

# Role of 5-Ht<sub>7</sub> Receptors in the Modulation of Learning and Memory

*Antonella Gasbarri<sup>1\*</sup>, Assunta Pompili<sup>1</sup>, Benedetto Arnone<sup>1</sup>, Maria Clotilde Tavares<sup>2</sup> and Carlos Tomaz<sup>2</sup>*

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## ABSTRACT

The abundance of serotonin (5-HT) in the central nervous system can explain its involvement in the modulation of several cognitive processes, such as sleep, feeding, sexual behavior, emotion, and pain. Moreover, 5-HT localized in cognitive pathways with hippocampal formation (HF) and frontal cortex as the main target structures, has an important role in learning and memory processes. Various types and subtypes of receptors, differentially associated to cognitive mechanisms, were recently discovered. Many data reveal that the administration of 5-HT<sub>2A/2C</sub> and 5-HT<sub>4</sub> receptor agonists, or 5-HT<sub>1A</sub>, 5-HT<sub>3</sub> and 5-HT<sub>1B</sub> antagonists improves memory and has a facilitatory effect on learning in situations involving a high cognitive demand. On the contrary 5-HT<sub>2A/2C</sub> and 5-HT<sub>4</sub> receptors antagonists, or 5-HT<sub>1A</sub>, 5-HT<sub>3</sub> and 5-HT<sub>1B</sub> receptors agonists have opposite effects. Although these results are contradictory, it is important to take into account the effect of global, and unspecific, stimulation of serotonergic receptors and the activation of other neurotransmission systems, together with the type of task used, the way of administration, and the ligand affinity.

Aim of this review is to highlight the involvement of the recently discovered 5-HT<sub>7</sub> type receptor in the modulation of learning and memory processes, thus providing a basis to obtain new therapeutic agents and strategies for the treatment of learning and memory disorders.

**KEY WORDS:** Neurotransmitters, Serotonin, 5-HT receptors, Learning and memory.

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<sup>1</sup> Department of Biomedical Sciences and Technologies, Faculty of Sciences of Education, University of L'Aquila, Italy.

<sup>2</sup> Department of Physiological Sciences, Laboratory of Neurosciences and Behavior, Institute of Biology, University of Brasília, CEP 70910-900 Brasília, DF, Brazil.

\* Corresponding author at: Department of Biomedical Sciences and Technologies, University of L'Aquila, Via Vetoio, Coppito 67100 L'Aquila, (Italy). Tel.: +39(331)6667030; e-mail: antonella.gasbarri@cc.univaq.it

## 1. INTRODUCTION

The monoaminergic neurotransmitter serotonin (5-HT) was discovered more than 50 years ago and several studies evidenced its role in the modulation of cognitive functions. The wide range of 5-HT actions can be explained not only by its wide localization in the central nervous system (CNS), but also by the high number of families (from 5-HT<sub>1</sub> to 5-HT<sub>7</sub>) and subtype receptors (more than 14 subtypes) (Hoyer et al, 2002; Raymond et al, 2001; Thomas and Hagan, 2004). Furthermore, 5-HT is known to interact with other neurotransmitter systems, particularly with cholinergic and dopaminergic systems (Buhot et al, 2000; González-Burgos and Feria-Velasco, 2008; Meneses, 2002; 2003; Olvera-Cortés et al, 2008). The differences in the roles of some 5-HT receptors, related to the numerous subtypes with action depending of their brain localization, have already been outlined (Müller and Huston, 2006). The cerebral 5-HT systems regulate many different physiological processes, such as learning and memory (Aghajanian et al, 2002; González-Burgos and Feria-Velasco, 2008; Olvera-Cortés et al, 2008)), fear, aggressive behavior, motivation (Barros et al, 2002; Barros and Tomaz, 2002; Thomas and Hagan, 2004) circadian rhythms (Hedlund and Sutcliffe, 2004; Thomas and Hagan, 2004), stress (Yau et al, 2001), sleep (Guscott et al, 2003; Hagan et al, 2000; Hedlund et al, 2003; Markov and Goldman, 2006; Monti and Jantos, 2006; Thomas et al, 2003), arousal (Abramas et al, 2005; Canli et al, 2005; Haller et al, 2005; Oberlander et al, 2007; Sanger et al, 2007; Scholes et al, 2007), feeding behavior (Ashraf et al, 2007; Halford and Blundell, 2000; Somerville et al, 2007; Vickers et al, 2001; Yokoyama et al, 2007), reward and reinforcement (Müller and Huston, 2006), pain (Butkevich et al, 2005; Djaldetti et al, 2007; Martikainen et al, 2007), thermoregulation, anxiety, neuropsychiatric disorders (Bonaventure et al, 2007; Guscott et al, 2005; Hedlund et al, 2004; 2005; Thomas and Hagan, 2004; Wesolowska et al, 2006; Yau et al,

2001), and cardiovascular responses (Faure et al, 2006; Varghese and Brown, 2001). Moreover, they are also involved in major pathologies, such as Down syndrome, Alzheimer's disease, and epilepsy (Sodhi and Sunders-Bush, 2004), and several new therapeutic agents are available since the 5-HT discovery (Jones and Blachburn, 2002). The 5-HT reuptake inhibitors (SSRIs) are among the most widely prescribed drugs for the treatment of depression (Nandam et al, 2007) and other disorders, including anxiety, schizophrenia, and panic disorders. Furthermore, within minutes hyperstimulation of the cerebral 5-HT system results in a behavioral pattern, indicated as "5-HT syndrome". In rodents it includes hindlimb abduction, forepaw treading, lateral head weaving, resting tremor, hindlimb rigidity, Straub tail, outstretched or flattened body posture, hyperreactivity, hyperlocomotion, intense salivation, backward walk and piloerection (Müller et al, 2007).

Several studies have evidenced the 5-HT role on the modulation of cognitive functions, including learning and memory processes (Aghajanian et al, 2002; Hedlund and Sutcliffe, 2007; Jovanovska and Prosser, 2002; Kandel, 2001; Luna-Munguía et al, 2005; Mahgoub et al, 2005; Manuel-Apolinar and Meneses, 2004; Meneses, 2004; 2007; Pérez-García et al, 2006; Roberts et al, 2004). In the rat, the administration of 8-OH-DPAT, a high-affinity 5-HT<sub>1A</sub> and 5-HT<sub>7</sub> agonist, impairs the acquisition of radial-arm-maze task, while the activation of 5-HT<sub>1B</sub> receptors through by the specific agonist CP 93129 preferentially impairs reference memory (Buhot et al, 2000). These opposite results underline the numerous functional properties of the two receptors, in particular their specific cellular and subcellular locations in the HF. Moreover, significant differences in the responses induced are known and are mediated by distinct 5-HT<sub>1A</sub> receptor mechanisms (Barros et al, 2002; Barros and Tomaz, 2002; Griebel et al, 2000). Post-training bilateral infusion of 5-HT<sub>2</sub> antagonist ketanserin in the rat striatum induces a dose-dependent retention deficit in an inhibitory

avoidance task (Prado-Alcalà et al, 2003), which could be due to blockade of HT<sub>2</sub> heteroreceptors, located in cortico- and/or pallido-striatal afferent axons, mediating inhibition of dopamine release within the striatum (Busber et al, 2001).

The involvement of 5-HT<sub>3</sub> receptors in the modulation of learning and memory has been reported; for example, the 5-HT<sub>3</sub> receptor antagonists have been shown to induce learning and memory improvement or to reverse the effects of anticholinergic ligand or age-induced memory loss in rodents and primates (Barnes and Sharp, 1999).

The presence of 5-HT<sub>4</sub> receptors in the limbic system emphasizes their role in cognition: in fact, it has been found that the number of these receptors is reduced in AD patients; in addition, their stimulation may increase the release of acetylcholine in the frontal cortex and the extracellular level of 5-HT in the HF (Lai et al, 2005; Lanctot et al, 2007; Pritchard et al, 2007). Similarly, the selective 5-HT<sub>6</sub> antagonist Ro 04-6790 induces an improvement of both acetylcholine neurotransmission and spatial memory (Meneses, 2001). These data show the important action of 5-HT<sub>6</sub> receptor in the regulation of central cholinergic function, indicating that it can represent a putative target for the treatment of cholinergic defects in cognitive dysfunctions, such as AD.

The aim of this review is to clarify the involvement of the recently discovered 5-HT<sub>7</sub> type receptor in the modulation of learning and memory processes, thus providing a basis for the possibility to obtain new therapeutic agents and strategies for the treatment of learning and memory disorders.

## 2. 5-HT<sub>7</sub> RECEPTORS LOCALIZATION AND MEMORY CONSOLIDATION

A great deal of evidence has underlined the involvement of 5-HT<sub>7</sub> receptors on mnemonic mechanisms, given also its large distribution in brain areas that are important for learning and memory, even though contradictory evidence regarding the role of the serotonergic system in normal and

impaired memory in mammals has been reported (Meneses, 2004; Pérez-García et al, 2006; Pérez-García and Meneses, 2005; Roberts et al, 2004; Roth et al, 2004; Sarnyai et al, 2000; Schechter et al, 2002; Woolley et al, 2004). These discrepancies could be explained by taking into account differences in the type and concentration of drug administered, timing and site (systemic or central) of administration, type of behavioral test, interaction with other neurotransmission systems (Meneses, 2001; 2003; Meneses et al, 2004).

Nevertheless, although the role of the 5-HT<sub>7</sub> receptors is yet to be clarified, the interest in its action derives mainly from the possibility that they can play a relevant role in normal or impaired memory (Meneses, 2004; Pérez-García et al, 2006; Roberts et al, 2004).

In several species, both the mRNA expression and binding studies display a similar distribution of the 5-HT<sub>7</sub> receptors in cerebral areas, containing relatively high expression in the thalamus, hypothalamus, HF, and generally lower expression in cerebral cortex and amygdala (Hedlund and Sutcliffe, 2004; Thomas and Hagan, 2004). This was confirmed by findings showing elevated 5-HT<sub>7</sub> receptors mRNA expression of vehicle-treated rats in raphe HF, which was attenuated when AS 19, a potent 5-HT<sub>7</sub> receptor agonist, was administered to autoshaping-trained animals (Pérez-García et al, 2006). Moreover, the autoradiographic analysis of [<sup>3</sup>H]-SB-269970 and the whole hemisphere cryosections of the human brain showed that high densities of 5-HT<sub>7</sub> receptors are localized in the anterior thalamus and hippocampal dentate gyrus (Varnas et al, 2004); intermediate levels of 5-HT<sub>7</sub> receptors are localized in other regions, including the hypothalamus, anterior cingulate gyrus, HF, amygdala and certain brainstem nuclei (Slassi et al, 2004), which represent brain areas involved in learning and memory processes (Meneses, 2003, 2004). These results are supported by the discovery of high affinity and selective ligand variety, which

allowed to demonstrate that the mRNA expression of 5-HT<sub>7</sub> receptors in prefrontal cortex, HF, and raphe nuclei is modulated by selective stimulation or blockade of these receptors during memory processes (Luna-Munguia, 2005). The above mentioned studies suggest that the 5-HT<sub>7</sub> receptor exerts a role inside the HF, which is consistent with its identification in this brain region evidenced by in situ hybridization, immunohistochemistry and radioligand binding studies (Leopoldo et al, 2004). Furthermore, stress has been shown to induce the upregulation of 5-HT<sub>7</sub> receptor mRNA in the HF, a brain region important in contextual learning (Roberts et al, 2004).

A recent study, utilizing an autoshaping task and autoradiographic analysis of [<sup>3</sup>H] 8-OH-DPAT followed by the analysis of 5-HT<sub>1A</sub> and 5-HT<sub>7</sub> receptors (Luna-Munguia et al, 2005), has reported that pharmacological naïve autoshaping-trained, compared to untrained animals, selectively showed increases in several brain areas, such as amygdala, lateral septal nucleus, parietal cortex, temporal cortex and raphe nuclei and decreases in hippocampal CA1 area, frontal cortex areas, occipital cortex and cingulate cortex areas, while no changes were shown in dentate gyrus, hippocampal CA3 area, frontal cortex and entorhinal cortex. These data clearly highlight that increase, decrease or no change (i.e., modulation) in 5-HT receptor expression mediate memory consolidation. Animals trained in Pavlovian/instrumental autoshaping task and treated with selective 5-HT<sub>1A/7</sub> receptor agonist 8-OH-DPAT at a low dose showed facilitated memory consolidation and increased cortical and hippocampal cAMP production (Meneses et al, 2004); both effects were modulated, at least in part, by selective 5-HT<sub>1A</sub> or 5-HT<sub>7</sub> receptor antagonists (Manuel-Apolinar and Meneses, 2004). It was hypothesized that the effect on enhancing memory consolidation of 5-HT<sub>1A</sub> and/or 5-HT<sub>7</sub> receptors would exert a cortical and hippocampal "tonic"

influence on cAMP formation (Manuel-Apolinar and Meneses, 2004), behaviorally observable when these receptors are stimulated or in case of amnesia.

### 3. 5-HT<sub>7</sub> RECEPTORS AND LEARNING AND MEMORY: MOLECULAR BASIS AND BEHAVIORAL EFFECTS

In situ hybridization and ligand binding approaches have mapped the distribution of 5-HT<sub>7</sub> receptors in the CNS (Vanhoenacker et al, 2000) indicating the greatest abundance in the thalamus, hypothalamus and HF with lower levels in the cerebral cortex and amygdala.

Enhanced memory consolidation and cAMP increases are reported in *Aplysia* (Kandel, 2001), where stimulation of 5-HT receptors improves cAMP production, activates cascade of signaling pathways/transcription factors and facilitates memory.

Involvement of cAMP signaling, PKA, and/or cAMP response element-binding (CREB) protein in long-term memory formation, depending on transcription and translation of proteins or mRNA, have been confirmed in several species (molluscs, flies, rats, mice) during behavioral learning tasks (Kandel, 2001; Manuel-Apolinar and Meneses, 2004). Links between mRNA translation and structural plasticity have been shown by studies on mammalian species focused on memory formation and synaptic plasticity have shown (Izquierdo et al, 2004; Meneses, 2007). It is important to note that autoshaped long-term memory formation requires synthesis of proteins (Meneses, 2007), 5-HT<sub>7</sub> receptors mRNA, 5-HT<sub>1A</sub> and 5-HT<sub>7</sub> receptors expression (Luna-Munguia et al, 2005). Modulation of memory consolidation and phase-shift in the suprachiasmatic nucleus, both induced by 8-OH-DPAT, require transcription and translation of proteins (Jovanovska and Prosser, 2002; Meneses, 2007; Pérez-García and Meneses, 2005), and are likely mediated by 5-HT<sub>1A</sub> and 5-HT<sub>7</sub> receptors. The interaction between neuromodulators and neuronal

activity could be linearly additive, that is the outcome in gene expression could be dependent on the negative or positive effect of the two stimuli on different targets within the signal transduction pathway; alternatively, the two extrinsic stimuli could have a more complex non-linear interaction. In absence of neural activity, stimulation of both the hippocampal 5-HT<sub>1A</sub> and 5-HT<sub>7</sub> receptors results in increased CREB phosphorylation (Mahgoub et al, 2005). Such findings were rather unexpected, considering that 5-HT<sub>1A</sub> receptors couple with G<sub>i</sub> to inhibit the cAMP pathway, while 5-HT<sub>7</sub> receptors couple with G<sub>s</sub> to stimulate the cAMP pathway in cell lines overexpressing these receptor subtypes (Mahgoub et al, 2005). Therefore, *in vivo*, the coupling of these receptor subtypes in central neurons may be more complex compared to their properties in heterologous expression systems. Interestingly, the activation of both the 5-HT<sub>1A</sub> and 5-HT<sub>7</sub> receptors has been suggested to stimulate CREB phosphorylation (Mahgoub et al, 2005).

Some behavioral studies evaluated the role of 5-HT<sub>7</sub> receptors in learning and memory. For example, data derived from our recent research (Gasbarri et al., 2008) led to the assessment of the role of 5-HT<sub>7</sub> receptors antagonist SB-269970 on learning and memory in radial arm maze task. Rats trained to resolve the task and not submitted to any drug treatment exhibit a high degree of choice accuracy in the standard maze task. Therefore, the possibility of observing drug-induced improvement in choice accuracy was optimized by employing a two-phase procedure, separated by a delay of varying duration to increase the difficulty of the task. In our study, a two phase procedure allowed to evaluate two forms of memory: working memory and reference memory; in particular, the acquisition phase was conducted to assess working memory, while the test phase assessed reference memory. Our research has demonstrated that 5-HT<sub>7</sub> receptors antagonist SB-269970 improves memory, decreasing the number of errors in test phase, and

then affecting reference memory, while no effects were observed in working memory.

Another study, using 5-HT<sub>7</sub> receptor knockout mice to evaluate action in behavioral and learning tasks (Thomas and Hagan, 2004), reported that knockout mice exhibited a specific impairment in contextual fear conditioning. In this task, the animals learn to associate the environment (context) with an aversive stimulus. This task, such as other types of place learning, is HF-dependent. However, in a Barnes maze test, in which the animal must learn how to escape from an open area by locating a chamber using environmental cues, no difference between the behavior of wild-type and knockout mice was reported (Thomas and Hagan, 2004). Moreover, no difference in three HF-independent learning tasks, including cued fear conditioning, operant food conditioning and motor learning (rotarod) was shown (Thomas and Hagan, 2004). The impairment observed in contextual fear conditioning was not due to alterations in motor skills, visual acuity or anxiety level (Thomas and Hagan, 2004).

#### **4. 5-HT<sub>7</sub> RECEPTORS AND THEIR ROLE IN AMNESIA AND RECOVERY FROM AMNESIA.**

Some evidence suggest an association among 5-HT<sub>7</sub> receptors mRNA expression, memory consolidation, amnesia and recovery from amnesia. An active role of pre- and post-synaptic 5-HT<sub>7</sub> receptors was suggested by autoradiography of [<sup>3</sup>H] 8-OH-DPAT studies (Luna-Munguia et al, 2005). Moreover, a null expression of these receptors under amnesia induced by scopolamine or dizocilpine treatment was observed, and this condition was reversed by the 5-HT<sub>7</sub> receptor agonist AS 19, likely due to its re-establishing mRNA expression or reversing down-regulation (Pérez-García et al, 2006).

It was suggested that learning processes enhances mRNA expression of 5-HT<sub>7</sub> receptors, while the 5-HT<sub>7</sub> receptor agonist AS 19 facilitates

memory consolidation by attenuating this expression, likely by desensitization mechanisms (Pérez-García et al, 2006). Therefore, future work should be aimed at determining whether endogenous 5-HT might activate some of its receptors and/or whether certain 5-HT receptors are essentially activated during memory processes. In addition, animals trained in an autoshaping task strongly expressed 5-HT<sub>1A</sub>, 5-HT<sub>4</sub>, 5-HT<sub>6</sub> or 5-HT<sub>7</sub> receptors, involving 5-HT itself and/or other neurotransmitters; such effect was not observed in untrained or control groups (Pérez-García et al, 2006). Nevertheless, the results revealing the aforementioned anti-amnesic effects of 5-HT<sub>7</sub> receptor agonist AS 19 (as well as those of 8-OH-DPAT) may appear inconsistent with previous data, showing that the 5-HT<sub>7</sub> antagonists SB-269970 and DR4004 reversed memory deficits, therefore indicating that these antagonists had no effects, when tested alone during memory formation (Meneses, 2004). For example, in the autoshaping learning task, post-training systemic injection of LY215840 (a 5-HT<sub>2/7</sub> antagonist) or WAY 100635 (a 5-HT<sub>1A</sub> antagonist) had no effect on memory consolidation (Lamprecht and LeDoux, 2004), whereas both drugs abolished the facilitatory effect of 8-OH-DPAT (a 5-HT<sub>1A/7</sub> receptor agonist), with LY215840 being slightly more effective in this respect. Notably, the 8-OH-DPAT facilitatory effect was induced by low doses, and prevented by 5-HT depletion or synthesis inhibition, suggesting a participation of presynaptic 5-HT<sub>1A</sub> receptors and also an additional mechanism, most likely involving 5-HT<sub>7</sub> receptors (Lamprecht and LeDoux, 2004). If drugs are administered before training, it is extremely difficult to determine whether they act on memory or on other processes that indirectly affect learning and retention (e.g. attention, motivation, motor activity, etc.) (McGaugh and Izquierdo, 2000).

Post-training administration of scopolamine (a centrally acting anticholinergic agent) or dizocilpine (a non-competitive NMDA receptor antagonist) significantly decreased the conditioned responses percentage in a Pavlovian/instrumental autoshaping learning task (Pérez-García et al, 2006). When either scopolamine or dizocilpine were injected immediately after autoshaping training

session, followed by the administration of SB-269970 or DR 4004 antagonists, their amnesic effects were reversed. The most important finding of this work is that selective 5-HT<sub>1A</sub> and 5-HT<sub>7</sub> receptor antagonists had no effect on memory processes, when tested alone, but significantly inhibited the facilitatory 8-OH-DPAT effect, in agreement with the involvement of 5-HT<sub>1A/7</sub> receptors in this 8-OH-DPAT effect. It is not clear whether in amnesic, AD or schizophrenic patients deregulation of 5-HT<sub>7</sub> receptors is a pathological condition or a compensatory mechanism. It is important to note that, during aging or AD, 5-HT<sub>7</sub> receptors seem to decline in raphe complex (Pérez-García et al, 2006).

In conclusion, although the role of 5-HT<sub>7</sub> receptors on learning and memory processes is yet to be clarified, the interest in its action is derived from the possibility that these receptors can improve memory, thus playing a role in normal or impaired memory (Meneses, 2004; Pérez-García et al, 2006; Roberts et al, 2004). Furthermore, even though high affinity selective agonists and antagonists are still to be developed, the research conducted so far, and reported in this paper, suggests an important participation of 5-HT<sub>7</sub> receptors on learning and memory. Further findings can lead to understanding the action mechanism of serotonergic system on cognitive functions, general behaviour, treatment of some cognitive disorders, considering the ability of antipsychotic and antidepressant drugs to interact with the 5-HT<sub>7</sub> receptor.

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