REVIEW

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

Peter B. Hedlund

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

P. B. Hedlund (✉)
Department of Molecular Biology, MB10,
The Scripps Research Institute,
10550 North Torrey Pines Road,
La Jolla, CA 92037, USA
e-mail: hedlund@scripps.edu

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 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 DR-4004 (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/6 J 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/6 J 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 intrahippocampal (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, b). 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

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, b
	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-García 2007; Martínez-García 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
	Tail flick	SB-269970	Inhibition of opioid analgesia	Dogrul and Seyrek 2009
	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

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, b, 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/6 J 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 model 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 pharmaco-

logical 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/2 J mice. All of the compounds tested inhibited 5-HT-stimulated 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 pro- 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 suggests 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/6 J 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/6 J 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/6 J 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, b). 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.

References

Abbas A, Hedlund PB, Huang XP, Tran TB, Meltzer HY, Roth BL (2009) Amisulpride is a potent 5-HT7 antagonist: relevance for antidepressant actions in vivo. Psychopharmacology (Berl.) 205:119–128

Adriani W, Leo D, Greco D, Rea M, di Porzio U, Laviola G, Perrone-Capano C (2006) Methylphenidate administration to adolescent rats determines plastic changes on reward-related behavior and striatal gene expression. Neuropsychopharmacology 31:1946–1956

Antle MC, Ogilvie MD, Pickard GE, Mistlberger RE (2003) Response of the mouse circadian system to serotonin 1A/2/7 agonists in vivo: surprisingly little. J Biol Rhythms 18:145–148

Ballaz SJ, Akil H, Watson SJ (2007a) Analysis of 5-HT6 and 5-HT7 receptor gene expression in rats showing differences in novelty-seeking behavior. Neurosci 147:428–438

Ballaz SJ, Akil H, Watson SJ (2007b) The 5-HT7 receptor: role in novel object discrimination and relation to novelty-seeking behavior. Neurosci 149:192–202

Bard JA, Zgombick J, Adham N, Vaysse P, Branchek TA, Weinshank RL (1993) Cloning of a novel human serotonin receptor (5-HT7) positively linked to adenylate cyclase. J Biol Chem 268:23422–23426

Beattie D, Smith J (2008) Serotonin pharmacology in the gastrointestinal tract: a review. Naunyn Schmiedebergs Arch Pharmacol 377:181–203

Belmaker R, Agam G (2008) Major depressive disorder. N Engl J Med 358:55–68

Berman RM, Fava M, Thase ME, Trivedi MH, Swanink R, McQuade RD, Carson WH, Adson D, Taylor L, Hazel J, Marcus RN (2009) Aripiprazole augmentation in major depressive disorder: a double-blind, placebo-controlled study in patients with inadequate response to antidepressants. CNS Spectr 14:197–206

Bonaventure P, Nepomuceno D, Hein L, Sutcliffe JG, Lovenberg T, Hedlund PB (2004) Radioligand binding analysis of knockout mice reveals 5-hydroxytryptamine7 receptor distribution and uncovers 8-hydroxy-2-(di-n-propylamino)tetralin interaction with α2 adrenergic receptors. Neurosci 124:901–911

Bonaventure P, Kelly L, Aluisio L, Shelton J, Lord B, Galici R, Miller K, Atack J, Lovenberg TW, Dugovic C (2007) Selective blockade of 5-hydroxytryptamine (5-HT)7 receptors enhances 5-HT transmission, antidepressant-like behavior, and rapid eye movement sleep suppression induced by citalopram in rodents. J Pharmacol Exp Ther 321:690–698

Bosker FJ, Folgering JHA, Gladkevich AV, Schmidt A, Hart MCGVD, Sprouse J, Boer JAD, Westerink BHC, Cremers TIFH (2009) Antagonism of 5-HT1A receptors uncovers an excitatory effect of SSRIs on 5-HT neuronal activity, an action probably mediated by 5-HT7 receptors. J Neurochem 108:1126–1135

Bourson A, Kapps V, Zwingelstein C, Rudler A, Boess FG, Sleight AJ (1997) Correlation between 5-HT7 receptor affinity and protection against sound-induced seizures in DBA/2 J mice. Naunyn Schmiedebergs Arch Pharmacol 356:820–826

Brenchat A, Romero L, García M, Pujol M, Burgueño J, Torrens A, Hamon M, Baeyens JM, Buschmann H, Zamanillo D, Vela JM (2009) 5-HT7 receptor activation inhibits mechanical hypersensitivity secondary to capsaicin sensitization in mice. Pain 141:239–247

Cohrs S (2008) Sleep disturbances in patients with schizophrenia: impact and effect of antipsychotics. CNS Drugs 22:939–962

Cryan JF, Holmes A (2005) The ascent of mouse: advances in modelling human depression and anxiety. Nat Rev Drug Discov 4:775–790

Cryan JF, Markou A, Lucki I (2002) Assessing antidepressant activity in rodents: recent developments and future needs. Trends Pharmacol Sci 23:238–245

Cuesta M, Clesse D, Pévet P, Challet E (2009) New light on the serotonergic paradox in the rat circadian system. J Neurochem 110:231–243

Dogrul A, Seyrek M (2009) Systemic morphine produce antinociception mediated by spinal 5-HT7, but not 5-HT1A and 5-HT2 receptors in the spinal cord. Br J Pharmacol 149:498–505

Dogrul A, Ossipov MH, Porreca F (2009) Differential mediation of descending pain facilitation and inhibition by spinal 5HT-3 and 5HT-7 receptors. Brain Res 1280:52–59

Doly S, Fischer J, Brisorgueil M, Verg D, Conrath M (2005) Pre- and postsynaptic localization of the 5-HT7 receptor in rat dorsal spinal cord: Immunocytochemical evidence. J Comp Neurol 490:256–269

Duncan MJ, Grear KE, Hoskins MA (2004) Aging and SB-269970-A, a selective 5-HT7 receptor antagonist, attenuate circadian phase advances induced by microinjections of serotonergic drugs in the hamster dorsal raphe nucleus. Brain Res 1008:40–48

East SZ, Burnet PWJ, Kerwin RW, Harrison PJ (2002) An RT-PCR study of 5-HT6 and 5-HT7 receptor mRNAs in the hippocampal formation and prefrontal cortex in schizophrenia. Schizophr Res 57:15–26

Ehlen JC, Grossman GH, Glass JD (2001) In vivo resetting of the hamster circadian clock by 5-HT7 receptors in the suprachiasmatic nucleus. J Neurosci 21:5351–5357

Eriksson TM, Golkar A, Ekström JC, Svenningsson P, Ögren SO (2008) 5-HT7 receptor stimulation by 8-OH-DPAT counteracts the impairing effect of 5-HT1A receptor stimulation on contextual learning in mice. Eur J Pharmacol 596:107–110

Freitas RL, Ferreira CMDR, Urbina MAC, Mariño AU, Carvalho AD, Butera G, de Oliveira AM, Coimbra NC (2009) 5-HT1A/1B, 5-HT6, and 5-HT7 serotonergic receptors recruitment in tonic-clonic seizure-induced antinociception: role of dorsal raphe nucleus. Exp Neurol 217:16–24

Galici R, Boggs J, Miller K, Bonaventure P, Atack J (2008) Effects of SB-269970, a 5-HT7 receptor antagonist, in mouse models predictive of antipsychotic-like activity. Behav Pharmacol 19:153–159

Gasbarri A, Cifariello A, Pompili A, Meneses A (2008) Effect of 5-HT7 antagonist SB-269970 in the modulation of working and reference memory in the rat. Behav Brain Res 195:164–170

Geyer MA, Krebs-Thomson K, Braff DL, Swerdlow NR (2001) Pharmacological studies of prepulse inhibition models of sensorimotor gating deficits in schizophrenia: a decade in review. Psychopharmacology (Berl.) 156:117–154

Glass JD, Grossman GH, Farnbauch L, DiNardo L (2003) Midbrain raphe modulation of nonphotic circadian clock resetting and 5-HT release in the mammalian suprachiasmatic nucleus. J Neurosci 23:7451–7460

Graf M, Jakus R, Kantor S, Levay G, Bagdy G (2004) Selective 5-HT (1A) and 5-HT(7) antagonists decrease epileptic activity in the WAG/Rij rat model of absence epilepsy. Neurosci Lett 359:45–48

Graveleau C, Paust HJ, Schmidt-Grimminger D, Mukhopadhyay AK (2000) Presence of a 5-HT7 receptor positively coupled to adenylate cyclase activation in human granulosa-lutein cells. J Clin Endocrin Met 85:1277–1286

Guscott M, Bristow LJ, Hadingham K, Rosahl TW, Beer MS, Stanton JA, Bromidge F, Owens AP, Huscroft I, Myers J, Rupniak NM, Patel S, Whiting PJ, Hutson PH, Fone KC, Biello SM, Kulagowski JJ, McAllister G (2005) Genetic knockout and pharmacological blockade studies of the 5-HT7 receptor suggest therapeutic potential in depression. Neuropharmacology 48:492–502

Hagan JJ, Price GW, Jeffrey P, Deeks NJ, Stean T, Piper D, Smith MI, Upton N, Medhurst AD, Middlemiss DN, Riley GJ, Lovell PJ, Bromidge SM, Thomas DR (2000) Characterization of SB-269970-A, a selective 5-HT7 receptor antagonist. Br J Pharmacol 130:539–548

Harte SE, Kender RG, Borszcz GS (2005) Activation of 5-HT(1A) and 5-HT(7) receptors in the parafascicular nucleus suppresses the affective reaction of rats to noxious stimulation. Pain 113:405–415

Hedlund PB, Sutcliffe JG (2004) Functional, molecular and pharmacological advances in 5-HT7 receptor research. Trends Pharmacol Sci 25:481–486

Hedlund PB, Sutcliffe JG (2007) The 5-HT7 receptor influences stereotypic behavior in a model of obsessive-compulsive disorder. Neurosci Lett 414:247–251

Hedlund PB, Danielson PE, Thomas EA, Slanina K, Carson MJ, Sutcliffe JG (2003) No hypothermic response to serotonin in 5-HT7 receptor knockout mice. Proc Natl Acad Sci USA 100:1375–1380

Hedlund PB, Huitron-Resendiz S, Henriksen SJ, Sutcliffe JG (2005) 5-HT7 receptor inhibition and inactivation induce antidepressant-like behavior and sleep pattern. Biol Psychiatry 58:831–837

Hedlund PB, Kelly L, Mazur C, Lovenberg T, Sutcliffe JG, Bonaventure P (2004) 8-OH-DPAT acts on both 5-HT1A and 5-HT7 receptors to induce hypothermia in rodents. Eur J Pharmacol 487:125–132

Heyman I, Mataix-Cols D, Fineberg NA (2006) Obsessive-compulsive disorder. BMJ 333:424–429

Hjorth S, Carlsson A, Lindberg P, Sanchez D, Wikström H, Arvidsson LE, Hacksell U, Nilsson JLG (1982) 8-Hydroxy-2-(di-n-propylamino) tetralin, 8-OH-DPAT, a potent and selective simplified ergot congener with central 5-HT-receptor stimulating activity. J Neural Transm 55:169–188

Ikeda M, Iwata N, Kitajima T, Suzuki T, Yamanouchi Y, Kinoshita Y, Ozaki N (2006) Positive association of the serotonin 5-HT7 receptor gene with schizophrenia in a Japanese population. Neuropsychopharmacology 31:866–871

Ishine T, Bouchelet I, Hamel E, Lee TJF (2000) Serotonin 5-HT7 receptors mediate relaxation of porcine pial veins. Am J Physiol Heart Circ Physiol 278:H907–H912

Jørgensen HS (2007) Studies on the neuroendocrine role of serotonin. Dan Med Bull 54:266–288

Kikuchi C, Nagaso H, Hiranuma T, Koyama M (1999) Tetrahydrobenzindoles: selective antagonists of the 5-HT7 receptor. J Med Chem 42:533–535

Kogan HA, Marsden CA, Fone KCF (2002) DR4004, a putative 5-HT7 receptor antagonist, also has functional activity at the dopamine D2 receptor. Eur J Pharmacol 449:105–111

Lawler CP, Prioleau C, Lewis MM, Mak C, Jiang D, Schetz JA, Gonzalez AM, Sibley DR, Mailman RB (1999) Interactions of the novel antipsychotic aripiprazole (OPC-14597) with dopamine and serotonin receptor subtypes. Neuropsychopharmacology 20:612–627

Lecrubier Y, Boyer P, Turjanski S, Rein W (1997) Amisulpride versus imipramine and placebo in dysthymia and major depression. J Affect Disord 43:95–103

Leo D, Adriani W, Cavaliere C, Cirillo G, Marco EM, Romano E, Porzio UD, Papa M, Perrone-Capano C, Laviola G (2009) Methylphenidate to adolescent rats drives enduring changes of accumbal Htr7 expression: implications for impulsive behavior and neuronal morphology. Genes Brain Behav 8:356–368

Li Y, Wang F, Pan Y, Qiang L, Cheng G, Zhang W, Kong L (2009) Antidepressant-like effects of curcumin on serotonergic receptor-coupled AC-cAMP pathway in chronic unpredictable mild stress of rats. Prog Neuropsychopharmacol Biol Psychiatry 33:435–449

Lovell PJ, Bromidge SM, Dabbs S, Duckworth DM, Forbes IT, Jennings AJ, King FD, Middlemiss DN, Rahman SK, Saunders DV, Collin LL, Hagan JJ, Riley GJ, Thomas DR (2000) A novel, potent, and selective 5-HT7 antagonist: (R)-3-(2-(2-(4-methylpiperidin-1-yl) ethyl)pyrrolidine-1-sulfonyl)phenol (SB-269970). J Med Chem 43:342–345

Lovenberg TW, Baron BM, de Lecea L, Miller JD, Prosser RA, Rea MA, Foye PE, Racke M, Slone AL, Siegel BW, Danielson PE, Sutcliffe JG, Erlander MG (1993) A novel adenylyl cyclase-activating serotonin receptor (5-HT7) implicated in the regulation of mammalian circadian rhythms. Neuron 11:449–458

Martínez-García E, García-Iglesias B, Terrón JA (2009) Effect of central serotonin depletion on 5-HT receptor-mediated vasomotor responses in the middle meningeal artery of anaesthetized rats. Autonom Autacoid Pharmacol 29:43–50

Monsma FJ, Shen Y, Ward RP, Hamblin MW, Sibley DR (1993) Cloning and expression of a novel serotonin receptor with high affinity for tricyclic psychotropic drugs. Mol Pharmacol 43:320–327

Mullins UL, Gianutsos G, Eison AS (1999) Effects of antidepressants on 5-HT7 receptor regulation in the rat hypothalamus. Neuropsychopharmacology 21:352–367

Nicolas LB, Kolb Y, Prinssen EP (2006) A combined marble burying-locomotor activity test in mice: a practical screening test with sensitivity to different classes of anxiolytics and antidepressants. Eur J Pharmacol 547:106–115

Pouzet B, Didriksen M, Arnt J (2002) Effects of the 5-HT7 receptor antagonist SB-258741 in animal models for schizophrenia. Pharmacol Biochem Behav 71:655–665

Read KE, Sanger GJ, Ramage AG (2003) Evidence for the involvement of central 5-HT7 receptors in the micturition reflex in anaesthetized female rats. Br J Pharmacol 140:53–60

Recio P, Barahona MV, Orensanz LM, Bustamante S, Martínez AC, Benedito S, García-Sacristán A, Prieto D, Hernández M (2009) 5-hydroxytryptamine induced relaxation in the pig urinary bladder neck. Br J Pharmacol 157:271–280

Roberts AJ, Krucker T, Levy CL, Slanina KA, Sutcliffe JG, Hedlund PB (2004) Mice lacking 5-HT7 receptors show specific impairments in contextual learning. Eur J Neurosci 19:1913–1922

Rocha-González HI, Meneses A, Carlton SM, Granados-Soto V (2005) Pronociceptive role of peripheral and spinal 5-HT7 receptors in the formalin test. Pain 117:182–192

Roth B, Craigo S, Choudhary M, Uluer A, Monsma FJ, Shen Y, Meltzer H, Sibley D (1994) Binding of typical and atypical antipsychotic agents to 5-hydroxytryptamine-6 and 5-hydroxytryptamine-7 receptors. J Pharmacol Exp Ther 268:1403–1410

Ruat M, Traiffort E, Leurs R, Tardivel-Lacombe J, Diaz J, Arrang JM, Schwartz JC (1993) Molecular cloning, characterization, and localization of a high-affinity serotonin receptor (5-HT7) activating cAMP formation. Proc Natl Acad Sci USA 90:8547–8551

Sarkisyan G, Hedlund PB (2009) The 5-HT7 receptor is involved in allocentric spatial memory information processing. Behav Brain Res 202:26–31

Saxena PR, Ferrari MD (1989) 5-HT1-like receptor agonists and the pathophysiology of migraine. Trends Pharmacol Sci 10:200–204

Semenova S, Geyer MA, Sutcliffe JG, Markou A, Hedlund PB (2008) Inactivation of the 5-HT7 receptor partially blocks PCP-induced disruption of prepulse inhibition. Biol Psychiatry 63:98–105

Shapiro DA, Renock S, Arrington E, Chiodo LA, Liu L, Sibley DR, Roth BL, Mailman R (2003) Aripiprazole, a novel atypical antipsychotic drug with a unique and robust pharmacology. Neuropsychopharmacology 28:1400–1411

Shelton J, Bonaventure P, Li X, Yun S, Lovenberg T, Dugovic C (2009) 5-HT7 receptor deletion enhances REM sleep suppression induced by selective serotonin reuptake inhibitors, but not by direct stimulation of 5-HT1A receptor. Neuropsychopharmacology 56:448–454

Shen Y, Monsma FJ, Metcalf MA, Jose PA, Hamblin MW, Sibley DR (1993) Molecular cloning and expression of a 5-hydroxytryptamine7 serotonin receptor subtype. J Biol Chem 268:18200–18204

Shireman BT, Bonaventure P, Carruthers NI (2008) Chapter 2. Recent advances on the 5-HT5A, 5-HT6 and 5-HT7 receptors. In Annual Reports in Medicinal Chemistry. Academic, New York, pp. 25–42.

Smeraldi E (1998) Amisulpride versus fluoxetine in patients with dysthymia or major depression in partial remission: a double-blind, comparative study. J Affect Disord 48:47–56

Sprouse J, Reynolds L, Li X, Braselton J, Schmidt A (2004) 8-OH-DPAT as a 5-HT7 agonist: phase shifts of the circadian biological clock through increases in cAMP production. Neuropharmacology 46:52–62

Sprouse J, Li X, Stock J, McNeish J, Reynolds L (2005) Circadian rhythm phenotype of 5-HT7 receptor knockout mice: 5-HT and 8-OH-DPAT-induced phase advances of SCN neuronal firing. J Biol Rhythms 20:122–131

Terrón JA, Falcón-Neri A (1999) Pharmacological evidence for the 5-HT7 receptor mediating smooth muscle relaxation in canine cerebral artery. Br J Pharmacol 127:609–616

Terrón JA, Martínez-García E (2007) 5-HT7 receptor-mediated dilatation in the middle meningeal artery of anesthetized rats. Eur J Pharmacol 560:56–60

Thomas DR, Hagan JJ (2004) 5-HT7 receptors. Curr Drug Target CNS Neurol Disord 3:81–90

Thomas DR, Melotto S, Massagrande M, Gribble AD, Jeffrey P, Stevens AJ, Deeks NJ, Eddershaw PJ, Fenwick SH, Riley G, Stean T, Scott CM, Hill MJ, Middlemiss DN, Hagan JJ, Price GW, Forbes IT (2003) SB-656104-A, a novel selective 5-HT7 receptor antagonist, modulates REM sleep in rats. Br J Pharmacol 139:705–714

Villalon CM, Centurion D, Lujan-Estrada M, Terron JA, Sanchez-Lopez A (1997) Mediation of 5-HT-induced external carotid vasodilatation in GR 127935-pretreated vagosympathectomized dogs by the putative 5-HT7 receptor. Br J Pharmacol 120:1319–1327

Wei Z, Wang L, Xuan J, Che R, Du J, Qin S, Xing Y, Gu B, Yang L, Li H, Li J, Feng G, He L, Xing Q (2009) Association analysis of serotonin receptor 7 gene (HTR7) and risperidone response in Chinese schizophrenia patients. Prog Neuropsychopharmacol Biol Psychiatry 33:547–551

Wesolowska A, Kowalska M (2008) Influence of serotonin 5-HT7 receptor blockade on the behavioral and neurochemical effects of imipramine in rats. Pharmacol Rep 60:464–474

Wesolowska A, Nikiforuk A, Stachowicz K, Tatarczynska E (2006a) Effect of the selective 5-HT(7) receptor antagonist SB 269970 in animal models of anxiety and depression. Neuropharmacology 51:578–586

Wesolowska A, Nikiforuk A, Stachowicz K (2006b) Potential anxiolytic and antidepressant effects of the selective 5-HT7 receptor antagonist SB 269970 after intrahippocampal administration to rats. Eur J Pharmacol 553:185–190

Wesolowska A, Tatarczynska E, Nikiforuk A, Chojnacka-Wojcik E (2007) Enhancement of the anti-immobility action of antidepressants by a selective 5-HT7 receptor antagonist in the forced swimming test in mice. Eur J Pharmacol 555:43–47

Willner P, Muscat R, Papp M (1992) Chronic mild stress-induced anhedonia: a realistic animal model of depression. Neurosci Biobehav Rev 16:525–534

Witkin JM, Baez M, Yu J, Barton ME, Shannon HE (2007) Constitutive deletion of the serotonin-7 (5-HT(7)) receptor decreases electrical and chemical seizure thresholds. Epilepsy Res 75:39–45

Yadid G, Nakash R, Deri I, Tamar G, Kinor N, Gispan I, Zangen A (2000) Elucidation of the neurobiology of depression: insights from a novel genetic animal model. Prog Neurobiol 62:353–378

Ying SW, Rusak B (1997) 5-HT7 receptors mediate serotonergic effects on light-sensitive suprachiasmatic nucleus neurons. Brain Res 755:246–254

Yu GD, Liu YL, Jiang XH, Guo SY, Zhang HQ, Yin QZ, Hisamitsu T (2001) The inhibitory effect of serotonin on the spontaneous discharge of suprachiasmatic neurons in hypothalamic slice is mediated by 5-HT(7) receptor. Brain Res Bull 54:395–398