrenia patients and 351 controls (Ikeda et al. 2006). It is unlikely, however, that the studied polymorphisms cause any differences in 5-HT_7 receptor function. In another population study no correlation was found between single nucleotide polymorphisms in the 5-HT_7 receptor gene and the clinical efficacy of risperidone (Wei et al. 2009), an antipsychotic with high affinity for the 5-HT_7 receptor (Roth et al. 1994).

Sleep

Depressed patients often present a dysregulated circadian rhythm and sleep disturbances (Belmaker and Agam 2008). Specifically, a decreased latency to and increased amount of rapid eye movement (REM) sleep can often be seen in EEG recordings (Yadid et al. 2000). That the 5-HT_7 receptor is directly involved in sleep regulation has been shown using selective antagonists and knockout mice. Both SB-269970 and SB-656104, a related selective antagonist (Thomas et al. 2003), when administered to Sprague-Dawley rats at the beginning of the light period, increased the latency to REM sleep and decreased the amount of time spent in REM sleep (Hagan et al. 2000; Thomas et al. 2003). Other sleep parameters were not affected. Another study has shown that mice lacking the 5-HT_7 receptor exhibit a similar reduction in time spent in REM sleep during the light period, again without affecting other sleep phases (Hedlund et al. 2005). The 5-HT_7 $^{-/-}$ mice also had less frequent and longer REM episodes than the 5-HT_7 $^{+/+}$ mice. In the 5-HT_7 $^{-/-}$ mice there was no change in latency to REM and citalopram was equally effective in increasing the latency to REM in both genotypes (Hedlund

et al. 2005). Interestingly, as in the depression models discussed above, an interaction between individually ineffective doses of SB-269970 and citalopram has been observed also for sleep where such a combination of drugs resulted in an increase in latency to REM and a decrease in the amount of REM sleep in rats (Bonaventure et al. 2007). It was observed that the decrease in the amount of REM sleep was due to a reduced number of REM episodes. Citalopram alone caused increased fragmentation of sleep as seen from an increase in the number of microarousals. This fragmentation could be reversed by SB-269970 (Bonaventure et al. 2007). Furthermore, three antidepressants of the SSRI class (citalopram, fluoxetine, and paroxetine), but not a tricyclic antidepressant (desipramine), have been demonstrated to augment the effects on latency to REM sleep and REM sleep duration seen in 5-HT_7 $^{-/-}$ mice (Shelton et al. 2009). Again the reduction in the amount of REM sleep was caused by a reduced number of REM episodes.

Sleep is also often disturbed in schizophrenia. It is interesting to note that atypical antipsychotics such as clozapine and risperidone show the greatest improvements on sleep parameters, and that these drugs in general have high affinity for the 5-HT_7 receptor (Roth et al. 1994; Cohrs 2008). This is an area that warrants further study.

Substance abuse

To our knowledge there are no studies establishing a direct link between the 5-HT_7 receptor and substance abuse. However, a phenomenon that is closely linked with drug addiction is novelty-seeking behavior. It has recently been hypothesized that the 5-HT_7 receptor influences such behavior (Ballaz et al. 2007a, 2007b). In this study Sprague-Dawley rats were classified as high or low responders when measuring the amount of locomotor activity after the animals were placed in an enclosed open arena (Ballaz et al. 2007a). There were differences in 5-HT_7 receptor mRNA expression in several brain regions between low and high responders. Notably, there was higher expression in the hippocampus in the low responding rats. This finding was interpreted to indicate that low levels of 5-HT_7 mRNA expression correlated with decreased aversion to forced exposure to novelty (Ballaz et al. 2007a). In a follow-up study it was found that the low responding rats showed increased exploration of a new object in a novel object discrimination task and that this increase could be diminished by SB-269970 (Ballaz et al. 2007b). Mice lacking the 5-HT_7 receptor, however, did not differ from 5-HT_7 $^{+/+}$ mice in novel object recognition, but did exhibit reduced novel location recognition (Sarkisyan and Hedlund 2009).

In a model of impulsivity, delayed reinforcement, with possible relevance for drug abuse and attention deficit hyperactivity disorder, it was found that rats treated with methylphenidate during adolescence showed reduced impulse behavior as adults (Leo et al. 2009). This behavior could be counteracted by SB-269970 administered at the time of testing. The observed behavioral changes are possibly related to changes in gene expression since methylphenidate has been shown to upregulate 5-HT_7 mRNA expression in the striatum (Adriani et al. 2006) and nucleus accumbens (Leo et al. 2009). For now it is unclear if and how these results relate to each other. Thus, any possible relevance for the 5-HT_7 receptor in novelty seeking, impulsivity, and substance abuse remains to be fully determined.

Concluding remarks

Over the last several years a number of studies have attempted to evaluate the role, if any, of the 5-HT_7 receptor in psychiatric and neurological disorders. For most of these disorders the results have been mixed with inconsistencies between species and the pharmacological and genetic manipulations performed. This is certainly true for anxiety, pain, and schizophrenia. In contrast, very consistent findings have been made for depression (also in combination with

sleep) and in more general terms, disorders currently treated with antidepressants. Of particular interest is the observation that inhibition of the 5-HT_7 receptor synergistically potentiates the effect of clinically used antidepressants. This opens up numerous possibilities for new individual therapies targeting the 5-HT_7 receptor or combinations of new drugs and current antidepressants. Indeed, the clinically established antidepressant effect of amisulpride is most likely mediated by the 5-HT_7 receptor. Tools still lacking that would make it possible to significantly enhance the understanding of 5-HT_7 receptor function are truly selective agonists and, more importantly, antagonists suitable for long-term *in vivo* treatment.

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Table 1

Effects of 5-HT_7 receptor inactivation or blockade in animal behavioral models of human disorders.

Disorder	Model	Method	Effect	Reference
Anxiety	Dark-light transfer	Knockout	No change	Roberts et al. 2004
	Conflict drinking	SB-269970	Anxiolytic-like	Wesolowska et al. 2006a, 2006b
	Four-plate	SB-269970	Anxiolytic-like	Wesolowska et al. 2006a
	Plus-maze	Knockout	No change	Guscott et al. 2005
	Plus-maze	SB-269970	Anxiolytic-like	Wesolowska et al. 2006a
Depression	Forced swim test	Knockout, SB-269970, SB-258719, amisulpride	Antidepressant-like	Guscott et al. 2005; Hedlund et al. 2005; Abbas et al. 2009
	Forced swim test	SB-269970 + antidepressants[a]	Antidepressant-like	Wesolowska et al. 2007; Wesolowska and Kowalska 2008
	Tail suspension test	Knockout, SB-269970, amisulpride	Antidepressant-like	Hedlund et al. 2005; Wesolowska et al. 2006a; Bonaventure et al. 2007; Abbas et al. 2009
	Tail suspension test	SB-269970 + citalopram[a]	Antidepressant-like	Bonaventure et al. 2007
Epilepsy	Audiogenic seizures	Affinity correlation	Reduced epileptic activity	Bourson et al. 1997
	Absence epilepsy	SB-269970	Reduced epileptic activity	Graf et al. 2004
	Chemically induced seizure	Knockout	Lower seizure threshold	Witkin et al. 2007
	Electrically induced seizure	Knockout	Lower seizure threshold	Witkin et al. 2007
Migraine	Meningeal artery dilation	SB-269970	Inhibition of dilation	Terrón and Martínez-Garzía 2007; Martínez-Garzía et al 2009
OCD	Marble burying	Knockout, SB-269970	Antidepressant-like	Hedlund and Sutcliffe 2007
Pain, peripheral	Formalin	SB-269970	Analgesic	Rocha-González et al. 2005
Pain, central	Tail-flick	Knockout	No change	Roberts et al. 2004

Disorder	Model	Method	Effect	Reference
	Tail-flick	SB-269970	Inhibition of opioid analgesia	Dogrul and Seyrek 2006
	Tail-shock	SB-269970	Pronociceptive	Harte et al. 2005
	Paw-flick	SB-269970	Inhibition of opioid analgesia	Dogrul et al. 2009
	Mechanical hypersensitivity	SB-258719	Pronociceptive	Brenchat et al. 2009
Schizophrenia	PPI	Knockout, SB-269970	No change	Guscott et al. 2005; Semenova et al. 2008; Galici et al. 2008
	Amphetamine-disrupted PPI	Knockout, SB 258741	No change	Pouzet et al. 2002; Semenova et al. 2008
	Amphetamine-disrupted PPI	SB-269970	Antipsychotic-like	Galici et al. 2008
	Phencyclidine-disrupted PPI	Knockout, SB 258741	Antipsychotic-like	Pouzet et al. 2002; Semenova et al. 2008
	Ketamine-disrupted PPI	SB-269970	No change	Galici et al. 2008
Sleep	Electroencephalogram	Knockout, SB-269970	Less time in REM-sleep, increased REM latency	Hagan et al. 2000; Hedlund et al. 2005; Bonaventure et al. 2007
	Electroencephalogram	Knockout + antidepressants	Less time in REM-sleep, increased REM latency	Shelton et al. 2009
Substance abuse	Novel object discrimination	SB-269970	Lower novelty-seeking	Ballaz et al. 2007b
	Delayed reinforcement	SB-269970	Counteracts methylphenidate reduced impulsivity	Leo et al. 2009

OCD, obsessive-compulsive disorder; PPI, prepulse inhibition; REM, rapid eye movement.

[a]Synergistic enhancement when using a combination of inactive doses. The synergistic interaction has been shown for SB-269970 together with citalopram, desipramine, imipramine, or moclobemide.