

# The role of serotonin in memory: interactions with neurotransmitters and downstream signaling

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**Abstract** Serotonin, or 5-hydroxytryptamine (5-HT), is found to be involved in many physiological or pathophysiological processes including cognitive function. Seven distinct receptors (5-HT<sub>1–7</sub>), each with several subpopulations, have been identified for serotonin, which are different in terms of localization and downstream signaling. Because of the development of selective agonists and antagonists for these receptors as well as transgenic animal models of cognitive disorders, our understanding of the role of serotonergic transmission in learning and memory has improved in recent years. A large body of evidence indicates the interplay between serotonergic transmission and other neurotransmitters including acetylcholine, dopamine,  $\gamma$ -aminobutyric acid (GABA) and glutamate, in the neurobiological control of learning and memory. In addition,

there has been an alteration in the density of serotonergic receptors in aging and Alzheimer's disease, and serotonin modulators are found to alter the process of amyloidogenesis and exert cognitive-enhancing properties. Here, we discuss the serotonin-induced modulation of various systems involved in mnemonic function including cholinergic, dopaminergic, GABAergic, glutamatergic transmissions as well as amyloidogenesis and intracellular pathways.

**Keywords** Serotonin · Memory · Signaling pathways

## Abbreviations

2PSDT	Two-platform spatial discrimination task
3xTg-AD	Triple-transgenic mouse model of Alzheimer's disease
5-HT	5-Hydroxytryptamine
AC	Adenylate cyclase
Ach	Acetylcholine
AD	Alzheimer's disease
APP	Amyloid precursor protein
ARN	Anterior raphe nucleus
A $\beta$	Amyloid $\beta$
cAMP	Cyclic adenosine monophosphate
cGMP	Cyclic guanosine monophosphate
CPP	Conditioned place preference
CREB	cAMP-response element binding
DA	Dopamine
DH	Dorsal hippocampus
DMTS	Delayed matching to sample
DNPTP	Delayed non-matching to position
DRN	Dorsal raphe nucleus
EPAC	Exchange proteins activated by cAMP
EPSCs	Excitatory postsynaptic currents
ERK	Extracellular signal-regulated kinase
FC	Frontal cortex

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GABA	Gamma ( $\gamma$ )-aminobutyric acid
GAD	Glutamic acid decarboxylase
G <sub>i</sub>	Inhibitory G-protein
Glu	Glutamate
GPCRs	G-protein-coupled receptors
G <sub>s</sub>	Stimulatory G-protein
GSK3	Glycogen synthase kinase 3
i.c.v.	Intracerebroventricular
i.p.	Intraperitoneal
i.v.	Intravenous
LTP	Long-term potentiation
LTD	Long-term depression
MAPK	Mitogen-activated protein kinases
MBN	Magnocellular nucleus basalis
mGluR	Metabotropic glutamate receptor
MS/vDB	Medial septum and the adjacent vertical limb of the diagonal band of Broca area
MWM	Morris water maze
NAc	Nucleus accumbens
NMDA	<i>N</i> -Methyl-D-aspartate
NO	Nitric oxide
ORT	Object recognition task
PA	Passive avoidance
PCA	p-Chloroamphetamine
PDE	Phosphodiesterase
PFC	Prefrontal cortex
PI	Pavlovian/instrumental autoshaping
PKA	Protein kinase A
PKC	Protein kinase C
PKG	Protein kinase G
PKM	Protein kinase M
PLA2	Phospholipase A2
PS1	Presenilin-1
PT	Pass through
s.c.	Subcutaneous
SA	Self-administration
sIPSC	Spontaneous inhibitory postsynaptic current
VTA	Ventral tegmental area

## Introduction

Serotonin, or 5-hydroxytryptamine (5-HT), plays a pivotal role in the cognitive function, and serotonin modulators are indicated for the treatment of an array of psychiatric disorders (Boulougouris and Tsaltas 2008; Kiser et al. 2012; Meltzer et al. 2012). A large body of evidence implicates the contribution of various serotonin receptors in mnemonic function (Perez-Garcia and Meneses 2008b; Geldenhuys and Van der Schyf 2009), though an interplay between serotonin and several other neurotransmitters including acetylcholine (ACh), dopamine (DA), glutamate (Glu) and  $\gamma$ -aminobutyric acid (GABA) is found to be involved in a

variety of neurophysiological processes including learning and memory (Nic Dhonnchadha and Cunningham 2008; Kranz et al. 2010; Lesch and Waider 2012).

Seven distinct families of serotonin receptors with several subpopulations have been identified which differ in terms of localization and downstream signaling (Barnes and Sharp 1999; Hoyer et al. 2002). Except for the 5-HT<sub>3</sub> receptors that are ligand-gated ion channels, the rest belong to the family of G-protein-coupled receptors (GPCRs); in this regard, 5-HT<sub>1</sub> and 5-HT<sub>5</sub> receptors are coupled to inhibitory G-protein (G<sub>i</sub>), whereas 5-HT<sub>4</sub>, 5-HT<sub>6</sub> and 5-HT<sub>7</sub> receptors are connected to the stimulatory G-protein (G<sub>s</sub>), and 5-HT<sub>2</sub> receptors activate G<sub>q/11</sub> (Pytliak et al. 2011).

Several imaging experiments have revealed a profound alteration in the density of serotonergic receptors in aging and Alzheimer's disease (AD) (Rodriguez et al. 2012). Furthermore, some of the serotonin modulators are found to change the expression or processing of amyloid precursor protein (APP) (Payton et al. 2003; Postina 2012). Therefore, to elucidate the role of serotonin in memory, it is crucial to clarify the detailed interactions with other neurotransmitters and second messengers related with mnemonic or amnesic effects.

Here, we review the serotonin-induced modulation of cholinergic, dopaminergic, GABAergic and glutamatergic systems regarding their effects on learning and memory. In addition, we discuss the serotonergic modulation of amyloidogenesis as well as the intracellular pathways through which serotonin influences mnemonic function.

## The effects of serotonin on cholinergic transmission

Early studies demonstrated that both serotonin and acetylcholine enhance performance in one-trial inhibitory avoidance task. Moreover, co-administration of the serotonin reuptake inhibitor (alaproclate) and cholinergic agonist (oxotremorine) produces synergistic effects on memory retrieval. Cholinergic blockade reverses the facilitation caused by either this co-administration or cholinergic activation, but not that caused by serotonergic stimulation (Altman et al. 1987). In addition, transplantation of embryonic raphe cells into the hippocampus can improve the impairment of spatial memory caused by a combination of serotonergic/cholinergic deficiencies (Richter-Levin and Segal 1989). Intrahippocampal grafts of mixed septal–raphe cell suspension restore the reduction in ACh concentration due to aspirative fimbria–fornix lesions. This effect is recapitulated by septal grafts but to a lower extent, suggesting a functional interaction between serotonergic raphe and cholinergic septal neurons (Hilgert et al. 2000).

5-HT<sub>1A</sub> receptors (5-HT<sub>1A</sub>R) are co-expressed with cholinergic markers on medial septum and diagonal band of Broca. However, the proportion of neurons expressing

both markers vary in dorsal, ventral or septal regions (Kia et al. 1996). Blockade of the postsynaptic 5-HT<sub>1A</sub> receptors by NAN-190 or WAY 100635 can ameliorate the scopolamine-induced impairment of working memory and spatial learning in passive avoidance (PA) (Misane and Ogren 2003), object recognition task (ORT) (Pitsikas et al. 2003), pass through (PT) (Ohno and Watanabe 1996) or in two-platform spatial discrimination task (2PSDT) (Carli et al. 1997a). In contrast, stimulation of the presynaptic 5-HT<sub>1A</sub>R in dorsal raphe nucleus (DRN) by 8-OH-DPAT corrects the errors in choice accuracy caused by intrahippocampal administration of scopolamine (Carli et al. 1998). Moreover, injection of WAY 100635 into DRN neither altered choice accuracy nor affected the scopolamine-induced errors, but it did reverse the 8-OH-DPAT mitigation of deficits due to scopolamine (Carli et al. 2000). A combined sigma/5-HT<sub>1A</sub> receptors agonist, OPC-14523, reverses scopolamine- and age-associated learning and memory deficits in passive avoidance or Morris water maze (MWM) (Tottori et al. 2002). These effects might be mediated by an increase in ACh release in dorsal hippocampus (DH; Tottori et al. 2002), although some studies demonstrated that non-cholinergic neurons might play the main role in serotonin effects on hippocampal memory processing (Koenig et al. 2011). Subcutaneous (s.c.) administration of 5-HT<sub>1B</sub> receptor (5-HT<sub>1B</sub>R) agonists impairs memory retention in one-trial PA. Furthermore, the 5-HT<sub>1B</sub>R antagonist, NAS-181, improves performance in PA test in a dose-dependent manner and reverses memory deficit induced by scopolamine (when administered prior, but not after, scopolamine) or MK-801, N-Methyl-D-aspartate (NMDA) receptor antagonist. This effect might be explained by the inhibitory effect of these heteroreceptors on cholinergic or glutamatergic neurons (Eriksson et al. 2008).

It has been shown that both p-chloroamphetamine (PCA, a serotonin releaser) and scopolamine impair the retrieval of electric shock avoidance in the step-down test (Matsuno et al. 1993). In addition, the 5-HT<sub>2</sub> receptor (5-HT<sub>2</sub>R) antagonists, ritanserin and mianserin, ameliorate the deficit caused by PCA but not that induced by scopolamine. In contrast, cholinomimetic agents offset both PCA- and scopolamine-induced amnesia (Matsuno et al. 1993), suggesting that cholinergic transmission might be downstream to 5-HT<sub>2</sub>R signaling.

The 5-HT<sub>3</sub> receptor (5-HT<sub>3</sub>R) antagonists, Y-25130 (Ohno and Watanabe 1997), DAU 6215 (also known as Itasetron) (Brambilla et al. 1993), ICS 205930 (also known as tropisetron) (Chugh et al. 1991) and ondansetron (Carli et al. 1997b), reverse the scopolamine-induced learning and memory deficit in different paradigms including step-through passive avoidance, dark chamber aversion or two-platform spatial discrimination task. Although less effective than direct nicotinic or muscarinic agonists, the

5-HT<sub>3</sub>R antagonist, WAY100289, was shown to ameliorate the impairment of spatial learning caused by lesions to the cholinergic projections in nucleus basalis and medial septal brain regions (Hodges et al. 1995). The 5-HT<sub>3</sub>R antagonist, RS-56812, was also reported to improve performance in delayed matching to sample (DMTS) task in monkeys (Terry et al. 1996). On the other hand, 5-HT<sub>3</sub>R antagonist, ondansetron, failed to attenuate scopolamine-induced impairments in episodic memory and processing speed in healthy volunteers (Broocks et al. 1998).

In vitro experiments revealed that 5-HT<sub>4</sub> receptor (5-HT<sub>4</sub>R) activation augmented [3H]choline efflux in electrically stimulated slices of cerebral cortex, hippocampus and nucleus basalis magnocellularis; however, it did not alter [3H]choline efflux in resting brain slices (Siniscalchi et al. 1999). Likewise, intracerebroventricular (i.c.v) administration of the 5-HT<sub>4</sub>R agonists augmented ACh release in the frontal cortex (FC) but not in the striatum or DH (Consolo et al. 1994). Moreover, 5-HT<sub>4</sub> receptor blockade does not affect ACh release, but prevents the facilitatory effect of agonists suggesting the lack of constitutive activity (Consolo et al. 1994). It is also shown that 5-HT<sub>4</sub>R agonists, BIMU 1 and RS 67333, recover scopolamine-induced impairment of performance in Y-maze (Lelong et al. 2003). The 5-HT<sub>4</sub>R knockout mice display similar spatial learning as well as short- and long-term retention to wild type in MWM. However, they are more sensitive to scopolamine-induced memory deficit, and show less choline acetyltransferase (ChAT) activity in the septum and the DH (Segu et al. 2010). The facilitatory effect of 5-HT<sub>4</sub>R agonist, SC 53116, on spike amplitude and tetanus-induced long-term potentiation (LTP) in the hippocampal CA1 is also blocked by scopolamine in electrophysiological experiments (Matsumoto et al. 2001).

The 5-HT<sub>6</sub> receptor (5-HT<sub>6</sub>R) antagonist, SB-271046, does not influence working memory, aversive learning or recognition memory (Da Silva et al. 2012). However Ro 046790 or SB 271046, 5-HT<sub>6</sub>R antagonists, reverse the scopolamine- or age- induced defect in novel object discrimination task (Woolley et al. 2003), PA (Foley et al. 2004; Da Silva et al. 2012), working memory (spontaneous alternation task in the T-maze) and conditioned emotion response (Da Silva et al. 2012), and partially alter scopolamine impaired recognition memory (Da Silva et al. 2012).

The 5-HT<sub>7</sub> receptor (5-HT<sub>7</sub>R) agonist, AS 19, enhances memory formation in autoshaping Pavlovian/instrumental (PI) learning task. This facilitatory effect is blocked by SB-269970, the 5-HT<sub>7</sub>R antagonist, but not by WAY100635, 5-HT<sub>1A</sub>R antagonist (Perez-Garcia and Meneses 2005). In addition, AS 19 reverses memory deficit due to scopolamine (cholinergic antagonist) or dizocilpine (NMDA antagonist) (Perez-Garcia and Meneses 2005),

whereas SB269970 augments scopolamine-induced impairment in delayed non-matching to position (DNPTP) task (Bonaventure et al. 2011). In contrast, 5-HT<sub>7</sub>R antagonists, SB-269970 and DR 4004, abrogate memory impairment due to scopolamine or dizocilpine in autoshaping PI learning task (Meneses 2004). This controversy may arise from the differences in scopolamine dose, strains of rats, the forms of memory (consolidation or working) and the protocol used in PI and DNPTP tests (Bonaventure et al. 2011).

The alpha7 nicotinic acetylcholine receptor ( $\alpha$ 7nAChR) has been associated with cognitive function as well as anxiety (Toyohara and Hashimoto 2010; Pandya and Yakel 2013). Serotonin denervation of the rat prefrontal cortex (PFC) by a chemical lesion in the anteroventral DRN changed the pattern of expression of nicotinic cholinergic receptors, while  $\alpha$ 4 receptors were overexpressed,  $\alpha$ 7nAChR underwent a significant decrease in denervated rats (Soria-Fregozo et al. 2013). Moreover, the 5-HT<sub>1A</sub> receptor antagonist, WAY-100135, blocked the anxiogenic effects of activation of the  $\alpha$ 7nAChR (Pandya and Yakel 2013). A novel  $\alpha$ 7nAChR agonist/5-HT<sub>3</sub>R antagonist, EVP-5141, restored scopolamine- or age-induced impairment of memory acquisition and retention in the PA task or spatial working memory in water maze. Moreover, EVP-5141 improved both objective and social recognition memory and was not substituted for nicotine in rats trained to discriminate nicotine from saline, suggesting less potential for abuse (Boess et al. 2013).

In summary, stimulation of the 5-HT<sub>7</sub> receptors as well as blockade of 5-HT<sub>3</sub>, 5-HT<sub>4</sub> and 5-HT<sub>6</sub> receptors seems to recover scopolamine-induced memory impairment in a variety of experiments. The effects of 5-HT<sub>1A</sub> ligands depend on the activation of pre- or postsynaptic neurons. In contrast, the 5-HT<sub>1B</sub> agonists impair memory retention possibly through an inhibitory effect on cholinergic or glutamatergic neurons. The  $\alpha$ 7nAChR agonist/5-HT<sub>3</sub>R antagonist has also been shown to produce positive effects on both scopolamine- or age-induced memory impairment (Table 1).

### The effects of serotonin on dopaminergic transmission

The mesocortical dopaminergic pathway is pivotal to the complex cognitive processes including selective attention and working memory. Likewise, the mesolimbic dopaminergic pathway is prominent in drug-induced reward and addiction memory (Wise and Rompre 1989; Nic Dhonnchadha and Cunningham 2008).

It has been shown that 5-HT<sub>1A</sub> receptors may increase or decrease mesolimbic neural firing depending on the activation of either pre- or postsynaptic receptors (Carey et al. 2004; Andrews et al. 2005). Moreover, hormesis (low-dose stimulation, high-dose inhibition) has been demonstrated

for the alteration in DA concentration in PFC by 5-HT<sub>1A</sub>R agonists (Diaz-Mataix et al. 2005). Both blockade of pre- and stimulation of postsynaptic 5-HT<sub>1A</sub> receptors augment cocaine-stimulated DA release and hyperlocomotion (Carey et al. 2004; Andrews et al. 2005). In addition, the 5-HT<sub>1A</sub>R antagonist, WAY 100635, attenuates cocaine- but not cue-primed reinstatement of cocaine self-administration (SA) (Burmeister et al. 2004). The 5-HT<sub>1B</sub>R agonists enhance cocaine-induced conditioned place preference (CPP) and SA (Parsons et al. 1998; Cervo et al. 2002). However, RU24969, 5-HT<sub>1B/1A</sub> agonist, interferes with the retrieval of cocaine- or sucrose-seeking response following extinction. These effects are blocked by GR127935, the 5-HT<sub>1B</sub>R antagonist (Acosta et al. 2005). In this regard, 5-HT<sub>1B</sub>R antagonism decreases cocaine-induced DA release and prevents its reinforcing effects (O'Dell and Parsons 2004). This suggests that blockade of the 5-HT<sub>1B</sub> receptors may inhibit reinforcement as well as memory formation due to drugs of abuse, while agonists at this receptor might help decrease the craving during abstinence and relapse.

The activation of 5-HT<sub>2A</sub> receptors (5-HT<sub>2AR</sub>) enhances dopaminergic activity both in nigrostriatal and in cortico-mesolimbic pathways (Alex and Pehek 2007) possibly through glutamatergic neurons (Kalivas et al. 1989; Kalivas 1993). The 5-HT<sub>2A</sub>R antagonist, M100907, suppresses cue-induced reinstatement of cocaine SA and retrieval of addiction-primed memories following extinction (Nic Dhonnchadha et al. 2009). The 5-HT<sub>2C</sub>R inverse agonists or antagonists boost cocaine-mediated DA release in nucleus accumbens (NAc) and hyperlocomotion (Filip and Cunningham 2003; Navailles et al. 2004). Likewise, injection of Ro60-0175, the 5-HT<sub>2C</sub>R agonist, into the ventral tegmental area (VTA) diminishes cocaine SA and hyperlocomotion (Fletcher et al. 2004). Moreover, 5-HT<sub>2C</sub>R agonists decrease contextual cue, cocaine or yohimbine-primed lever response and reinstatement of cocaine-seeking behavior after extinction training (Neisewander and Acosta 2007; Fletcher et al. 2008). These observations suggest that inhibition of 5-HT<sub>2A</sub>R and stimulation of 5-HT<sub>2C</sub>R hamper memory formation and retrieval in addiction, and should be considered as potential interventions to decrease craving for drugs of abuse (Nic Dhonnchadha and Cunningham 2008).

The stimulation of 5-HT<sub>3</sub> receptors leads to the depolarization of host cells. These receptors are expressed presynaptic on dopaminergic terminals (Chen et al. 1992), and may increase DA release in the NAc (Jiang et al. 1990). Furthermore, antagonists of this receptor are shown to attenuate morphine-, ethanol-, nicotine- or cocaine-stimulated DA release in the NAc as well as their rewarding effects (Carboni et al. 1989; Imperato and Angelucci 1989; Grant and Barrett 1991; Pei et al. 1993; Campbell and McBride 1995; Rodd-Henricks et al. 2003;

**Table 1** Interactions between serotonergic and cholinergic pathways in memory

Receptors	Ligand		Test	Effect on memory impairment due to cholinergic blockade or lesions	References	
	Agonists	Antagonists				
5-HT <sub>1A</sub>	OPC-14523 <sup>a</sup> (oral) 8-OH-DPAT (dorsal raphe)		MWM & PA	Improvement	Tottori et al. (2002)	
			2PSD	Improvement	Carli et al. (1998)	
		NAN-190 (s.c.), WAY 100635 (s.c.)	PA	Improvement	Misane and Ogren (2003)	
		WAY 100635 (s.c.)	ORT	Improvement	Pitsikas et al. (2003)	
		NAN-190 (intrahippocampal)	PT	Improvement	Ohno and Watanabe (1996)	
		WAY 100635 (s.c.) WAY 100635 (dorsal raphe)	2PSD 2PSD	Improvement No effect	Carli et al. (1997a) Carli et al. (2000)	
5-HT <sub>1B</sub>		NAS-181 (s.c.)	PA	Improvement <sup>b</sup>	Eriksson et al. (2008)	
5-HT <sub>2</sub>		Ritanserin and mianserin	PA	No effect	Matsuno et al. (1993)	
5-HT <sub>3</sub>		Y-25130 (intrahippocampal)	PT	Improvement	Ohno and Watanabe (1997)	
		DAU 6215 (i.p.)	PA and hypermotility	Improvement	Brambilla et al. (1993)	
		ICS 205–930 (s.c.)	PA	Improvement	Chugh et al. (1991)	
		Ondansetron (s.c.)	2PSD	improvement	Carli et al. (1997b)	
		WAY100289 (s.c.)	MWM	Improvement	Hodges et al. (1995)	
		Ondansetron (iv) <sup>c</sup>	Word, target, distance recall	No effect	Broocks et al. (1998)	
5-HT <sub>4</sub>	BIMU 1 and RS 67333 (i.p.) SC 53116 (i.c.v.)		Y-maze	Improvement	Lelong et al. (2003)	
			PA	Improvement	Matsumoto et al. (2001)	
5-HT <sub>6</sub>		Ro 04-6790	ORT	Improvement	Woolley et al. (2003)	
		SB-271046 (oral, i.p.)	PA, T-maze, place recognition <sup>d</sup>	Improvement	Foley et al. (2004), Da Silva et al. (2012)	
5-HT <sub>7</sub>	AS 19 (s.c.)		P/I	Improvement	Perez-Garcia and Meneses (2005)	
			SB269970 (i.p.)	DNMTP	Worsening	Bonaventure et al. (2011)
			SB-269970 & DR 4004 (i.p.)	P/I	Improvement	Meneses (2004)
alpha7 nAChR agonist/5-HT <sub>3</sub> antagonist	EVP-5141 (i.p.)		PA	Improvement	Boess et al. (2013)	

PA passive avoidance, ORT object recognition task, PT pass through, 2PSD two-platform spatial discrimination, MWM Morris water maze, DMST delayed matching to sample, DNPTP delayed non-matching to position, P/I autoshaping Pavlovian/instrumental, s.c. subcutaneous, i.p. intraperitoneal, i.v. intravenous, i.c.v. intracerebroventricular

<sup>a</sup> Combined sigma/5HT<sub>1A</sub> agonist

<sup>b</sup> Reverts the memory deficit when administered prior to, but not after, scopolamine

<sup>c</sup> In human

<sup>d</sup> Partial blockade of scopolamine-induced deficit in episodic-like memory (place recognition)

De Deurwaerdere et al. 2005). Meanwhile, some studies have shown that the 5-HT<sub>3</sub>R antagonists (ICS 205930 or MDL 72222) do not influence the discriminative stimulus

properties of cocaine (Paris and Cunningham 1991). This suggests that 5-HT<sub>3</sub>R activation plays a prominent role in the reinforcing effects of drugs of abuse. However, the



**Table 2** Interactions between serotonergic and dopaminergic pathways in memory

Receptors	Ligand		Test	Effect on cue/drug-primed reinstatement of SA	References
	Agonists	Antagonists			
5-HT <sub>1A</sub>		WAY 100635 (s.c.)	SA	No effect/attenuation	Burmeister et al. (2004)
5-HT <sub>1B</sub>	RU24969 (i.p.)		SA	Attenuation/attenuation	Acosta et al. (2005)
5-HT <sub>2A</sub>		M100907 (i.p.)	SA	Attenuation/no data	Nic Dhonnchadha et al. (2009)
5-HT <sub>2C</sub>	Ro60-0175 (s.c.)		SA	Attenuation/attenuation	Fletcher et al. (2008)
	MK 212 (i.p.)		SA	Attenuation/attenuation	Neisewander and Acosta (2007)
		SB242084 (i.p.)	SA	No effect/no effect	Burmeister et al. (2004)
5-HT <sub>2A/2C</sub>		Ketanserin (i.p.)	SA	Attenuation/no effect	Burmeister et al. (2004)
5HT <sub>3</sub>				No data <sup>a</sup>	Johnson et al. (2008a)
5-HT <sub>6</sub>		SB-271046 and Ro-04-6790	SA	Attenuation/no data	van Gaalen et al. (2010)

SA self-administration, s.c. subcutaneous, i.p. intraperitoneal

<sup>a</sup> Ondansetron did not change methamphetamine abuse, withdrawal or craving in human

potential effect of 5-HT<sub>3</sub>R modulation on reinstatement and retrieval of addiction-induced memories requires further investigation. In this regard, a preliminary randomized, double-blind, placebo-controlled trial revealed that ondansetron failed to affect methamphetamine abuse, withdrawal, or craving in humans (Johnson et al. 2008a).

The 5-HT<sub>4</sub> receptor antagonists have been shown to decrease the morphine-enhanced dopaminergic firing in striatum but not in VTA (Porrás et al. 2002). Moreover, pretreatment with a mixed 5-HT<sub>3</sub>R and 5-HT<sub>4</sub>R antagonist, DAU 6285, eliminated morphine-induced place conditioning (Bisaga et al. 1993). Although these receptors have been implicated in cocaine-induced hyperlocomotion (McMahon and Cunningham 1999), antagonists at this receptor did not influence cocaine- or amphetamine-mediated DA exocytosis (Porrás et al. 2002). The role of these receptors in potentiation of addictive behaviors is yet to be elucidated.

Pretreatment with SB 258510A, the 5-HT<sub>6</sub>R antagonist, potentiates amphetamine- but not cocaine-induced hyperlocomotion and SA. Furthermore, it enhances amphetamine-stimulated DA release especially in the FC (Frantz et al. 2002). The 5-HT<sub>6</sub>R agonist, ST1936, was self-administered by the rats, underlining the possible implication of this receptor in reinforcement. Furthermore, the 5-HT<sub>6</sub>R antagonist, SB271046, decreased cocaine SA as well as cocaine-stimulated DA concentration in the NAc shell but not in the PFC (Valentini et al. 2013). Likewise, the 5-HT<sub>6</sub>R antagonists, SB-271046 and Ro04-6790, diminished cue-induced cocaine-seeking behavior, although they did not influence cocaine SA and reinforcement (van Gaalen et al. 2010). In addition, overexpression of the 5-HT<sub>6</sub> receptors in the NAc by viral-mediated gene transfer abolished CPP to cocaine, but did not influence cocaine-induced locomotor sensitization (Ferguson et al. 2008). This suggests a potential role for 5-HT<sub>6</sub> receptors in reward learning as well as retrieval

of addition-induced memory; antagonists at this receptor may help decrease relapse to the drug of abuse after extinction.

Taken together, serotonin receptors appear intriguing targets to study emotional/addiction-related learning and memory processes. Activation of 5-HT<sub>1B</sub> and 5-HT<sub>2C</sub> receptors as well as blockade of 5-HT<sub>1A</sub>, 5-HT<sub>2A</sub>, 5-HT<sub>2A/2C</sub> and 5-HT<sub>6</sub> receptors have been shown to decrease cue/drug-primed relapse of drug SA (Table 2).

### The effects of serotonin on GABAergic/glutamatergic transmission

GABAergic interneurons in PFC contribute substantially to the inhibition of disproportionate dopaminergic activity by atypical antipsychotic drugs. This effect is proposed to be the main mechanism of cognitive enhancement by these drugs compared to the typical DA receptor blockers (Alex and Pehek 2007). Escitalopram, selective serotonin reuptake inhibitor (SSRI), reportedly boosts object recognition memory, and increases dopaminergic neuronal activity in VTA- and NMDA-induced currents in pyramidal neurons (Schilstrom et al. 2011).

Tryptophan hydroxylase-2 knockdown abolishes serotonin synthesis in the brain. Although these mice develop serotonergic neurons and projections, there have been alterations in GABAergic neurons in limbic regions of heterozygote or homozygote animals (Waider et al. 2013). Mice lacking p11, an adaptor protein of 5-HT<sub>1B</sub>R, display global reduction in hippocampal GABAergic inhibition. In addition, 5-HT<sub>1B</sub>R stimulation impairs emotional memory in the wild type, but enhances emotional memory as well as hippocampal glutamatergic transmission in adapter p11 knockout mice (Eriksson et al. 2013). Blockade of the brain 5-HT<sub>1B</sub>R by NAS-181 has also been shown to improve

memory retention in the PA test. This facilitatory effect was reversed by muscarinic (scopolamine) or glutamatergic (MK-80) antagonists (Eriksson et al. 2008).

The 5-HT<sub>1A</sub> receptors are expressed as presynaptic heteroreceptors on pyramidal and GABAergic neurons (Santana et al. 2004, 2009) or postsynaptic in hippocampus (Carli et al. 2000). Although endogenous serotonin inhibits pyramidal firing in medial PFC through 5-HT<sub>1A</sub> receptors, systemic administration of the 5-HT<sub>1A</sub> receptor agonists, 8-OH-DPAT, stimulates VTA projecting pyramidal neurons, which thereby results in enhanced firing of mesocortical dopaminergic receptors (Llado-Pelfort et al. 2012). This effect is thought to be mediated through GABAergic interneurons, in which 5-HT<sub>1A</sub> receptor agonists abolishes the inhibition of GABAergic interneurons on dopaminergic transmission (Llado-Pelfort et al. 2012). Injection of the 5-HT<sub>1A</sub>R agonist, 8-OH-DPAT, into the DRN reverses the impairment of choice accuracy due to intrahippocampal administration of 7-Cl-Kyn, an NMDA receptor antagonist (Carli et al. 2001). In addition, systemic or intrahippocampal administration of the 5-HT<sub>1A</sub>R antagonist, WAY 100635, mitigates spatial learning deficit caused by blockade of hippocampal NMDA receptors in a two-platform spatial discrimination task (Carli et al. 1999; Schiapparelli et al. 2005). Intraseptal administration of 8-OH-DPAT does not influence spatial memory (in water maze), but impairs emotional memory (in PA test); moreover, combination of intraseptal 8-OH-DPAT and subthreshold dose of the NMDA antagonist causes a profound impairment of spatial memory retention as well as mild deficit in spatial acquisition (Elvander-Tottie et al. 2009). Although the localization of 5-HT<sub>1A</sub> receptors in relation to the glutamatergic neurons in medial septum and the adjacent vertical limb of the diagonal band of Broca area (MS/vDB) is still not characterized (Elvander-Tottie et al. 2009), in the hippocampus, 5-HT<sub>1A</sub> receptors are expressed on both glutamatergic pyramidal cells and inhibitory GABAergic interneurons (Aznar et al. 2003). Postsynaptic 5-HT<sub>1A</sub> receptors are suggested to be co-located along with NMDA receptors in the dendritic compartments (Takumi et al. 1998). NMDA infusion into the magnocellular nucleus basalis (MBN) triggers apoptotic neurodegeneration that lasts for several days and results in excitotoxic lesions (Harkany et al. 2000). Moreover, oral postlesion administration of the 5-HT<sub>1A</sub>R agonists (repinotan and 8-OH-DPAT) ameliorates NMDA excitotoxicity and improves survival of cholinergic neurons and memory performance in rats (Harkany et al. 2001). These results indicate a dual role for 5-HT<sub>1A</sub> receptors in the modulation of Glu-induced excitatory input to hippocampus. On the one hand, activation of these receptors may hamper the NMDA-induced memory retention, thereby enhancing memory deficit caused by NMDA blockade (Elvander-Tottie et al. 2009); on the other hand, they may

ameliorate NMDA-induced excitotoxicity and consequent memory deficit (Harkany et al. 2001). Taken together, the final outcome of 5-HT<sub>1A</sub> receptor activation depends on (1) their localization in different brain areas, (2) interaction with inhibitory or excitatory neurons, (3) G-protein selectivity [5-HT<sub>1A</sub> receptors are coupled to G<sub>i3</sub> in the anterior raphe nucleus (ARN), while they mainly interact with G<sub>o</sub> proteins in the hippocampus (Mannoury la Cour et al. 2006)], and (4) agonist-directed receptor trafficking, and consequent adaptive modifications (Kenakin 1995; Li et al. 1997; Raap et al. 1999; Hensler 2002).

The activation of 5-HT<sub>2C/2B</sub> but not 5-HT<sub>2A</sub> receptors produces a potent inhibitory effect on the mesolimbic and nigrostriatal dopaminergic firing (Di Giovanni et al. 1999; Di Matteo et al. 1999). This phenomenon is explained by the 5-HT<sub>2C</sub>R-mediated potentiation of GABAergic inhibition on dopaminergic neurons (Di Giovanni et al. 1999, 2001). Alstonine, a putative antipsychotic agent, decreases Glu uptake, which is abolished by the 5-HT<sub>2A/2C</sub> receptor antagonists. Glu dysfunction is also suggested to play a role in social interaction and working memory deficits (Herrmann et al. 2012). Stimulatory output from postsynaptic 5-HT<sub>2A</sub> receptors on GABAergic interneurons enhances their inhibitory impulse, and may have potential therapeutic benefits in hippocampal and amygdala dysfunction (Bombardi and Di Giovanni 2013). In addition, M100907, a highly selective 5-HT<sub>2A</sub> antagonist, facilitates LTP in CA1 synapses, and potentiates NMDA responses and excitatory postsynaptic currents (EPSCs) due to electrical stimulation of CA1 hippocampal pyramidal cells (Wang and Arvanov 1998).

Using a combination of immunohistochemistry and double in situ hybridization, it has been shown that 5-HT<sub>3A</sub> receptors are expressed on GABA neurons in the rat telencephalon. This suggests a functional interaction between these neurotransmitters (Morales et al. 2004). The 5-HT<sub>3</sub>R signaling influences both emotional and working memory. Activation of these receptors alters the expression of GABA receptor clustering protein, gephyrin, in amygdala and hippocampus after cued or contextual fear extinction, respectively, and may promotes extinction of fearful memories (Park and Williams 2012). This suggests the possible involvement of GABAergic transmission in beneficial effects of 5-HT<sub>3</sub>R on memory. In addition, 5-HT<sub>3</sub> receptors affect working memory in the pass-through panel gates test. Intrahippocampal administration of the 5-HT<sub>3</sub>R antagonist, Y-25130, recovers the working memory errors caused by cholinergic antagonism but not those due to the NMDA receptor blockade (Ohno and Watanabe 1997). Serotonergic brainstem projections to hippocampus, via 5-HT<sub>3</sub> receptors, are believed to increase the GABA<sub>B</sub>-mediated inhibition in the dendritic region of pyramidal cells. In this regard, the 5-HT<sub>3</sub> antagonist, ondansetron, facilitates theta

frequency and significantly augments the magnitude and duration of LTP due to electrical stimulation in freely moving rats (Staubli and Xu 1995).

Modulation of the 5-HT<sub>6</sub> receptor activity has shown promise in the treatment for cognitive disorders. The 5-HT<sub>6</sub> R antagonist SB-271046 increases extracellular Glu levels in both FC and DH, but not in striatum or NAc (Dawson et al. 2001). The enhancement of excitatory neurotransmission is involved in the augmented Ach release by 5-HT<sub>6</sub>R antagonists (Marcos et al. 2006). The 5-HT<sub>6</sub>R antagonist, Ro 04-6790, enhances memory consolidation, and prevents delay-induced extinction of object discrimination (King et al. 2004). Moreover, post-training administration of Ro 04-6790 recovers recognition deficit, hypermotility and ataxia produced by MK-801, an NMDA antagonist (Pitsikas et al. 2008). Similarly, pretreatment with NMDA antagonists prevents the beneficial effects of 5-HT<sub>6</sub>R blockade on memory (King et al. 2004). In this regard, the favorable effects of 5-HT<sub>6</sub> receptor antagonism on memory and schizophrenia are reviewed elsewhere (Mitchell and Neumaier 2005; Johnson et al. 2008b; Marsden et al. 2011). The serotonin-6 receptors are co-localized with glutamic acid decarboxylase (GAD) in GABAergic neurons within multiple brain regions (Woolley et al. 2004), suggesting that increased Glu concentration due to 5-HT<sub>6</sub> blockade can be indirectly mediated through GABAergic system (Dawson et al. 2001; West et al. 2009). The 5-HT<sub>6</sub> receptor agonist, E-6801, is also demonstrated to enhance object recognition memory mainly through cholinergic and glutamatergic pathways (Kendall et al. 2011). In this regard, combination of sub-effective doses of E-6801 (1 mg/kg) with donepezil (indirect cholinergic agonist) or memantine (NMDA antagonist) significantly enhances object recognition memory. Moreover, the efficacy of E-6801 in reversing scopolamine (0.5 mg/kg)-induced impairment is comparable to that of donepezil (0.3 and 1 mg/kg) (Kendall et al. 2011). In addition, both blockade and activation of 5-HT<sub>6</sub> receptors reverse scopolamine or MK-801-induced memory deficit in cue-linked emotional fear response (Woods et al. 2012). It should be noted that the 5-HT<sub>6</sub> R agonists, WAY-181187, attenuates LTP, and enhances spontaneous inhibitory postsynaptic current (sIPSC) in brain slices containing CA1 of the hippocampus through an increase in extracellular GABA concentration (West et al. 2009).

The 5-HT<sub>7</sub> receptor antagonist, SB269970, alleviates object recognition impairment due to the NMDA antagonists, phencyclidine (Horiguchi et al. 2011b) and MK-801 (Bonaventure et al. 2011), but aggravates the deficit caused by anticholinergic agents (Bonaventure et al. 2011). Electrophysiological studies on hippocampal slices, however, revealed that 5-HT<sub>7</sub>R activation reverses metabotropic Glu receptor-induced long-term depression (LTD) (Costa et al. 2012).

Activation of the metabotropic Glu 2/3 receptor (mGlu<sub>2/3</sub>R) enhances clozapine alleviation of phencyclidine-induced impairment in object recognition. Moreover, positive effects of clozapine are also reversed by LY341495, an mGlu<sub>2/3</sub>R antagonist, suggesting a possible crosstalk between serotonin and metabotropic Glu receptors (Horiguchi et al. 2011a).

In summary, blockade of 5-HT<sub>1B</sub> and 5-HT<sub>7</sub> receptors improves memory deficit caused by glutamatergic blockade or lesions. In this regard, the effect of 5-HT<sub>1A</sub> and 5-HT<sub>6</sub> receptors depends on the activity of specific receptors in different brain areas, where both agonists and antagonists have been shown to produce beneficial effects (Table 3).

### The effects of serotonin on amyloidogenesis

The APP is a type I integral membrane glycoprotein in mammalian cells. Cleavage of APP at the N-terminus of amyloid  $\beta$  peptide (A $\beta$ ) by  $\beta$ -secretase or at the C-terminus by  $\gamma$ -secretase results in amyloidogenesis and aggregation of A $\beta$  in the brain. In contrast,  $\alpha$ -secretase activity yields a large soluble N-terminal ectodomain named sAPP $\alpha$  into the extracellular space, which offers neuroprotective and memory-enhancing properties (Postina 2012). Degeneration of the serotonergic neurons is suggested to be involved in A $\beta$ -induced cognitive damage in dogs (Bernedo et al. 2009). In addition, high tryptophan diet (0.40 g/100 g for 1 month) reduced intraneuronal A $\beta$  deposits in triple transgenic mouse model of AD (3xTg-AD). This suggests a potential benefit for elevated 5-HT content in the reduction in amyloidogenesis in AD (Noristani et al. 2012). Moreover, A $\beta$  injection is proposed to cause a transient overexpression of 5-HT<sub>1A</sub> receptors in astroglial cells in response to the local neuronal loss (Verdurand et al. 2011).

Paroxetine, an SSRI, is shown to decrease APP expression (Payton et al. 2003). Moreover, direct infusion of serotonin into the hippocampus as well as treatment with several SSRIs decreases the levels of A $\beta$  in brain interstitial fluid in presenilin-1 (PS1)/APP double-transgenic mice model of AD (Cirrito et al. 2011). Similarly, imipramine and citalopram enhance the secreted APP from primary rat basal forebrain neurons (Pakaski et al. 2005). In addition, a retrospective positron emission tomography (PET) analysis has revealed lower load of amyloid in patients treated with anti-depressants (Cirrito et al. 2011); thereby, a variety of these agents have been evaluated for cognitive-enhancing properties in AD (Rodriguez et al. 2012).

Stimulation of 5-HT<sub>2a/2c</sub> receptors in cultured 3T3 cells accelerates the secretion of the soluble APP mainly through phospholipase A2 (PLA2) or protein kinase C (PKC) (Nitsch et al. 1996). Moreover, dexnorfenfluramine, the 5-HT<sub>2c</sub>R agonist, as well as meta-chlorophenylpiperazine



**Table 3** Interactions between serotonergic and glutamatergic transmission in memory

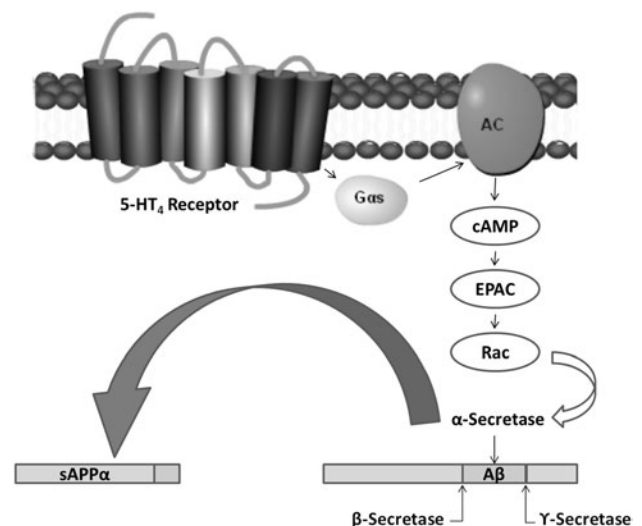
Receptors	Ligand		Test	Effect on memory deficit due to glutamatergic blockade or lesions	References
	Agonists	Antagonists			
5HT <sub>1A</sub>	8-OH-DPAT (dorsal raphe)		2PSD	Improvement	Carli et al. (2001)
	Repinotan and 8-OH-DPAT (oral)		PA, neural survival	Improvement	Harkany et al. (2001)
			WAY 100635 (S.C., intrahippocampal)	Improvement	Carli et al. (1999)
5-HT <sub>1B</sub>		NAS-181 (s.c.)	PA	Improvement	Eriksson et al. (2008)
5-HT <sub>3</sub>		Y-25130 (intra hippocampal)	PT	No effect	Ohno and Watanabe (1997)
5-HT <sub>6</sub>	E-6801 (i.p.), EMD 386088 (i.p.)		CER	Improvement	Woods et al. (2012)
		SB-270146 (i.p.)	CER	Improvement	Woods et al. (2012)
5-HT <sub>7</sub>		SB269970 (i.p.)	ORT, DNMTPT	Improvement	Bonaventure et al. (2011), Horiguchi et al. (2011a, b)

PA passive avoidance, ORT object recognition task, PT pass through, 2PSD two-platform spatial discrimination, DNPTP delayed non-matching to position, CER conditioned emotional response

(mCPP), the 5-HT<sub>2b/2c</sub>R agonist, increases the soluble APP concentration in cerebrospinal fluid of guinea pigs (Arjona et al. 2002). As the production of soluble APP precludes the formation of amyloidogenic derivatives, agonists at this receptor are potential targets for the treatment of AD.

The 5-HT<sub>3</sub> receptors are ligand-gated ion channels, which cause neural depolarization and excitation (Maricq et al. 1991). Blockade of these receptors is shown to protect against ischemia-induced injury in hippocampal slices (Kagami et al. 1992) or A $\beta$  (25–35)-induced neurotoxicity in cultured cortical neurons (Ju Yeon and Yeon Hee 2005). These effects are contributed to the inhibition of A $\beta$ -mediated increase in levels of calcium, Glu, TNF- $\alpha$ , NF- $\kappa$ B, iNOS, COX-2, active caspase 3, cytochrome c and calcineurin phosphatase (Ju Yeon and Yeon Hee 2005; Rahimian et al. 2013). This suggests 5-HT<sub>3</sub> blockers as potential therapeutic agents for the inhibition of amyloid-induced neurotoxicity (Fakhfoury et al. 2012).

Activation of the 5-HT<sub>4</sub> receptors switches the APP metabolism to the non-amyloidogenic pathway resulting in the production of sAPP $\alpha$  in cultured CHO cells (Robert et al. 2001). Moreover, this effect was demonstrated to be due to specific alterations in  $\alpha$ -secretase activity. The pathways downstream of this process has been reported to include the cAMP-regulated guanine nucleotide exchange factor, exchange proteins activated by cAMP (EPAC) and the small GTPase, Rac (Fig. 1) (Robert et al. 2005). Similarly, the 5-HT<sub>4</sub>R partial agonist, RS67333, increases survival and prevents the production of A $\beta$  peptide in primary cortical cultures of transgenic mice expressing human APP (Cho and Hu 2007). The possible correlation of serotonin



**Fig. 1** The effects of 5-HT<sub>4</sub> receptor activation on amyloidogenesis. Activation of the 5-HT<sub>4</sub> receptors alters  $\alpha$ -secretase activity and switches the metabolism of amyloid precursor protein (APP) toward the generation of soluble form of APP (sAPP $\alpha$ ). The pathways downstream to the receptor have been reported to include the cAMP-regulated guanine nucleotide exchange factor, Epac and the small GTPase, Rac (Robert et al. 2001, 2005; Lezoualc'h 2007). AC, adenylate cyclase; G $\alpha$ s, Stimulatory G-protein; EPAC, exchange proteins activated by cAMP; A $\beta$ , amyloid beta

transmission with amyloid plaque formation was also investigated in AD patients using PET. No significant change was observed in cerebral 5-HT<sub>4</sub> receptor density in AD patients based on the clinical criteria. In contrast, patients with positive A $\beta$  burden displayed upregulation of

cerebral 5-HT<sub>4</sub> receptors (Madsen et al. 2011). This finding points to the upregulation of 5-HT<sub>4</sub> receptor as a potential diagnostic marker in early stages of the disease. Additionally, agonists at this receptor may help reduce the formation of amyloid deposits (Lezoualc'h 2007).

The 5-HT<sub>6</sub> receptors are also positively coupled to adenylyl cyclase (AC) activation; therefore, a similar effect to that of 5-HT<sub>4</sub> receptors (formation of non-amyloidogenic derivatives) is conceivable for this subtype, though yet to be elucidated (Postina 2012). Meanwhile, antagonists at this receptor improve cognitive function in a number of hippocampal-dependent tasks (see previous sections) and are undergoing clinical trials as novel cognitive-enhancing agents for AD (Upton et al. 2008).

Taken together, 5-HT<sub>2</sub> and 5-HT<sub>4</sub> receptors agonists as well as 5-HT<sub>3</sub> blockers appear promising therapeutic approaches to reduce the progression of neurodegeneration in Alzheimer's disease.

### The effects of serotonin on intracellular pathways

Multiple intracellular pathways are involved in neural plasticity, memory formation and sensitization by 5-HT. A large body of evidence in vertebrates and/or invertebrates indicates that serotonin influences memory through second messengers and effectors including cyclic adenosine monophosphate (cAMP) (Bevilaqua et al. 1997; Perez-Garcia and Meneses 2008a; Lee et al. 2009; McLean et al. 2009), cyclic guanosine monophosphate (cGMP) (van Donkelaar et al. 2008), PKC (Byrne and Kandel 1996; Barbas et al. 2003), mitogen-activated protein kinases (MAPK) (Cammarota et al. 2008; Carlini et al. 2012) and glycogen synthase kinase 3 (GSK3) (Polter and Li 2010).

Serotonin prolongs action potentials and increases neural excitability, spike duration and synaptic strength in a cAMP-dependent manner in marine *Aplysia* (Goldsmith and Abrams 1992). In addition, overexpression of *Aplysia* 5-HTapAC1 in mammalian HEK293 cells and in *Xenopus* oocytes increases cAMP content of the cell. Likewise, 5-HTapAC1 dsRNA hinders 5-HT-induced cAMP production, membrane excitability, spike duration and synaptic facilitation in non-depressed or partially depressed synapses (Lee et al. 2009). The 5-HT<sub>1A</sub> receptor (negatively coupled to AC) agonist, tandospirone, has been shown to inhibit hippocampal LTP in vivo (Mori et al. 2001), whereas 5-HT<sub>4</sub> R (positively coupled to AC) agonists are shown to facilitate LTP (Matsumoto et al. 2001). In contrast, the activation of the 5-HT<sub>6</sub> receptors, though positively couple to AC, attenuates LTP in hippocampus mainly through an increase in GABAergic transmission (West et al. 2009).

Serotonin modulation of cyclic nucleosides is also involved in memory formation and consolidation. Acute tryptophan depletion impairs ORT performance in rats (Rutten et al. 2007a). The phosphodiesterase 4 (PDE4) inhibitor, rolipram, increases cAMP level and subsequently restores memory impairment due to tryptophan depletion (Yuan et al. 2000; Rutten et al. 2007a). A role for cAMP/protein kinase A (PKA)/cAMP-response element-binding protein (CREB) in the hippocampus is also suggested for memory consolidation downstream of 5-HT<sub>1A</sub> receptors in rats using passive avoidance test (Bevilaqua et al. 1997). In this regard, post-training intrahippocampal injection of NAN-190, the 5-HT<sub>1A</sub>R antagonist, increases memory retention in one-trial step-down test, whereas 8-OH-DPAT, the 5-HT<sub>1A</sub>R agonist, causes retrograde amnesia (Bevilaqua et al. 1997). Activation of 5-HT<sub>4</sub> receptors by RS 67333 enhances information acquisition in object recognition test. Moreover, stimulation of 5-HT<sub>4</sub> receptors results in the activation of particulate PDE in the PFC and the hippocampus (Levallet et al. 2009). The 5-HT<sub>4</sub>R partial agonist, SL65.0155, reportedly increased cAMP production and improved learning and memory. Furthermore, it improved scopolamine- or age-induced cognitive deficits in the MWM, and showed synergistic therapeutic effects when combined with rivastigmine (a cholinesterase inhibitor) (Moser et al. 2002). The 5-HT<sub>1A/7</sub>R agonist, 8-OH-DPAT as well as the 5-HT<sub>7</sub>R agonist, AS19, facilitated memory formation and consolidation in PI autoshaping test. The raphe nuclei and PFC have shown higher cAMP contents in trained animals treated with AS19, but there has been a reduction in cAMP levels in the raphe nuclei of those treated with 8-OH-DPAT. These results are attributed to positive (5-HT<sub>7</sub> R) or negative (5-HT<sub>1A</sub> R) coupling to AC (Perez-Garcia and Meneses 2008a). Another study reported an increased cAMP production in cortical and hippocampal areas following the administration of 8-OH-DPAT (Manuel-Apolinar and Meneses 2004). This discrepancy could emerge from different time courses in training and testing sessions (Perez-Garcia and Meneses 2008a). Acute administration of MDMA in rats augmented LTP in CA3–CA1 synapses through presynaptic 5-HT<sub>2</sub> receptors and postsynaptic DA (D<sub>1</sub>/D<sub>5</sub>) receptors (Rozas et al. 2012). This effect was abolished by PKA inhibitors, suggesting the involvement of cAMP-dependent mechanisms (Rozas et al. 2012). Serotonin depletion of olfactory bulb impaired conditioned odor preference, which was further restored by 5-HT<sub>2A/2C</sub> agonists (Price et al. 1998; Yuan et al. 2003) or when cAMP levels were increased by adrenergic stimulation (Yuan et al. 2000) or cilomilast, PDE inhibitor, in the neonate rats (McLean et al. 2009).

Long-term potentiation by serotonin in *Aplysia* involves the activation of PKC (Sacktor et al. 1988), protein kinase

M (PKM) (Cai et al. 2011), phosphoinositide 3-kinase (PI3K) (Hu et al. 2011), MAPK (Martin et al. 1997) and synapsin (Angers et al. 2002; Hart et al. 2011). Long-term facilitation in invertebrates and vertebrates involves gene expression downstream to CREB. Moreover, serotonin-facilitated synaptic transmission can be explained by the subsequent activation of PKC, which itself causes ubiquitination and degradation of CREB repressor (Upadhyay et al. 2004). PKC is also the main mediator of serotonin-augmented membrane excitability at depressed synapses (Sacktor et al. 1988; Byrne and Kandel 1996). The possible involvement of these signaling pathways in other species requires further investigation (Cammara et al. 2008). In this regard, serotonin caused an early depression (lasting for 30–50 min, via 5-HT<sub>1A</sub> receptors) or a late, long-lasting facilitation (lasting for more than 5 h, via 5-HT<sub>4</sub> receptors) in amygdala slice recordings. The later effect was blocked by the inhibitors of PKA and extracellular signal-regulated kinase (ERK), suggesting the possible involvement of these pathways in serotonin-mediated facilitation (Huang and Kandel 2007). Moreover, disinhibition of 5-HT<sub>1A</sub>R/MEK/Arc or stimulation of 5-HT<sub>4</sub>R/MEK/Arc signaling cascades improved emotional memory in PA test in genetic models of depression (Eriksson et al. 2012).

Although cGMP/protein kinase G (PKG)/nitric oxide (NO) pathway is involved in memory formation and consolidation (Blokland et al. 2006; Rutten et al. 2007b), the possible involvement of these pathways in serotonin-mediated alteration in cognitive functions is yet to be elucidated. In this regard, it is reported that PDE-5 inhibition, which reduce cGMP degradation, mitigates the impairment of objective memory due to acute tryptophan depletion in male Wistar rats (van Donkelaar et al. 2008).

## Conclusion

The effects of serotonin on memory depend on the activation of pre/post-synaptic serotonergic receptors located on distinct subsets of neurons. To add to the complexity, in different experimental settings, activation of these receptors leads to the effects, which are not always consistent. Many of these effects are produced through the modification of cholinergic, dopaminergic, GABAergic or glutamatergic transmission. As discussed here, the activation state of serotonin receptors can affect memory deficits due to muscarinic/glutamatergic blockade or lesions. Moreover, serotonin receptor ligands influence emotional/fearful learning and memory. Interestingly, 5-HT<sub>3</sub>R antagonists as well as 5-HT<sub>4</sub>R agonists have been demonstrated to decrease amyloidogenesis and appear promising in the treatment for Alzheimer's disease.

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