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The 5-HT$_7$ receptor in learning and memory. Importance of the hippocampus

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Abstract

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. The present paper reviews to what extent the use of animal models of learning and memory and other techniques have implicated the 5-HT$_7$ receptor in such processes. The studies have used a combination of pharmacological and genetic tools targeting the receptor to evaluate effects on behavior and cellular mechanisms. In tests such as the Barnes maze, contextual fear conditioning and novel location recognition that involve spatial learning and memory there is a considerable amount of evidence supporting an involvement of the 5-HT$_7$ receptor. Supporting evidence has also been obtained in studies of mRNA expression and cellular signaling as well as in electrophysiological experiments. Especially interesting are the subtle but distinct effects observed in hippocampus-dependent models of place learning where impairments have been described in mice lacking the 5-HT$_7$ receptor or after administration of a selective antagonist. While more work is required, it appears that 5-HT$_7$ receptors are particularly important in allocentric representation processes. In instrumental learning tasks both procognitive effects and impairments in memory have been observed using pharmacological tools targeting the 5-HT$_7$ receptor. In conclusion, the use of pharmacological and genetic tools in animal studies of learning and memory suggest a potentially important role for the 5-HT$_7$ receptor in cognitive processes.

Keywords

place learning; spatial learning; Barnes maze; object exploration; fear conditioning

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, 2009; 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 (Bard et al., 1993; Lovenberg et al., 1993; Meyerhof et al., 1993; Plassat et al., 1993; Ruat et al., 1993; Shen et al., 1993). Nevertheless, over 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). A role has also been suggested in

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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).

Much attention has been devoted to the possible role of 5-HT_7 receptors in psychiatric disorders. This interest was originally due to 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). The resulting preclinical studies have thus evaluated 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, these compounds 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 that also penetrates into the brain is not available. The most frequently used candidate is AS19. This compound most likely passes the blood-brain barrier as it affects firing of raphe neurons after systemic administration (Bosker et al., 2009), but recent binding profiles have shown that it has affinity also for other receptors (Bosker et al., 2009; Brenchat et al., 2009). The current status of 5-HT_7 receptor pharmacology has recently been extensively reviewed (Leopoldo et al., 2010). 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).

Probably the most consistent body of evidence supports a role for the 5-HT_7 receptor in depression. In fact, recent studies suggest that the clinically established antidepressant effect of certain atypical antispsychotics with high affinity for the 5-HT_7 receptor, such as amisulpride and aripiprazole, is due to their action at 5-HT_7 receptors (Abbas et al., 2009; Sarkisyan et al., 2010).

The focus of the present review, however, is on recent interesting findings supporting a role for the 5-HT_7 receptor in various cognitive processes. The interest in 5-HT_7 receptors derives mainly from the possibility that they can play a relevant role in normal or impaired memory (Eriksson et al., 2008; Gasbarri et al., 2008; Liy-Salmeron and Meneses, 2007; Meneses, 2004; Perez-García and Meneses, 2008, 2005; Perez-García et al., 2006; Roberts et al., 2004; Sarkisyan and Hedlund, 2009). Together these and other studies have aggregated a great deal of evidence supporting the involvement of 5-HT_7 receptors in mnemonic mechanisms. 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). Much attention has also been devoted to Pavlovian autoshaping models and effects on short- and long-term memory (Cifariello et al., 2008; Gasbarri et al., 2008; Perez-Garcia and Meneses, 2009). Such an involvement is reasonable considering the widespread distribution of 5-HT_7 receptors within the brain with among the highest concentrations within the hippocampus (Bonaventure et al., 2004; García-Alcocer et al., 2006; Martin-Cora and Pazos, 2004; Varnäs et al., 2004). With processes as complex as learning and memory it is not surprising that some studies present potentially contradictory findings. To a certain degree, such differences can probably be attributed to the use of different drugs, doses, times, and routes of administration, the behavioral test used as well as if the studies have

been performed in wild-type or knockout animals. However, it is also evident that further work is needed to answer many outstanding questions.

Distribution of 5-HT_7 receptors in relation to learning and memory

The distribution of 5-HT_7 receptors has been studied using several different techniques, but with similar results. In all species studied, 5-HT_7 receptor mRNA has been identified in the central nervous system. Particularly high levels have been detected in the hypothalamus (notably within the suprachiasmatic nucleus), thalamus and hippocampus (Gustafson et al., 1996; Kohen et al., 2000; Lovenberg et al., 1993; Neumaier et al., 2001; Shen et al., 1993). Interestingly, as will be discussed later it has been demonstrated that 5-HT_7 receptor mRNA expression levels are altered in tissue extracts of the raphe nuclei and the hippocampus from rats that had been exposed to an autoshaping task (Perez-García et al., 2006).

The first attempts to visualize the distribution of 5-HT_7 receptor binding sites used [^{3}H]5-CT in the presence of various masking agents (Gustafson et al., 1996; Mengod et al., 1996; To et al., 1995; Waeber and Moskowitz, 1995). The distribution of 5-HT_7 receptor binding sites was found to be largely consistent with that reported for 5-HT_7 receptor mRNA. The highest densities were in the medial thalamic nuclei and related limbic and cortical regions. In order to enhance discrimination of 5-HT_7 receptor binding, one study used 5-HT_{1A} receptor knockout and 5-$HT_{1A/B}$ receptor double knockout mice (Bonaventure et al., 2002). The anatomical distribution of [^{3}H]8-OH-DPAT binding sites observed in these knockout mice matched the distribution of 5-HT_7 receptor mRNA and 5-HT_7 receptor immunoreactivity reported in the literature. Within the hippocampal formation, strong labeling was found in the CA3 region, whereas the densities in CA1 were low. 5-HT_7 receptor binding sites were also found within the dorsal raphe where the receptor has been suggested to directly (autoreceptor) or indirectly (heteroreceptor) regulate the activity of serotonergic neurons (Harsing et al., 2004). High densities of 5-HT_7 receptor binding sites were observed throughout the hypothalamus (including the suprachiasmatic nucleus). More recently, the selective and high-affinity radioligand [^{3}H]SB-269970 has been used to visualize the distribution of 5-HT_7 receptors in human whole hemisphere brain sections (Varnäs et al., 2004). The data were in good agreement with other autoradiographic studies. [^{3}H]SB-269970 binding was mainly found in the thalamus, hypothalamus and hippocampal formation of the human brain.

Immunohistochemistry has been used to localize the distribution of 5-HT_7 receptors in rat forebrain. 5-HT_7 receptors were detected within the cerebral cortex, hippocampal formation, tenia tecta, thalamus, and hypothalamus (Belenky and Pickard, 2001; Neumaier et al., 2001). Again, the results were in accordance with the reported localization of 5-HT_7 receptor mRNA.

5-HT_7 receptor-mediated effects on learning and memory

There are several issues to consider when exploring the involvement of a particular system in learning and memory, including the timing and type of manipulations (before or after training, genetic or pharmacological), the timing of measurement (i.e. sensory, short-term vs. long-term memory), and, perhaps especially importantly, the type of learning and memory involved (i.e. associative, non-associative, spatial, emotional). Based on 5-HT_7 receptor localization, place-based learning such as spatial and contextual memory and navigational abilities, all involving hippocampal function, have been a focus of studies examining the role of this receptor system in cognitive processes.

If drugs are administered before training, it is many times difficult to determine whether they act on memory or on other processes that indirectly affect learning and retention

(McGaugh and Izquierdo, 2000). In order to circumvent possible problems associated with administering drugs before training, studies often use post-training drug administration. This crucial problem also confronts studies that use brain lesions or genetic manipulations (e.g. transgenics) to investigate memory. That said, several studies have found corroborating results whether using genetic inactivation or pharmacological blockade of the 5-HT_7 receptor in studies on thermoregulation (Hedlund et al., 2004) and in behavioral models of depression (Hedlund et al., 2005; Sarkisyan et al., 2010). For example, 5-$HT_7^{-/-}$ mice showed decreased immobility in both the tail suspension and forced swim tests, an effect also observed following administration of the 5-HT_7 receptor antagonist SB-269970 in wild-type mice. Since there are multiple processes involved in learning and memory, however, future studies will be required to specifically examine the role of the 5-HT_7 receptor in the encoding, consolidation, expression, and retention of memory by administration of short-acting drugs at various times after training.

Several different tests for place-based learning have been used in the study of 5-HT_7 receptor function. These include novel location recognition, contextual fear conditioning, Barnes maze, and radial arm maze. Other related types of learning have also been included in these studies for comparison or have been performed independently. Tests used include novel object recognition, cued fear conditioning, operant food conditioning and passive avoidance. The main findings from these studies are summarized in Table 1. Several of these studies have involved genetically manipulated animals, either constitutive 5-HT_7 receptor knockouts or outbred rats selected based on behavior in a novel environment. 5-HT_7 receptor knockout mice have normal visual acuity, normal horizontal and vertical (rearing) locomotor activity, balance, and motor learning ability (Roberts et al., 2004), behaviors that might, if altered, confound cognitive test results. Place learning involves the processing of information relating to the location of food sources, predators, escape routes and immediate kin, and therefore is of utmost importance in mammals. The hippocampus is considered essential for the integration of polymodal contextual information important in place learning (O'Keefe and Nadel, 1978).

Spatial and Contextual Learning

Novel location and novel object tests

In this test animals are allowed to explore an environment containing one or more objects until they show habituation (object exploration significantly decreases). Then the object or one of the objects is moved to a new spatial location (novel location test) or an object is replaced with a unique one (novel object test) and renewal of interest indicates that the animal has detected the change (i.e. has a memory of the original configuration).

5-HT_7 receptor knockout mice (5-$HT_7^{-/-}$) habituated in a similar way as 5-$HT_7^{+/+}$ mice in the initial exploration phase of this experiment (Sarkisyan and Hedlund, 2009). In the novel location test it was found that 5-$HT_7^{-/-}$ mice were indifferent to spatial changes in their environment in comparison with 5-$HT_7^{+/+}$ mice. A similar effect could be induced in C57BL/6J mice with the selective 5-HT_7 receptor antagonist SB-269970. However, 5-$HT_7^{+/+}$ and 5-$HT_7^{-/-}$ mice performed comparably in the novel object test, as did vehicle and SB-269970 treated mice. The finding that both genetic inactivation and pharmacological blockade of the 5-HT_7 receptor yielded the same result strongly supports an involvement of the 5-HT_7 receptor in novel location recognition, but not novel object recognition. It is generally believed that the novel location and novel object tests involve hippocampus-dependent and independent processes, respectively. It has previously been shown that the ability to recognize novel objects in the environment is unaltered by hippocampal lesions (Benice and Raber, 2008; Ennaceur et al., 1997), whereas novel location recognition is. Therefore, this test is particularly useful in determining hippocampus-specific cognitive

differences. Thus, it is likely that there was a direct involvement of the hippocampus in the observed impairment in novel location recognition seen in the 5-$HT_7^{-/-}$ mice.

Another set of studies looked at novel location/novel object recognition from a different perspective. The experiments were designed to use these tests as a way to evaluate novelty seeking behavior. It was hypothesized that the 5-HT_7 receptor might influence such behavior (Ballaz et al., 2007a, 2007b). Sprague-Dawley rats were classified as high or low responders based on the amount of locomotor activity measured after the animals were placed in an enclosed open arena. It was found that 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 (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). These authors concluded that 5-HT_7 receptor activity might modulate emotion-based cognitive processing, based on the dependence on novelty seeking, under changing environmental conditions. Although low 5-HT_7 receptor activity in the mouse study was associated with impaired location discrimination and high 5-HT_7 receptor activity in the rat study was associated with impaired object discrimination and high novelty seeking, both studies supported a role for 5-HT_7 receptors in context-dependent cognitive processes.

Barnes maze

Two published studies have used the Barnes maze to investigate the involvement of the 5-HT_7 receptor in place learning (Roberts et al., 2004; Sarkisyan and Hedlund, 2009). The maze is a circular platform with 20 holes around its perimeter, one of which leads to an escape chamber the animal has to reach in order to avoid aversive noise and bright light (Barnes, 1979). The test has similarities to the Morris water maze (Morris et al., 1982), which was developed for rats but has been used successfully also in mice (Wolfer et al., 1998). Nevertheless, several investigators prefer to use the Barnes maze for testing mice (Bach et al., 1995).Use of the Barnes maze will also avoid the confounding factor of hypothermia induced by swimming, which is important to consider since 5-HT_7 receptor manipulations affect thermoregulation (Hedlund et al., 2003, 2004). Both studies compared 5-$HT_7^{+/+}$ and 5-$HT_7^{-/-}$ mice; however, using different experimental designs and scoring techniques. In a more classic version of this test 5-$HT_7^{-/-}$ mice performed similarly to their 5-$HT_7^{+/+}$ siblings during the initial 12 sessions (Roberts et al., 2004). This would indicate that the 5-$HT_7^{-/-}$ mice did not exhibit learning impairments and/or dysfunctions in short-term memory if the environment remains static. In a retention session performed a month after the initial sessions the 5-$HT_7^{-/-}$ mice had no impairments in long-term memory and memory consolidation compared with their wild-type siblings since both genotypes were able to efficiently locate the escape box.

In the more recent study two additional trials were added (Sarkisyan and Hedlund, 2009). In a probe session with the escape box removed and in a reversal session with the escape box moved 180 degrees the 5-$HT_7^{-/-}$ mice spent significantly more time in the quadrant of the maze where the escape box had originally been located. The generally observed behavior was that both 5-$HT_7^{+/+}$ and 5-$HT_7^{-/-}$ mice initially followed a direct path towards the presumed position of the escape box. However, the authors made the observation that when the 5-$HT_7^{-/-}$ mice reached the now empty previous location of the escape box during the reversal and the probe tests they began exploring the maze, but when they happened to pass the vicinity of the starting position, these mice took the initial route back to the previous location of the escape box. A possible explanation for this type of behavior is the reliance on a mainly striatum-dependent, egocentric memory formed as a result of overtraining. It is reasonable to assume that striatum-dependent egocentric memory is spared in 5-$HT_7^{-/-}$

mice because of the low abundance of 5-HT7 receptors in this area (Bonaventure et al., 2004). The 5-$HT_7^{+/+}$ mice in contrast exhibited less backtracking compared with the 5-$HT_7^{-/-}$ mice. Thus, their search strategy most likely involved a more continuous and active information processing that included triangulation and dynamic reference memory, which in turn likely translates into greater hippocampus-dependent allocentricity in the spatial memory (Berke et al., 2009; Sanders et al., 2008). Anatomically it has been demonstrated that the 5-HT_7 receptor is present in all parts of the hippocampus, with the highest densities in the CA3 region and the dentate gyrus, regions of the hippocampus that have been shown to be involved in the response to changes in the environment (Goodrich-Hunsaker et al., 2008; Hunsaker et al., 2008).

Fear conditioning

The possible involvement of the 5-HT_7 receptor in fear conditioning has been studied in one report (Roberts et al., 2004). Both cued and contextual fear conditioning were evaluated in 5-$HT_7^{+/+}$ and 5-$HT_7^{-/-}$ mice. In these tests, the animals learn to associate either a cue (e.g. a sound) or the environment (context) with an aversive stimulus. The contextual portion of the task, as other types of place learning, is hippocampus-dependent, whereas the cued conditioning is not when a delay conditioning approach is used in which the shock is administered at the end of, but overlapping, the cues (Kim and Fanselow, 1992; Phillips and LeDoux, 1992). It was found that 5-$HT_7^{-/-}$ mice had impaired contextual, but not, cued fear conditioning. Fear conditioning is based on memories of stressful events and it has been shown that stress induces an upregulation of 5-HT_7 receptor mRNA in the hippocampus (Yau et al., 2001). The dissociation between contextual-based learning and the cued fear conditioning indicates that the 5-HT_7 receptor is needed for the more complex integrative learning mechanisms involved in the contextual experiments (Anagnostaras et al., 2001). This is also supported by the specific 5-HT_7 receptor related impairments seen in the Barnes maze test and contextual processing in the object exploration tests (see above).

Radial arm maze

A recent study evaluated the involvement of 5-HT_7 receptors in a radial arm maze test with a working memory and a reference memory component (Gasbarri et al., 2008). In the working memory component (involving short-term memory in which the rats are actively monitoring their ongoing behavior), the rats are trained to visit 7 of the 8 arms in the maze (the 8^{th} arm is blocked off) without reentering a previously visited arm. In the reference memory component (in this case longer-term, spatially-mediated), the rats learn that the only arm that will have a food reward is the arm that was blocked during the working memory component. The overall finding was that the 5-HT_7 receptor antagonist SB-269970 improved memory by decreasing the number of errors in the reference memory component, while not affecting working memory. This effect could be explained based on 5-HT_7 receptor localization: a high concentration of 5-HT_7 receptors is found in the hippocampus, which exerts an important role in reference memory, while relatively low concentrations are present in the prefrontal cortex, an area involved in working memory (Bard et al., 1993; Shen et al., 1993).

While, again, an effect of the 5-HT_7 receptor system was observed in a spatial learning and memory test, in this case receptor antagonism resulted in an improvement in performance as opposed to the worsening observed in the other spatial tests described above. In the radial arm maze test, SB-269970 may have reduced the dynamic nature of arm location (more hippocampal, possibly involving the 5-HT_7 receptor), favoring a more rigid strategy (more striatal, 5-HT_7 receptor-independent) that might actually be a more efficient strategy in this particular test. For example, while speculative, if the rats have used egocentric representations (coordinates relative to the start position) to locate the food-baited arm, then

the more complex hippocampus-mediated intra- and extra-maze spatial representations may interfere with performance. These more complex representations are important to develop even if they are not as efficient because they are critical in allowing for adjustments in strategy if the task contingencies change (i.e. the start position changes or the food reward is moved to another arm). This speculation is based on the findings in the Barnes maze test, where 5-HT_7 receptor knockout impacted this more complex allocentric spatial strategy under changing conditions. Although this is an interesting notion, it is also possible that the differences between the results in other spatial tests and the radial arm maze test are due to the use of a pharmacological approach vs. a genetic approach, species differences, or other differences between these cognitive tests.

Non-Spatial Learning

Instrumental (or operant) conditioning is a classic procedure for studying the processes involved in the acquisition and retention of a response to obtain reward or to avoid an aversive stimulus. 5-$HT_7^{-/-}$ and 5-$HT_7^{+/+}$ mice were trained to nosepoke for food reward, with the number of nosepokes required for pellet delivery increasing from 1 to 10 across trials. Both genotypes learned this task over the first few days, as evidenced by an almost complete shift to active hole responding, and then stabilized their food pellet deliveries by increasing responding as the response requirement increased. These data suggest that the lack of 5-HT_7 receptors does not produce a deficit in operant conditioning for food. Meneses and colleagues (Meneses, 2004; Meneses and Terrón, 2001; Perez-García and Meneses, 2005) have examined the role of 5-HT_7 receptors in a combined Pavlovian/instrumental learning procedure. Rats learn that the presence of a lever signals eventual food reward without action (Pavlovian), but also that by pressing the lever the food reward comes immediately instead of after a delay (instrumental). While SB-269970 and DR4004 had no effect on their own on the percent of lever pressing trials, they reversed the increase in conditioned responding for food induced by a low dose of the 5-$HT_{1A/7}$ agonist 8-OH-DPAT (Meneses, 2004) or by the 5-HT_7 receptor agonist AS19 (Perez-García and Meneses, 2005). In addition, these 5-HT_7 receptor antagonists reversed the amnesic effects of scopolamine or dizoclipine (Meneses, 2004). The authors suggested that a role for the 5-HT_7 receptor was unmasked under both procognitive and amnesic conditions. This is consistent with the finding described above using the knockout mice, as there was no baseline effect of 5-HT_7 receptor manipulation.

A passive avoidance instrumental conditioning test also was used to explore the role of 5-HT_7 receptors in mice (Eriksson et al., 2008). While instrumental in nature this test has been shown to be hippocampus-dependent (Baarendse et al., 2008). In this test, mice were exposed to a light compartment for 120 sec and then allowed to pass through to a (preferred) dark compartment. However, dark compartment entry resulted in a mild electrical shock. Mice learn in a single trial to avoid the dark compartment. A modification was also explored in which mice experienced the dark side with no shock in an initial trial, prior to the shock trial. In this case latencies to enter the dark compartment are certainly increased, but some mice do enter the dark compartment. In the standard procedure, pre-training administration of SB-269970 had no effect on learning; however, using the modified approach this antagonist impaired memory. In addition, SB-269970 enhanced the amnesic effect of a moderate dose of 8-OH-DPAT in the standard protocol, suggesting that 5-HT_7 receptor activity can actually counteract the 5-HT_{1A} receptor activity of 8-OH-DPAT. These data suggest that decreased 5-HT_7 receptor activity can impair learning and memory even in instrumental learning paradigms under at least some conditions, for example perhaps those that involve a contextual component.

Intracellular signaling and molecular mechanisms

As we have seen there is considerable behavioral evidence supporting a role of the 5-HT_7 receptor in learning and memory. Studies have also been performed using other techniques with the aim to elucidate the underlying cellular and molecular mechanism involved. The 5-HT_7 receptor is functionally coupled to G_s and G_{12} G-proteins (Hedlund and Sutcliffe, 2004; Hoyer et al., 2002; Kvachnina et al., 2009, 2005; Thomas et al., 1999; Thomas and Hagan, 2004). Thus, stimulation of the receptor will increase intracellular cAMP. In broader terms, cAMP increases have been linked to enhanced memory consolidation (Kandel, 2001). The involvement of cAMP signaling, PKA, and/or cAMP response element-binding (CREB) protein in long-term memory formation has been confirmed in several species (molluscs, flies, rats, mice) during behavioral learning tasks, and that this process is depending on mRNA transcription and protein translation (Kandel, 2001; Manuel-Apolinar and Meneses, 2004).

An ex vivo analysis of cAMP production showed that animals trained in the combined Pavlovian/instrumental learning task described above had higher cAMP values relative to the untrained group in raphe nuclei, and hippocampus, but not in prefrontal cortex (Perez-García and Meneses, 2008). Overtrained animals expressed less or higher cAMP production in raphe nuclei and prefrontal cortex. The changes in cAMP levels in the raphe nuclei and prefrontal cortex of overtrained animals are indicative of an already consolidated memory. Thus, it could be concluded that this type of memory formation required cAMP increments in serotonergic pre- (raphe nuclei) and post-synaptic (hippocampus) areas and that retrieval of a consolidated memory (i.e., overtraining) was associated with less cAMP in the raphe nuclei but more in the prefrontal cortex. Using AS19 and 8-OH-DPAT evidence was found for a complex interaction between 5-HT_{1A} and 5-HT_7 receptors that needs further work to be fully clarified (Perez-García and Meneses, 2008).

It has been demonstrated that long-term memory formation in the Pavlovian/instrumental learning task discussed above requires protein synthesis and expression of 5-HT_{1A} and 5-HT_7 receptors (Luna-Munguia et al., 2005; Meneses, 2007). It has also recently been reported that other effects likely mediated by 5-HT_{1A} and 5-HT_7 receptors such as 8-OH-DPAT-induced modulation of memory consolidation (Meneses, 2007) and phase-shift in the suprachiasmatic nucleus (Jovanovska and Prosser, 2002; Kawahara et al., 1994) require transcription and translation of proteins.

Stimulation of both 5-HT_{1A} and 5-HT_7 receptors in the hippocampus results in increased CREB phosphorylation (Mahgoub et al., 2006). Such a finding might appear counterintuitive given that 5-HT_{1A} receptors couple with G_i to inhibit cAMP formation while 5-HT_7 receptors couple with G_s to stimulate cAMP formation. Nevertheless, such findings can most likely be explained by the subcellular localization of the different receptor types. Physiologically, activation of the two receptor subtypes both induce hypothermia (Hedlund et al., 2004) and decrease immobility in the forced swim test (Sarkisyan et al., 2010).

Electrophysiology

A number of studies have used electrophysiology in order to find mechanisms possibly correlating with the involvement of 5-HT_7 receptors in learning and memory. Hippocampal recordings have been made in 5-$HT_7^{+/+}$ and 5-$HT_7^{-/-}$ mice aiming to detect possible neuronal mechanisms underlying the learning deficits observed in contextual fear conditioning (Roberts et al., 2004). 5-HT_7 receptors are present in the CA1 region and this region also receives input from the CA3 region where the 5-HT_7 receptor is more abundant (Bonaventure et al., 2002, 2004). It was observed that short-term synaptic plasticity was not

altered in the 5-$HT_7^{-/-}$ mice. Instead, the 5-HT_7 receptor-dependent learning mechanisms seem to involve long-term synaptic plasticity as a reduced ability to induce LTP was observed in the 5-$HT_7^{-/-}$ mice. It has been shown that contextual fear conditioning in itself induces a reduction in LTP formation within the CA1 region (Sacchetti et al., 2002). This change in synaptic plasticity may represent an adaptive response no longer possible in the 5-$HT7^{-/-}$ mice.

As noted above, co-administration of 8-OH-DPAT and SB-269970 resulted in an augmentation of the impairing effect of 8-OH-DPAT in a passive avoidance model (Eriksson et al., 2008). In support of this, it has been found in electrophysiological recordings performed in rodent hippocampal slices that activation of 5-HT_7 receptors and stimulatory G_s-proteins can counteract inhibitory effects of 5-HT_{1A}. The 5-HT_{1A} receptor antagonist WAY-100635 blocks the decreases of hippocampal burst firing via 5-HT_{1A} receptor-coupled $G_{i/o}$ protein activation and hyperpolarization (Bickmeyer et al., 2002). However, the combination of WAY-100635 and either 8-OH-DPAT or 5-carboxamidotryptamine (5-CT) results in a net excitation of CA1/CA3 pyramidal neurons, which is attenuated by SB-269970, and most likely is 5-HT_7 receptor-mediated (Bickmeyer et al., 2002; Tokarski et al., 2003). It has been demonstrated that the 5-HT_7 receptor-induced changes affect after-hyperpolarizations, which in turn modulate the activity of hippocampal neurons (Bacon and Beck, 2000).

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 learning and memory. There appears to be a general consensus that 5-HT_7 receptors play an important role in hippocampus-dependent cognitive processes. These findings are observed in both mice and rats and using both genetic and pharmacological approaches, strengthening this conclusion. It should however be noted that to our knowledge there are no studies that have used hippocampal lesions or intra-hippocampal administration of drugs to even more directly implicate this brain region in the processes studied. There are discrepancies in findings, however, that seem to relate at least in part to the tests used and possibly more importantly to the strategies required to accomplish the various tasks. For example, it has been suggested that the 5-HT_7 receptor might be important in the ability to utilize hippocampus-dependent allocentric memory (Sarkisyan and Hedlund, 2009). Although egocentric representations (for example coordinates relative to one's body) provide the format for sensory perception and motor action and lay the groundwork for short-term sensorimotor integration, it has been argued that memory over the longer term is likely better served by allocentric representations centered on environmental landmarks (Burgess, 2008). As the body moves and as time passes, relying on only egocentric representations can lead to errors; therefore, the ability to form representations centered on environmental landmarks become of considerable use. It is possible that the tests in which 5-HT_7 receptor knockout or pharmacological antagonism was associated with performance deficits were more reliant on these hippocampal based allocentric representations. For example, this was likely true in the mouse novel location test as the animals would need to have formed a representation of the position of the three objects used in relationship to each other in order to discern a change in the location of one of the objects. Although egocentric representations are likely involved, it might be speculated that allocentric representations are an important component of contextual fear conditioning, as complex information concerning external cues in the shock-paired environment is committed to memory. As discussed above, data from the Barnes maze test supported a specific deficit in allocentric memory in 5-HT_7 receptor knockout mice (Sarkisyan and Hedlund, 2009). In the radial arm maze test, working memory would rely on egocentric representations and therefore be independent of 5-HT_7 receptor activity. The reference memory portion of this test would be expected to involve

both egocentric and allocentric representations, but perhaps the allocentric representations add additional complexity that is not needed for the basic test, but that would be of utmost importance if the starting place for the trials randomly moved to different arms instead of staying in one place or if the baited arm was changed. Clearly, while intriguing, a specific role for the 5-HT_7 receptor in allocentric memory will require further investigation using tests designed to require more or less allocentricity.

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Table 1

Effects of 5-HT$_7$ receptor inactivation or blockade in animal behavioral models of learning and memory.

Model	Method	Effect	Reference
Novel location recognition	Knockout mice	Reduced exploration	Sarkisyan and Hedlund, 2009
	SB-269970	Reduced exploration	Sarkisyan and Hedlund, 2009
Novel object recognition	Knockout mice	No change	Sarkisyan and Hedlund, 2009
	SB-269970	No change	Sarkisyan and Hedlund, 2009
	Sprague-Dawley rats with reduced spontaneous locomotor activity[1]	Increased exploration	Ballaz et al., 2007b
	Same rats + SB-269970	Reduction of exploration change	Ballaz et al., 2007b
Barnes maze	Knockout mice, 12-session habituation	No change	Roberts et al., 2004
	Knockout mice, 1 month	No change	Roberts et al., 2004
	retention		Sarkisyan and Hedlund, 2009
	Knockout mice, escape box moved or removed	Increased time spent at original location of escape box	Sarkisyan and Hedlund, 2009
Cued fear conditioning	Knockout mice	No change	Roberts et al., 2004
Contextual fear conditioning	Knockout mice	Impaired conditioning	Roberts et al., 2004
Radial arm maze	SB-269970	No change in working memory	Gasbarri et al., 2008
	SB-269970	Improved reference memory	Gasbarri et al., 2008
Operant food conditioning	Knockout mice	No change	Roberts et al., 2004
Pavlovian/instrumental	SB-269970, DR4004	Reversal of 8-OH-DPAT-induced increase in conditioning	Meneses, 2004
	SB-269970	Reversal of AS19-induced increase in conditioning	Perez-Garcia and Meneses, 2005
	SB-269970, DR4004	Reversal of scopolamine or dizoclipine-induced amnesia	Meneses, 2004
Passive avoidance	SB-269970	No change (standard protocol)	Eriksson et al., 2008
	SB-269970	Impaired memory (modified protocol)	Eriksson et al., 2008
	SB-269970	Enhanced 8-OH-DPAT-induced amnesia	Eriksson et al., 2008

[1] These rats had higher hippocampal 5-HT$_7$ receptor mRNA expression than rats with higher spontaneous locomotor activity.