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REVIEW ARTICLE

Effects of serotonin in the hippocampus: how SSRIs and multimodal antidepressants might regulate pyramidal cell function

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The hippocampus plays an important role in emotional and cognitive processing, and both of these domains are affected in patients with major depressive disorder (MDD). Extensive preclinical research and the notion that modulation of serotonin (5-HT) neurotransmission plays a key role in the therapeutic efficacy of selective serotonin reuptake inhibitors (SSRIs) support the view that 5-HT is important for hippocampal function in normal and disease-like conditions. The hippocampus is densely innervated by serotonergic fibers, and the majority of 5-HT receptor subtypes are expressed there. Furthermore, hippocampal cells often co-express multiple 5-HT receptor subtypes that can have either complementary or opposing effects on cell function, adding to the complexity of 5-HT neurotransmission. Here we review the current knowledge of how 5-HT, through its various receptor subtypes, modulates hippocampal output and the activity of hippocampal pyramidal cells in rodents. In addition, we discuss the relevance of 5-HT modulation for cognitive processing in rodents and possible clinical implications of these results in patients with MDD. Finally, we review the data on how SSRIs and vortioxetine, an antidepressant with multimodal activity, affect hippocampal function, including cognitive processing, from both a preclinical and clinical perspective.

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Key words: Hippocampus, pyramidal cell, serotonin, SSRI, vortioxetine.

Clinical Implications

- The hippocampus is involved in the regulation of emotional and cognitive processing, both of which are compromised in patients with major depressive disorder (MDD).
- Serotonin (5-HT) plays an important role in hippocampal function.
- Multiple 5-HT receptors are often co-expressed on the same cell types in the hippocampus with functions that can either be complementary or opposing. Overall, 5-HT appears to inhibit pyramidal cells in the hippocampal circuit in rodents.
- While selective serotonin reuptake inhibitors (SSRIs) have the potential to normalize hippocampal output under stress conditions and to treat mood symptoms in MDD, their effects on cognitive function are less clear.
- The multimodal antidepressant vortioxetine has shown clinical efficacy on mood as well as cognitive symptoms in patients with MDD. 5-HT_3 receptor inhibition of GABAergic interneurons is thought to play an important role in mediating these effects.

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Introduction

There is extensive evidence that depression and other stress-related conditions are associated with hippocampal dysfunction.[1,2] In several magnetic resonance studies, patients with major depressive disorder (MDD) have reduced hippocampal volumes compared with matched control subjects.[3–5] Furthermore, Sheline *et al*[6]

have shown that there is an inverse correlation between hippocampal volume and the duration of untreated depression. A meta-analysis of 12 clinical studies indicated that the number of depressive episodes may be correlated with a reduction of hippocampal volume in the right hemisphere.[7] Reduced hippocampal volume in MDD patients has also been associated with impaired memory (eg, MacQueen *et al*[8]). Memory function related to hippocampal integrity decreases with increasing numbers of depressive episodes.[9] In addition, functional magnetic resonance imaging (fMRI) studies of depressed patients have consistently shown overactivity in the frontolimbic circuitry, including the dorsolateral prefrontal cortex and hippocampus during working memory performance.[10,11]

In addition to disturbances in mood and emotional processing, MDD is associated with deficits in several cognitive domains, including executive function, processing speed, and attention, as well as learning and memory.[12–14] There is evidence that cognitive impairment varies independently of mood state and does not necessarily resolve when the patient is considered to be in clinical remission.[15] This may imply that cognitive control and the regulation of emotion have distinct neuronal bases in depression.[16] While the literature suggests that antidepressants may potentially treat cognitive dysfunction in some patients with MDD, these studies were not designed to distinguish between the direct effects on cognitive domains versus indirect effects on cognition via improvements in mood. Overall, small sample sizes, methodological constraints, and the absence of replication make it difficult to draw firm conclusions from the majority of these studies.[17,18]

Since the selective serotonin (5-HT) reuptake inhibitors (SSRIs) and serotonin norepinephrine (NE) reuptake inhibitors (SNRIs) are the predominant pharmacotherapies used for the treatment of MDD, modulation of serotonergic neurotransmission is assumed to play a pivotal role in achieving their antidepressant efficacy. Many 5-HT receptor subtypes are extensively expressed in the hippocampus. However, even though a large number of preclinical studies in rodents are strongly supportive of antidepressant treatments restoring hippocampal function, their mechanisms of action have not been fully elucidated. Furthermore, it is not well understood how the clinical efficacy of currently used antidepressants might be related to changes in hippocampal function in patients with MDD.[19] Therefore, a thorough understanding of how 5-HT receptor modulation affects hippocampal functions is essential to the understanding of how antidepressants might work. Here we review the current knowledge of how 5-HT, through its various receptor subtypes, might modulate hippocampal activity in rodents. In addition, we discuss its relevance for cognitive processing and the possible clinical implications for patients with MDD. Finally, we review available data on how SSRIs and vortioxetine, an antidepressant that, in addition to inhibition of 5-HT reuptake, also modulates a number of 5-HT receptor subtypes, affect hippocampus function from a preclinical and clinical perspective.

Anatomy of the Hippocampus

To understand how 5-HT modulates hippocampal function at a molecular level, it is necessary to gain insights into how 5-HT modulates the different cell types and subregions that comprise the hippocampal microcircuits. Along the longitudinal axis, the hippocampus is segregated into dorsal, intermediate, and ventral regions in rodents (reviewed in Fanselow and Dong[20] and Moser and Moser[21]), and analogous posterior and anterior regions in primates and humans[22] that project to distinct brain areas.[23] Lesion and electrophysiology studies in rodents have shown that the dorsal hippocampus is primarily involved in the cognitive functions, including spatial learning and memory,[24,25] whereas the ventral hippocampus is primarily involved in regulating stress, emotion, and anxiety.[26–28] However, this division of functions is somewhat ambiguous, since parts of the ventral hippocampus have been also shown to be involved in memory tasks.[29]

The hippocampus is subdivided into several distinct zones: the dentate gyrus (DG), CA3, CA2, CA1, and the subiculum regions that were first described by Ramon y Cajal in 1911[30] and Lorente de Nó in 1934 [31] (Figure 1). The CA3, CA2, and CA1 regions are sometimes called the hippocampal gyrus or Ammon's horn. Granule cells in the DG receive projections from the surrounding entorhinal cortex and send their axons, called mossy fibers, to the CA3 area. Pyramidal cells in the CA3 area project axons, known as Schaffer collaterals, to the CA2 and CA1 areas. Pyramidal cells in the CA1 area send their axons to the surrounding deep cortical layers of the entorhinal cortex and to the subiculum which is the final processing stage of the hippocampal microcircuitry (Figure 1). In addition to this main "trisynaptic circuit," there are direct connections from the superficial layers of the entorhinal cortex to the CA3 and CA1 areas, and synaptic connections from inhibitory gamma-butyric acid (GABA)ergic interneurons to excitatory glutamatergic pyramidal and granule cells within the hippocampus.[32]

There are 2 types of principal cells in the hippocampal circuit: glutamatergic pyramidal cells in the Ammon's horn and subiculum regions, and glutamatergic granule cells in the DG (Figure 1). They generally have excitatory effects on the neurons to which they send axon terminals including other glutamatergic and GABAergic, as well

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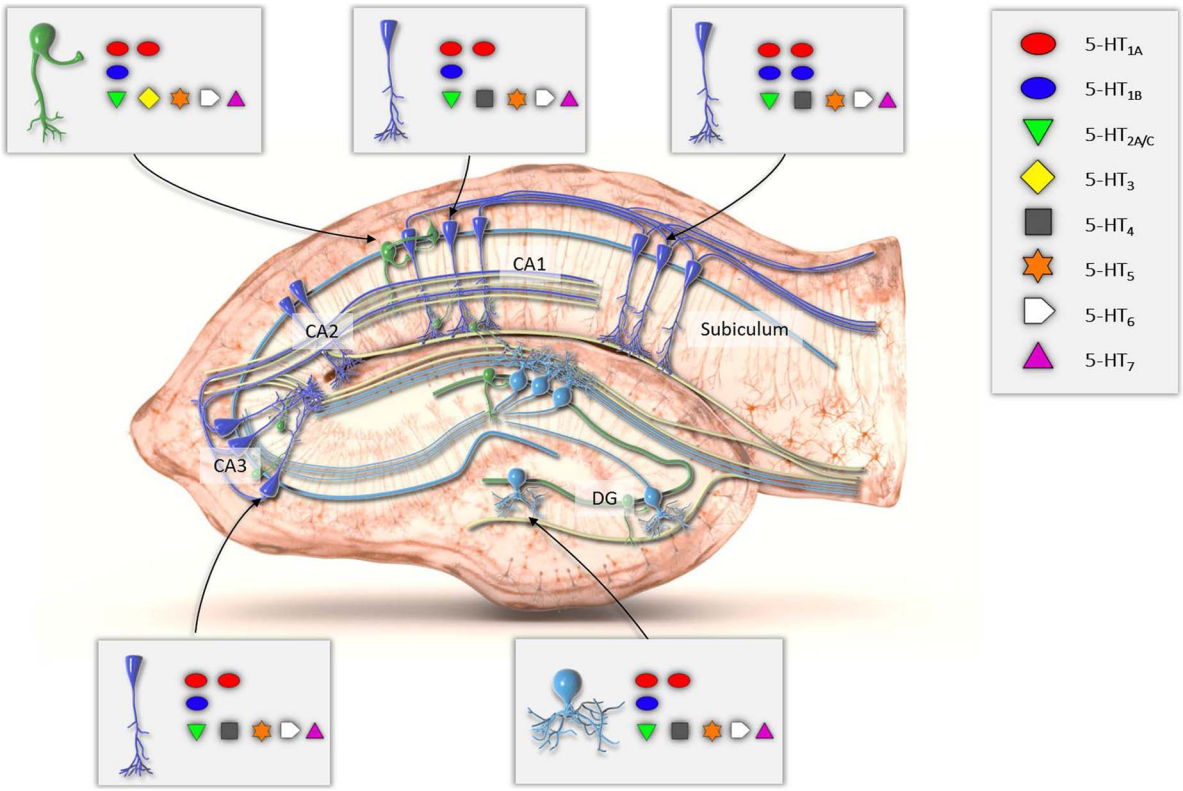

FIGURE 1. Schematic illustration of the rat hippocampal circuit with 5-HT receptor localization. The main areas of the hippocampus, including the dentate gyrus (DG), CA3, CA2, CA1, and the subiculum regions, and synaptic connections between them are indicated. Principal (granule and pyramidal) cells are shown in blue, and interneurons are shown in green. Expression of 5-HT receptor subtypes on hippocampal CA1 and CA3 pyramidal cells, granule cells, and interneurons are shown. References for 5-HT receptor localization are listed Table 1. At least 16 subtypes of interneurons have been identified in the hippocampus; one representative interneuron is shown for illustrative purposes. Note that the 5-HT_{1A} heteroreceptor is expressed at high levels throughout the hippocampus. The 5-HT_{1B} receptor is found at highest levels in the subiculum. Based on histology data, the 5-HT_{3} receptor is only expressed on the interneurons, and the 5-HT_{4} receptor is only expressed on pyramidal cells. Other 5-HT receptors subtypes are found on both principal cells and interneurons.

monoaminergic [5-HT, norepinephrine (NE), dopamine (DA)], cholinergic, and histaminergic (HA) cells. There are also 3 major populations of GABAergic inhibitory interneurons that can be identified by the expression of the calcium-binding proteins parvalbumin, calbindin, and calretinin. These interneurons can be further subdivided based on their morphology and presence of receptors for neuropeptides and other neurotransmitters. In total at least 16 different subtypes of interneurons have been identified in the hippocampus with different firing properties and functions.[33,34] Each of these interneuron subpopulations has a distinct placement within the network, as well as a distinct role in modulating the behavior of pyramidal neurons.

Parvalbumin-immunoreactive interneurons are present within the pyramidal cell body layer (divided into stratum oriens and pyramidale), and synapse onto the soma and/or axons of pyramidal neurons.[35] In contrast, calbindin immunoreactive interneurons are present in the dendritic layers of the hippocampus (divided into stratum radiatum and moleculare)[36] and are thought to synapse onto pyramidal neuron dendrites.[37] Finally, calretinin immunoreactive interneurons frequently form local synaptic connections onto other interneurons.[38] Thus, hippocampal interneurons can modulate the activity of both pyramidal cells and other interneurons.[38]

The processing of information within the hippocampus is complex and is influenced by multiple neurotransmitters and neuromodulators, including glutamate, GABA, DA, NE, HA, acetylcholine (ACh), and 5-HT. Serotonergic receptors are found on both excitatory cells and inhibitory interneurons. As will be discussed in the following sections, 5-HT neurotransmission can have a direct effect on pyramidal neuron firing by modulating its membrane potential and indirect effects via modulating GABA neurotransmission.

5-HT Receptors in the Rodent Hippocampus

Nearly all of the identified 5-HT receptor subtypes are expressed in the hippocampal circuit in rodents.[39] Interestingly, 5-HT fibers often lack direct synaptic

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contacts, and in many cases 5-HT receptors have been detected on neurons that do not receive serotonergic innervation.[40–42] This suggests that in the hippocampus, as in other brain areas, 5-HT is released diffusely by volume transmission and acts more as a neuromodulator whose function might be to maintain homeostasis in the brain.

The specificity and diversity of 5-HT signaling arises from at least 14 different receptor subtypes grouped in 7 receptor families with distinct characteristics and expression patterns (Table 1, Figures 1 and 2). The 5-HT_1 receptor family is inhibitory; it is coupled to G-protein-coupled inwardly rectifying potassium (GIRK) channels and $G_{i/o}$ proteins. Activation of GIRK channels exerts hyperpolarizing effects on cell function. Activation of $G_{i/o}$ proteins inhibits adenylyl cyclase and decreases cyclic adenosine monophosphate (cAMP) concentration. The 5-HT_2 receptor family is stimulatory and signals via activation of G_q proteins that are coupled to phospholipase C. Phospholipase C hydrolyses membrane phosphoinositides into inositol triphosphate (IP3) and diacylglycerol (DAG), which elevate intracellular calcium. One of the downstream targets of 5-HT_2 receptors are potassium leak channels. Activation of 5-HT_2 receptors closes these channels, resulting in cell depolarization. The 5-HT_3 receptor family is stimulatory and the only non-G-protein coupled receptor. Activation of 5-HT_3 receptors opens a non-selective Na^+/K^+ ion channel that depolarizes neurons and increases neurotransmitter release. The 5-HT_4, 5-HT_6, and 5-HT_7 receptors are stimulatory and increase neuronal excitability. They are coupled to G_s protein and signal via activation of adenylyl cyclase and elevation in cAMP levels. Finally, 5-HT_5 receptors are inhibitory, and, as for the 5-HT_1 receptor family members, are coupled to $G_{i/o}$ proteins that suppress adenylyl cyclase and decrease cAMP levels.[43,44] In the hippocampus, cells often co-express several types of 5-HT receptors that can have either complementary or opposing effects on cell function (Figure 1 and Table 1). Moreover, 5-HT receptors can form homodimers or heterodimers with other G-protein coupled receptors, which adds further complexity to 5-HT signaling.[45] For example, heterodimers of 5-HT_{1A}-5HT_7 receptors and 5-HT_{2A}-mGlu2 (metabotropic glutamate 2) receptors have been shown to have characteristics that differ from their individual counterparts.[45–47] Below we describe the expression patterns of 5-HT receptors and discuss their effects on hippocampal circuitry and hippocampus-mediated behavioral responses based on published results and our data in rodents. We chose to only include behavioral models of memory and learning, since these models have the best link to hippocampal function.[48–50]

5-HT_{1A} receptors

Among all 5-HT receptor subtypes, 5-HT_{1A} receptors have the highest affinity for 5-HT (Table 1). In the hippocampus, they are found on non-serotonergic cells as heteroreceptors and inhibit cellular activity via activating GIRK channels.[51] They are defined as heteroreceptors because they control release of neurotransmitters other than 5-HT. 5-HT_{1A} receptors are moderately to highly expressed throughout the hippocampus[52] (Figure 2A). They have been detected on both glutamatergic principal cells and at least two subtypes of GABAergic interneurons (Table 1).

Activation of 5-HT_{1A} receptors primarily leads to inhibition of hippocampal pyramidal cells.[53–59] Interestingly, in the prefrontal cortex, 5-HT_{1A} receptor agonists produce both excitatory and inhibitory effects on cortical

TABLE 1. 5-HT receptor subtypes in the rodent hippocampus

Receptor	Structure	Affinity for 5-HT (Ki/Kd, nM)*	Function	Expression	Cell type	Ref.
5-HT_{1A}	GPCR	0.20–0.79	**I** ↓cAMP, ↑GIRK	++/+++	Pyr, Gran, Calbin-(+) IN, PV-(+) IN	37,52
5-HT_{1B}	GPCR	4.0–32	**I** ↓cAMP, ↑GIRK	+/+++	Pyr, Gran	63,65,155
5-HT_{1D}	GPCR	2.5–6.3	**I** ↓cAMP, ↑GIRK	–/+	?	64,66
5-HT_{2A}	GPCR	1.3	**S** ↑PLC	+/+++	Pyr, Gran, Calbin-(+) IN, Calre-(+) IN, PV-(+) IN	71,72
5-HT_{2C}	GPCR	2.5–160	**S** ↑PLC	?	?	163
5-HT_3	Ligand-gated ion channel	130–320	**S** ↑ Ion conductance (K^+, Na^+)	+/++ Stronger in ventral/caudal hippocampus	CCK-(+) IN, Calbin-(+) IN, Calre-(+) IN	76,77,79
5-HT_4	GPCR	1.6–4.0	**S** ↑cAMP	+/++	Pyr	89–91
5-HT_5	GPCR	130–200**	**I** ↓cAMP	+/++	Pyr, Gran, IN	95
5-HT_6	GPCR	13	**S** ↑cAMP	++/+++	Pyr, Calbin-(+) IN, Calre-(+) IN	97,98
5-HT_7	GPCR	1.0–7.9	**S** ↑cAMP	+/+++	Pyr, IN?	104

* Affinities for 5-HT were calculated from pKi/pKd data obtained from the IUPHAR data base. For further details and references see http://www.iuphar-db.org.

** 5-HT_{5a}. Expression strength is indicated by –: absent, +: low, ++: moderate, +++: strong, ?: unknown.

Abbreviations used: GPCR: G-protein-coupled receptor; I: inhibitory; S: stimulatory; ↑: increase; ↓: decrease; Pyr: pyramidal; Gran: granule; IN: interneuron; PV: parvalbumin; CCK: cholecystokinin; Calbin: calbindin; Calre: calretinin.

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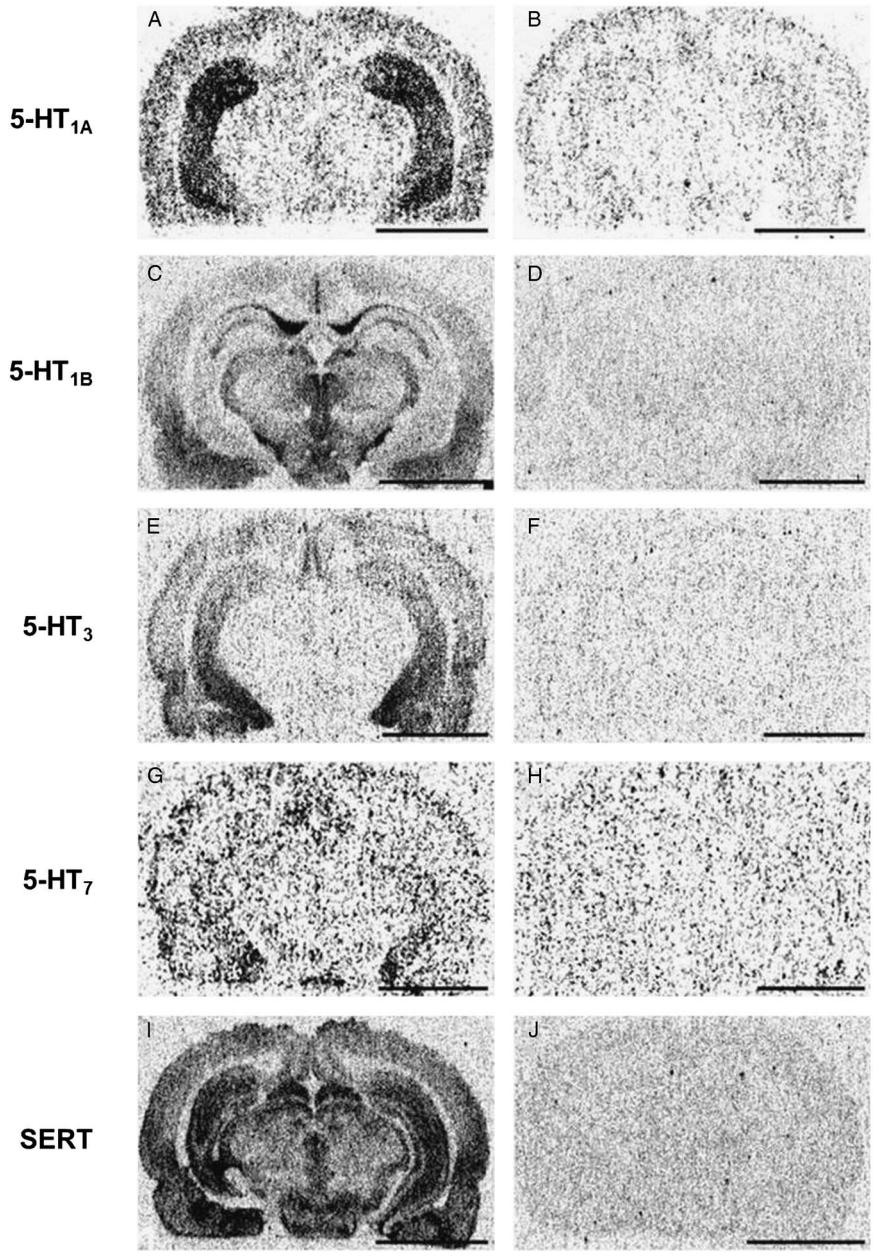

FIGURE 2. Expression of several classes of 5-HT receptors and the 5-HT reuptake transporter (SERT) by ex vivo autoradiography in the rat hippocampus. Autoradiographic images representing total (*left panels*) and non-specific binding (*right panels*) for each of 5 separate serotonergic targets in coronal brain sections (20 μm in thickness). 5-HT_{1A} receptors were mapped using 3 nM [^{3}H]8-OH-DPAT (A) alone or (B) in combination with 1 μM of the 5-HT_{1A} receptor selective antagonist WAY100635 to determine the level of nonspecific binding. 5-$HT_{1B/1D}$ receptors were mapped using 1 nM [^{3}H] GR125743 (C) alone or (D) in combination with 1 μM of the 5-HT_{1B} receptor preferring SB216641 to determine the level of nonspecific binding. 5-HT_3 receptors were mapped using 3 nM [^{3}H] LY278584 (E) alone or (F) in combination with 1 μM ondansetron to determine the level of nonspecific binding. 5-HT_7 receptors were mapped using 4.5 nM [^{3}H] SB269970 (G) alone or (H) in combination with 1 μM of unlabeled SB269970 to determine the level of nonspecific binding. Finally, SERT was mapped using 4.5 nM [^{3}H] escitalopram (I) alone or (J) in combination with 1 μM paroxetine to determine the level of nonspecific binding. Scale bars represent 5 mm.

pyramidal cells.[60] This might be ascribed to a difference in the distribution of 5-HT_{1A} receptors on interneurons versus pyramidal cells in these 2 brain regions.

The function of 5-HT_{1A} receptors has been extensively studied in multiple behavioral studies, 16 of which are listed in Table 2. Modulation of 5-HT_{1A} receptor activity in animal models of memory and learning has produced inconsistent results that range from impairment to improvement (Table 2). Some of these inconsistencies might be due to differences in experimental design

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TABLE 2. Effects of serotonergic manipulations on hippocampal dependent memory tests in rodents

Mechanism	Species	**Spatial memory tasks** (Morris water maze (MWM), Radial arm maze (RAM), Barnes maze (BM), Object placement/preference (OP))	**Associative/Affective memory tasks** (Contextual fear conditioning (CFC), Pattern separation (PS))	**Working memory tasks** (Spontaneous alternation (SA), Forced alternation (FA), Delayed alternation (DA))
↑5-HT tone				
Increase tryptophan or other 5-HT precursor	Rat	↑[164,165] or ÷ [165] MWM; ↑ [122] or ↓ [166] RAM	↓ CFC [167]	
5-HTT KO	Mouse or Rat	↓ MWM [168]; ÷ BM [168]	↑ [169] or ÷ [170] CFC	
SSRIs				
Fluoxetine, paroxetine, citalopram, escitalopram	Mouse or Rat	↓ [171–173] or ÷ [174–176] MWM; ↑ BM [177]; ÷ RAM [178,179]; ↓ OP [171,172]	↓ or ÷ CFC [167] when administrated before the testing session; ↑ CFC [180] when administrated before training	↓ FA [181]; ÷ pCPA deficit in SA [182]
Multimodal				
Vortioxetine	Rat		↑ CFC [183]	Ø pCPA deficit in SA [182,184]
↓5-HT tone				
5,7-DHT	Rat	÷ [185–190] or ↓ [191,192] MWM; ÷ RAM [186–190]		÷ [185,188] or ↓ [187] FA; ÷ SA [186]; ↓ DA [185]
pCPA	Rat	÷ MWM [193]; ÷ RAM [194]		↓ SA[182]
Tryptophan depletion	Mouse or Rat	÷ MWM [195,196]	↓ CFC [196]	
Conditional KO Lmx1b transcription factor lack all central 5-HT neurons	Mouse	↓ MWM [197]	↑ CFC [197]	
5-HT$_{1A}$ receptors				
5-HT$_{1A}$ Over-expression	Mouse	↓ [198] or ÷ [199] MWM		
5-HT$_{1A}$ KO	Mouse	↓ in young mice; ÷ in old mice in MWM [200]	↑ CFC [201]; ↓ PS [201]	
5-HT$_{1A}$ receptor agonists				
8-OH-DPAT (also activates 5-HT$_7$ receptors); S15535; flesinoxan	Mouse or Rat	↑ [61]; ÷ [202] or ↓ [61] MWM; ↓ [203-206] or ÷ [207] RAM	↓ CFC [208,209]	Ø pCPA deficit in SA [184]
5-HT$_{1A}$ receptor antagonists				
WAY100635, WAY100135, WAY101405, NAN-190, NAD-299	Mouse or Rat	↑ MWM [210]; ÷ RAM [204]	↑ [209] or ÷ [167] CFC	
5-HT$_{1B}$ receptors				
5-HT$_{1B}$ over-expression (in dorsal raphe nucleus)	Rat		↓ CFC [211]	
5-HT$_{1B}$ KO	Mouse	↑ MWM [212,213]	÷ CFC [213]	÷ SA [213]
5-HT$_{1B}$ receptor agonists				
CP93129, Anpirtoline	Rat	↓ MWM [214]; ↓ RAM [207]	↓ CFC [211]	
5-HT$_{1B}$ receptor antagonists				
GR127935 (5-HT$_{1B/1D}$), NAS-181	Rat	÷ MWM [214]	÷ CFC [167]	
5-HT$_2$ receptor agonists				
DOI, mCPP	Rat	↑ MWM [215]; ↓ RAM, [166]		
5-HT$_2$ receptor antagonists				
Ritanserin, ketanserin, ICI169369	Rat	↑ [216] or ↓ [215] MWM; ÷ RAM [217]	÷ CFC [167]	
5-HT$_{2A}$ receptor				
5-HT$_{2A}$ antisense	Rat	↑ MWM [218]		
5-HT$_{2A}$ KO	Mouse		÷ CFC [208]	
5-HT$_{2A}$ receptor agonist				
TCB-2	Mouse		↑ CFC [219] (both consolidation and extinction)	
5-HT$_{2A}$ receptor antagonist				
MDL 11,939	Mouse		↓ CFC [219] (extinction)	
5-HT$_{2C}$ receptor				
5-HT$_{2C}$ null mutant	Mouse	↓ MWM [220]	↓ CFC [220]; ÷ PS [220]	
5-HT$_{2C}$ receptor antagonist				
SB242084	Rat		÷ CFC [221]	
5-HT$_3$ receptor				
5-HT$_3$ over expression	Mouse		↑ CFC [224]	
5-HT$_{3A}$ KO	Mouse		÷ CFC [208]	

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TABLE 2: Continued

Mechanism	Species	Spatial memory tasks (Morris water maze (MWM), Radial arm maze (RAM), Barnes maze (BM), Object placement/preference (OP))	Associative/Affective memory tasks (Contextual fear conditioning (CFC), Pattern separation (PS))	Working memory tasks (Spontaneous alternation (SA), Forced alternation (FA), Delayed alternation (DA))
5-HT$_3$ receptor antagonists				
WAY 100289, granisetron, tropisetron, ondansetron, DAU6215	Mouse or Rat	↓ [216] or ÷ [222,223] MWM; ↑ RAM [88]	↓ [167,208,224] or ÷[221] in CFC	÷ pCPA deficit in SA [184]
5-HT$_4$ receptor				
5-HT$_4$ KO	Mouse	÷ MWM [225]		
5-HT$_4$ receptor agonist				
prucalopride, RS 67333	Rat	÷ MWM [226]		↑ FA[227]
5-HT$_4$ receptor antagonist				
RS 67532	Rat	÷ MWM [228]		
5-HT$_6$ receptor				
Antisense oligonucleotide	Rat	↑ MWM [229]		
5-HT$_6$ receptor antagonists				
SB271046, SB357134, Ro046790	Mouse or Rat	↑ [229-231], ÷ or ↓ [232] MWM		
5-HT$_7$ receptor				
KO	Mouse	÷ BM [233]; ↓ OP [233]	↓ CFC [233]	
5-HT$_7$ receptor antagonists				
SB656104A, SB269970	Mouse or Rat	↑ RAM [233,234] ↓ OP[233]		

÷: no effect; ↑: increase/improve; ↓: decrease/impair; Ø: prevented/reduced deficits. *Abbreviations used:* MWM: Morris Water Maze; RAM: Radial Arm Maze; BM: Barnes Maze; OP: Object Placement (Preference); CFC: Contextual Fear Conditioning; PS: Pattern Separation; SA: Spontaneous Alternation; FA: Forced Alternation; DA: Delayed Alternation.

across studies. Multiple factors, such as drug dose, length of treatment (acute vs chronic), whether the drug was administered before or after the training period, and also the age and stain of animals, could all influence the behavioral outcome. However, in some studies (eg, Haider *et al*[61]), opposing results were obtained with different doses of the same compound under the same experimental conditions. This suggests that the variability in results might be partially due to the complex effects of 5-HT$_{1A}$ receptors expressed on different cell types. For instance, 5-HT$_{1A}$ receptors can inhibit both principal (glutamatergic) neurons and GABAergic interneurons. Inhibition of GABAergic interneurons would disinhibit principal cells and thus counteract the direct effects of 5-HT$_{1A}$ receptors expressed on principal neurons. Therefore, selectively targeting 5-HT$_{1A}$ receptors may not be an optimal strategy for modulating hippocampal function, unless these receptors could be targeted in a regional or cell-specific manner.[62]

5-HT$_{1B}$ and 5-HT$_{1D}$ receptors

5-HT$_{1B}$ heteroreceptors are found throughout the hippocampus at levels ranging from low to very high.[63–65] They are expressed on axonal terminals and dendrites of principal cells, which include pyramidal cells in Ammon's horn and granule cells in the DG (Table 1). The highest expression is found in the dorsal subiculum, which might originate from axonal terminals of CA1 pyramidal cells that project to that region (Figure 2C).[65] Interestingly, in our experiments, the subiculum had the strongest signal for 5-HT$_{1B}$ receptor expression in the rodent forebrain.

Much less is known about the 5-HT$_{1D}$ receptor. 5-HT$_{1D}$ receptors are generally thought to be expressed at much lower levels than 5-HT$_{1B}$ receptors in the rodent brain.[64,66] 5-HT$_{1D}$ and 5-HT$_{1B}$ receptors are often expressed in the same brain regions.[64] However, no 5-HT$_{1D}$ receptor-specific binding has been detected in the dorsal subiculum, where 5-HT$_{1B}$ receptor-specific binding is very strong.[66] Interestingly, Xie *et al*[67] suggest that when 5-HT$_{1B}$ and 5-HT$_{1D}$ receptors are co-expressed, they might exist in a heterodimerized state. Thus, it can be questioned if the effects of 5-HT$_{1B}$ and 5-HT$_{1D}$ receptors should be considered separately.

Activation of 5-HT$_{1B}$ receptors attenuates glutamate transmission in the subiculum and CA1 regions of the hippocampus.[68,69] The effect of 5-HT$_{1B}$ receptor modulation in behavioral models of memory and learning has been far less studied than that for 5-HT$_{1A}$ receptors (Table 2). In general, several studies suggest that 5-HT$_{1B}$ receptor stimulation may negatively affect performance in hippocampal-dependent memory tests. Antagonism of 5-HT$_{1B}$ receptors, in spite of its associated increase in extracellular ACh levels in the dorsal hippocampus,[70] does not seem be effective in these models (Table 2).

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5-HT$_{2A}$ and 5-HT$_{2C}$ receptors

5-HT$_{2A}$ receptors are broadly present within the hippocampus, but little is known about the expression of 5-HT$_{2C}$ receptors.[71,72] 5-HT$_{2A}$ receptors are expressed on both principal glutamatergic cells (on their somatic and dendritic regions) and on all known subtypes of hippocampal interneurons (Table 1). There is also some evidence suggesting that 5-HT$_{2A}$ receptors are expressed on mossy fibers in the CA3 region.[71,73] Thus, since 5-HT$_{2A}$ receptors are stimulatory and are expressed on both principal cells and GABAergic interneurons, it would be expected that they would have mixed effects on the firing of principal cells. However, data from 2 electrophysiological studies in brain slices suggest that the effects that 5-HT$_2$ receptors have on interneurons might overwhelm their direct excitatory effects on principal cells.[74,75] Further research is needed to confirm these observations and clarify which of the 2 effects of 5-HT$_2$ receptors (indirect inhibition or direct excitation of principal neurons) prevails in physiological conditions.

Studies of selective 5-HT$_2$ receptor ligands in behavioral models show variable effects (Table 2), possibly reflecting differences in experimental design across studies and the fact that 5-HT$_2$ receptors are expressed on multiple cell types in the hippocampus (Table 1). Little is known about the effects of 5-HT$_{2C}$ receptor modulation due to a lack of selective compounds. Thus, as with the 5-HT$_{1A}$ receptor, selective targeting of 5-HT$_2$ receptors may not be an optimal strategy for modulating hippocampal function due to their varying functions in this brain region.

5-HT$_3$ receptors

5-HT$_3$ receptors are also found throughout the hippocampus.[76,77] Autoradiographic data from our laboratory suggest that 5-HT$_3$ receptors have a distinct expression gradient within the hippocampus, with the highest expression observed in the caudal and ventral portions (Figure 2E). Interestingly, histological evidence in the rodent forebrain suggests that 5-HT$_3$ receptors are almost exclusively expressed on GABAergic interneurons.[78,79] 5-HT$_3$ receptor-expressing interneurons are generally immunopositive for cholecystokinin, and for the calcium binding proteins calretinin and calbindin.[79]

Based on this histological evidence, it can be hypothesized that 5-HT$_3$ receptors provide a fast excitatory drive onto hippocampal GABAergic interneurons and inhibit hippocampal principal cells. Consistent with this hypothesis, pharmacological activation of 5-HT$_3$ receptors depolarizes hippocampal interneurons[80,81] and increases inhibitory drive onto CA1 pyramidal cells.[82–85] Conversely, 5-HT$_3$ receptor antagonists inhibit hippocampal interneurons, increase the firing rate of pyramidal cells, and enhance long-term potentiation (LTP) in *in vivo* electrophysiology recordings in rats.[86–88] Taken together, these mechanistic findings might point to a pro-cognitive effect of 5-HT$_3$ receptor antagonism. However, behavioral studies of selective 5-HT$_3$ receptor antagonists in models of memory and learning have again shown inconsistent results (Table 2).

5-HT$_4$ receptors

Autoradiographic studies have demonstrated the presence of 5-HT$_4$ receptors throughout the hippocampus.[89,90] In general, protein expression is low-to-moderate, with the highest levels found in the stratum oriens and pyramidale of Ammon's horn, subiculum, and the molecular layer of the DG (Table 1). 5-HT$_4$ receptor mRNA has been detected in hippocampal pyramidal cells.[91] Interestingly, 5-HT$_4$ receptor mRNA was not found in cells expressing glutamic acid decarboxylase 65 (GAD65), which is thought to be a selective marker of GABAergic neurons.[91] Thus, it appears that 5-HT$_4$ receptors preferentially act to stimulate pyramidal neurons, without directly modulating GABA neurotransmission. In support of this hypothesis, 2 electrophysiology studies have shown that stimulation of 5-HT$_4$ receptors increases the excitability of CA1 pyramidal cells.[92,93]

5-HT$_4$ receptors have been shown to modulate the cholinergic system. In microdialysis recordings, application of the 5-HT$_4$ receptor agonist SC53116 causes a release of ACh, and this effect is blocked by the 5-HT$_4$ receptor antagonist GR113808.[94] Thus in theory, 5-HT$_4$ receptor agonists should be pro-cognitive. This hypothesis has been investigated in preclinical models, but the results to date have been disappointing (Table 2).

5-HT$_5$ receptors

Immunohistochemical expression studies have shown that 5-HT$_5$ receptors are present in some portions of the hippocampus. For example, Oliver *et al*[95] observed moderate immunoreactivity levels in CA1, CA2, and CA3 regions and weak immunoreactivity levels in the DG. This study also reported that 5-HT$_5$ receptors were present on pyramidal and granule principal cells and on interneurons in the DG.[95] Due to the lack of selective compounds, no mechanistic and behavioral studies targeting 5-HT$_5$ receptors have been performed in rodents.

5-HT$_6$ receptors

Histochemical studies suggest that 5-HT$_6$ receptors are expressed at moderate-to-high levels in all subfields of the rodent hippocampus.[96,97] The expression is particularly strong in the molecular layer of the DG and in the stratum oriens and stratum radiatum of CA1,

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where 5-HT$_6$ receptors are thought to be expressed on dendritic processes of pyramidal cells.[97] Moderate levels of 5-HT$_6$ receptor immunoreactivity have been observed in CA2 and CA3 regions. There has been also one report showing the expression of 5-HT$_6$ receptors on a subset of calretinin- and calbindin-positive hippocampal interneurons.[98]

Pharmacological stimulation of 5-HT$_6$ receptors by the 5-HT$_6$ receptor agonist WAY-181187 increases GABA transmission and attenuates LTP in the CA1 area of the hippocampus.[99] Both of these effects were blocked by the selective 5-HT$_6$ receptor antagonists SB-399885.[99] Furthermore, systemic administration of WAY-181187 increases GABA levels in several brain regions, including the dorsal hippocampus.[100] Consistent with its enhancing effect on GABA transmission, antagonism of 5-HT$_6$ receptors increases extracellular glutamate levels in the frontal cortex and dorsal hippocampus.[101] However, although the potentiating effects of 5-HT$_6$ receptors on GABA transmission have been well documented, it is not clear whether these responses are due to direct effects of 5-HT$_6$ receptors on GABAergic interneurons.[102]

Several 5-HT$_6$ receptor antagonists are currently in clinical development for the treatment of Alzheimer's disease.[103] However, in rodent hippocampus-dependent behavioral models, the effects of 5-HT$_6$ receptor antagonists have been only investigated in a small number of studies with variable results (Table 2).

5-HT$_7$ receptors

Immunohistochemical data suggest that 5-HT$_7$ receptors are expressed throughout Ammon's horn, especially on the soma and dendrites of pyramidal neurons.[104] There is also weak 5-HT$_7$ receptor expression in the DG.[104] It is important to note that in the rodent brain expression of 5-HT$_7$ receptors changes during development. It is the highest during the first 2 post-natal weeks and progressively decreases with age.[105–107] Our autoradiographic data using the selective 5-HT$_7$ receptor antagonist [^{3}H] SB269970 did not show strong binding in the hippocampal sections taken from adult rats (Figure 2G). This result raises questions regarding the level of expression of 5-HT$_7$ receptors in the adult rodent hippocampus.

5-HT$_7$ receptor stimulation increases the firing of pyramidal neurons and glutamatergic transmission in hippocampal brain slices.[108–111] Stimulation of 5-HT$_7$ receptors also enhances inhibitory transmission in the hippocampus.[112] This suggests that 5-HT$_7$ receptors might be expressed on GABAergic interneurons; however, there are no histological data available to support this notion. In behavioral studies, both 5-HT$_7$ agonists and antagonists have shown both memory-enhancing and memory-impairing properties depending on the animal model and test conditions (such as 5-HT tone) (Table 2).[113,114] Thus, additional research is needed to determine the role of 5-HT$_7$ receptors on cognition and memory function.

Effect of 5-HT and SSRIs on CA1 Pyramidal Cells and Hippocampal Function

Given that most 5-HT receptors are expressed on both excitatory cells and inhibitory interneurons and can function in either a stimulatory or inhibitory manner depending on the receptor subtype, it would be expected that the net effect of 5-HT on hippocampal function depends on local 5-HT concentration, the ratio of different 5-HT receptor subtypes expressed, and the density of 5-HT receptors in a particular population of cells. In general, 5-HT inhibits CA1 pyramidal cells and thereby decreases hippocampal output in rodents (reviewed by Ciranna[108]). Stimulation of the serotonergic projection from the dorsal raphe nucleus to the hippocampus decreases the firing rate of CA1 pyramidal cells in anesthetized animals.[55,115–118] In a similar manner, application of 5-HT to hippocampal brain slices inhibits the function of pyramidal neurons by hyperpolarizing their membrane potential and increasing local GABA transmission.[53,74,83–85] There have also been reports of excitatory effects of 5-HT on pyramidal cell function, but the magnitude of excitation was much smaller than the 5-HT-induced inhibition.[53,119] However, one has to be careful in interpreting the *ex vivo* results obtained in brain slices; in most of these studies, 5-HT was exogenously applied at moderately high concentrations (15–50 micromolar), which might be higher than physiologically relevant concentrations of 5-HT in the brain. Therefore, these studies might exaggerate a contribution of certain subtypes of 5-HT receptors to its overall response. In summary, it seems that the overall effect of 5-HT on the hippocampal circuit in rodents is to inhibit pyramidal cell output. However, a majority of the studies that have led to this conclusion were either done in anesthetized animals or in brain slice preparations, and conclusions from such studies should be therefore interpreted with caution.

The inhibitory effect of 5-HT in the hippocampus is mediated via its actions on 5-HT$_{1A}$, 5-HT$_{1B}$, 5-HT$_{2A}$/5-HT$_{2C}$, 5-HT$_3$, 5-HT$_6$, and possibly 5-HT$_7$ receptors.[53–55,74,81–84,99,112,120] Activation of 5-HT$_{1A}$ receptors has a direct inhibitory effect on pyramidal cell firing by hyperpolarizing their membrane potential via activating a potassium conductance.[53–55] Other 5-HT receptors subtypes decrease the activity of pyramidal cells indirectly by mainly activating interneurons and enhancing GABA transmission onto pyramidal cells.[74,81–84,99,112,120] Multiple synaptic connections from hippocampal interneurons onto pyramidal cells might further amplify the inhibitory effect of 5-HT in the hippocampus.[102]

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SSRIs, which act through the inhibition of the 5-HT transporter, are among the most studied serotonergic agents. Microdialysis studies in rodents have shown that systemic administration of SSRIs rapidly enhances extracellular 5-HT concentrations in multiple brain regions, including the ventral hippocampus.[121–123] Although SSRIs are selective for the serotonergic system, they do not show selectivity for 5-HT receptor subtypes and could, in theory, simultaneously activate all 5-HT receptors. However, since 5-HT receptors have different affinities for 5-HT, with 5-HT_{1A} receptors being the most sensitive type (Table 1), local 5-HT concentrations in the brain would determine which 5-HT receptor subtypes become engaged upon SSRI treatment. In addition, chronic treatment with SSRIs, which is often required to achieve clinical efficacy, can desensitize and change expression patterns of 5-HT receptor subtypes.[124] For instance, chronic treatment with paroxetine desensitizes presynaptic 5-HT_{1A} autoreceptors in the raphe nuclei, which leads to increased serotonergic transmission.[125,126]

In electrophysiology studies, the effect of SSRIs in the hippocampus has been mostly studied in relationship to hippocampal LTP, which is thought to be important for learning and memory.[127] In a majority of studies in normal animals, both the application of 5-HT and acute and chronic treatments with SSRIs inhibit hippocampal LTP.[87,128–132] Interestingly, exposure to stress also impairs LTP in the CA1 and DG regions of the hippocampus (reviewed by Pittenger *et al*[133] and Popoli *et al*[134]). Chronic treatments with SSRIs can reverse these stress-induced deficits in LTP,[135,136] which suggests that SSRIs can restore hippocampal function in disease-like conditions. The positive effects of SSRIs are thought to be mediated, at least in part, by increasing the expression of brain-derived neurotrophic factor (BDNF) and neurogenesis in the hippocampal and cortical circuits.[23,133]

Consistent with the hypothesis that SSRIs might stimulate multiple hippocampal 5-HT receptors expressed on different cell types, their net effects in behavioral cognition models have been limited and variable. The clinical experience with SSRIs is aligned with the preclinical data. Thus, while fMRI studies reveal that the neural systems important for emotional processing are adequately normalized by SSRIs in the treatment of depression,[137] SSRIs are unable to correct the over-activation of the frontolimbic circuitry important for the non-emotional cognition.[11] Although there are studies showing that SSRIs can remediate "hippocampal-related" cognitive deficits in patients with depression,[19] a recent study by Herzallah *et al*[138] indicates that SSRIs can also impair hippocampus-dependent generalization of past learning to novel contexts.

In conclusion, the regulation of hippocampal function by 5-HT is complex, involving multiple receptor subtypes and diverse expression patterns of 5-HT receptors on principal glutamatergic cells and GABAergic interneurons. Thus, administration of an SSRI may not be a rational approach to achieve enhanced hippocampal output and subsequent improvement of cognitive function in patients with MDD due to the potential of activation of multiple receptor subtypes, which may have opposing effects on cell function. On the other hand, targeting a single 5-HT receptor subtype may not be a viable strategy either due to redundancies in the serotonergic system. The consequences of modulating one 5-HT receptor may be attenuated by effects through other 5-HT receptor subtypes. Drugs designed to target single 5-HT receptors have so far not yielded new pharmacological treatments. For example, the selective 5-HT_{1A} receptor agonist flesinoxan was under development for the treatment of generalized anxiety disorder for many years, but its clinical program was stopped in the late 1990s after it failed to show efficacy in 2 large phase-3 clinical trials.[139] The 5-$HT_{1B/1D}$ receptor antagonist elzasonan (CP-448187) was recently under development for the treatment of MDD and was tested in several phase-2 clinical trials, but its development program was also discontinued.[140] An alternative approach to targeting a single receptor subtype could be to target a combination of 5-HT receptor subtypes that would work in a concerted manner. The multimodal antidepressant vortioxetine is an example of such an approach.

Effects of the Multimodal Antidepressant Vortioxetine on Hippocampus Function

Vortioxetine is a 5-HT_3, 5-HT_7, and 5-HT_{1D} receptor antagonist, a 5-HT_{1B} receptor partial agonist, a 5-HT_{1A} receptor agonist, and a SERT inhibitor in cellular assays.[141,142] Vortioxetine has been approved for the treatment of MDD in the US, the EU, Australia and several other countries. Furthermore, clinical studies with cognitive outcome measures have shown that vortioxetine significantly improves cognitive function in MDD patients compared with placebo treatment. The efficacy of vortioxetine on cognitive function has been demonstrated in 3 randomized, double-blinded, placebo-controlled studies in MDD patients.[143–145] One clinical trial was conducted in elderly MDD patients with cognition as a secondary pre-defined outcome and included 128 patients in the placebo group, 136 patients in the vortioxetine-treated group, and 128 patients in the duloxetine-treated group.[143] The other 2 clinical trials were designed to compare the efficacy of vortioxetine to that of placebo on cognitive function as the primary efficacy outcome and on depressive symptoms as the secondary efficacy outcome.[144,145] The study by McIntyre *et al*[144] included 196 patients in the placebo group, 195 patients in the 10 mg vortioxetine group, and 207 patients in the 20 mg vortioxetine group. The study

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by Mahableshwarkar *et al*[145] had 194 patients in the placebo group, 198 patients in the vortioxetine-treated group, and 210 patients in the duloxetine-treated group. These clinical studies demonstrated that vortioxetine improves objective measures of processing speed, executive function, attention and learning, and memory, including hippocampus-dependent memory measures.[143,144,145] Path analyses suggested that the effect on cognitive function was largely independent of its effect on improvements in mood symptoms, supporting the hypothesis that these domains do not necessarily track together. Furthermore, an fMRI study showed that vortioxetine reduced neural activity in the left hippocampus during a working memory task in patients remitted from depression.[146] This indicates that vortioxetine, unlike SSRIs, might restore compensatory overactivation in the hippocampus by increasing neural efficiency.[11]

Consistent with clinical findings, vortioxetine has shown antidepressant as well as pro-cognitive activities in a number of preclinical animal models.[147] Furthermore, in several behavioral and mechanistic studies that engaged hippocampal and cortical circuitry, vortioxetine's effects differentiated from those of SSRIs and SNRIs.[147] In the following paragraphs, we review these preclinical results and discuss how vortioxetine might modulate hippocampal function and affect hippocampus-dependent cognitive behaviors in rodents.

Acute and chronic treatments with vortioxetine increase extracellular 5-HT levels in the rat ventral hippocampus to a much greater extent than those observed with SSRIs.[148,149] Interestingly, combining an SSRI with the 5-HT_3 receptor antagonist ondansetron resulted in a similar potentiating effect on 5-HT levels.[148] This suggests that the effect of vortioxetine was at least partially due to its 5-HT_3 receptor antagonism. Since 5-HT_3 receptors are expressed on GABAergic neurons,[76,150] it was hypothesized that vortioxetine, through its blockade of 5-HT_3 receptors, reduces GABA release and thereby attenuates the inhibitory effect that GABA exerts on 5-HT release in the hippocampus.[151] Recent data by Riga *et al*[151] support this hypothesis. In their study, local application of ondansetron to the ventral hippocampus augmented the effect of the SSRI escitalopram on increasing extracellular 5-HT levels. This effect was reversed by the local application of the $GABA_B$ receptor agonist baclofen, which restored $GABA_B$ receptor tone in the hippocampus.[151] Locally applied baclofen also attenuated the potentiating effect of vortioxetine on extracellular 5-HT. Taken together, these results indicate that 5-HT_3 receptor antagonism plays a prominent role in the vortioxetine's effect on 5-HT levels in the hippocampus.

Although 5-HT_3 receptor antagonism is important in the pharmacology of vortioxetine, contributions from its other receptor activities cannot be ruled out. For instance, an *in vivo* electrophysiology study of pyramidal neurons in the CA3 area of the hippocampus by El Mansari *et al*[152] showed that vortioxetine acts as a partial agonist of 5-HT_{1B} receptors and can function as either an agonist or an antagonist depending on the endogenous 5-HT tone. Vortioxetine enhanced the inhibitory effect of the stimulation of the 5-HT bundle at a high, but not at a low frequency, and reversed the inhibitory effect of the 5-HT_{1B} receptor agonist CP 94253.[152] Thus, vortioxetine also modulates the intra-hippocampal circuitry through its effects at 5-HT_{1B} receptors. 5-HT_{1B} receptors are densely expressed in the subiculum, the main output area of the hippocampus (Figure 2C), and are believed to play an important role in memory function.[153,154] Thus, vortioxetine, through its partial agonism at 5-HT_{1B} receptors, might have a positive outcome on memory processing. Additional studies are needed to confirm this hypothesis, as well as to test the potential role of vortioxetine's other receptor activities on hippocampal function.

Acute and sub-chronic treatments with vortioxetine also increase extracellular levels of NE and HA in the ventral hippocampus.[149,155] Increases in DA and ACh levels have also been observed, but only after the acute treatment.[148,149] Furthermore, a study in rat hippocampal slices showed that vortioxetine disinhibited CA1 pyramidal neurons in response to 5-HT, again most likely through its 5-HT_3 receptor antagonism, whereas escitalopram had no effect on this measure.[82] In line with these findings, several results indicate that vortioxetine promotes glutamate-dependent neuronal plasticity in the hippocampus to a greater degree than SSRIs. For example, vortioxetine, unlike escitalopram, produced a significant increase in LTP in rat hippocampal slices.[82] Furthermore, in mice aged 12 months, chronic treatment with vortioxetine activated neuronal plasticity-related genes and improved hippocampus-dependent, visual-spatial memory deficits, whereas fluoxetine had no effect on these readouts.[156] In another study performed in rats, vortioxetine increased cell proliferation in the hippocampal DG faster than fluoxetine (3 days for vortioxetine compared to 10 days for fluoxetine).[157] Vortioxetine also produced a larger degree of hippocampal dendritic branching than fluoxetine after 2 weeks of dosing in mice.[158] In line with these mechanistic data, vortioxetine showed pro-cognitive effects in hippocampus-dependent cognition models in rodents, such as footshock-induced fear conditioning and spontaneous alternation (Table 2). However, these findings are relatively recent, and vortioxetine has been studied less than other serotonergic drugs and receptors. For instance, there have been only 3 behavioral studies on the effects of vortioxetine on hippocampal-dependent memory versus 16 studies on 5-HT_{1A} receptors and 10 studies on 5-HT_2 receptors with different

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pharmacological and genetic approaches (Table 2). Thus, confirmation and expansion of these results are important.

Taken together, vortioxetine's effects in the hippocampus support the notion that its antidepressant activities and pro-cognitive effects are mediated, at least to some extent, through increased glutamate neurotransmission and increased neuroplasticity. It is important to note that although increased glutamate neurotransmission is thought to favor neuronal plasticity, it is also clear that excessive glutamate release (for instance, in relation to stress) can be neurotoxic (reviewed in Sanacora and Banasr[159] and Sanacora *et al*[160]). Vortioxetine's effects on glutamate are limited to enhanced neuronal function. This has been shown in microdialysis studies, where the treatment with vortioxetine did not result in measureable changes in extracellular glutamate in the ventral hippocampus and prefrontal cortex.[161]

In conclusion, vortioxetine's combined inhibition of 5-HT reuptake and 5-HT receptor modulation results in a differentiated effect on hippocampus function and hippocampal-dependent behavior compared to SSRIs. The full implication of vortioxetine's modulation of multiple neurotransmitter systems on its antidepressant and pro-cognitive potential is complex and remains to be elucidated in future studies.

Overall Conclusion and Future Directions

There is considerable evidence to support the notion that the hippocampus plays an important role in emotional and cognitive processing, and that both of these functions are affected in patients with MDD. SSRIs and SNRIs are the predominant pharmacotherapies for treating MDD, and their enhancing effects on 5-HT levels are believed to be important for their therapeutic efficacy. However, the biological processes that lead to the recovery from the depressive state remain poorly understood. Furthermore, despite several decades of extensive research, the role of 5-HT in regulating hippocampal function in normal or disease states is not well understood, probably due to the high degree of complexity of the serotonergic system.

Multiple classes of 5-HT receptors are often co-expressed on the same cell types with functions that can either be complementary or opposing, and little is known about the interactions between different 5-HT receptors subtypes. Furthermore, the majority of 5-HT receptors in the hippocampus are found on both principal glutamatergic cells and GABAergic interneurons. The 2 known exceptions are the 5-HT_3 receptor subclass, which has only been found on interneurons, and the 5-HT_4 receptor subclass, which has only been found on pyramidal cells. 5-HT_3 receptors are also the only non-G-protein-coupled receptors that function as a ligand-gated ion channel. The impact of the unique expression pattern and effector system of the 5-HT_3 receptor remains to be elucidated. However, given the key role that 5-HT_3 receptor antagonism appears to have in mediating the pharmacological effects of vortioxetine, at least in preclinical behavioral, electrophysiology, and microdialysis studies,[148,157,162] this receptor subtype might have an important role in the hippocampus. 5-HT_4 receptors have been less studied, and understanding their function in the hippocampus remains to be elucidated in further detail.

The effect of SSRIs on hippocampal function remains poorly defined. While SSRIs have the potential to normalize hippocampal plasticity under stress conditions and to treat mood symptoms in MDD, their effects on cognitive function are less clear. Since SSRIs do not possess selectivity for 5-HT receptor subtypes, their efficacy might be weakened due to opposing activities of different 5-HT receptor subtypes. In this context, multitarget drugs or combination therapies might be a better strategy to modulate both emotional and cognitive processes in the hippocampus. Future insights into interactions between different serotonergic subtypes might therefore lead to novel treatment options for the treatment of MDD.

Disclosures

All authors are full-time employees of H. Lundbeck A/S.

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