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THE SEROTONERGIC SYSTEM AND COGNITIVE FUNCTION

Dubravka Švob Štrac*#,
Nela Pivac,
Dorotea Mück-Šeler#

Division of Molecular Medicine,
Ruđer Bošković Institute,
Zagreb, Croatia

#These authors contributed equally

Abstract

Symptoms of cognitive dysfunction like memory loss, poor concentration, impaired learning and executive functions are characteristic features of both schizophrenia and Alzheimer's disease (AD). The neurobiological mechanisms underlying cognition in healthy subjects and neuropsychiatric patients are not completely understood. Studies have focused on serotonin (5-hydroxytryptamine, 5-HT) as one of the possible cognition-related biomarkers. The aim of this review is to provide a summary of the current literature on the role of the serotonergic (5-HTergic) system in cognitive function, particularly in AD and schizophrenia.

The role of the 5-HTergic system in cognition is modulated by the activity and function of 5-HT receptors (5-HTR) classified into seven groups, which differ in structure, action, and localization. Many 5-HTR are located in the regions linked to various cognitive processes. Preclinical studies using animal models of learning and memory, as well as clinical *in vivo* (neuroimaging) and *in vitro* (*post-mortem*) studies in humans have shown that alterations in 5-HTR activity influence cognitive performance.

The current evidence implies that reduced 5-HT neurotransmission negatively influences cognitive functions and that normalization of 5-HT activity may have beneficial effects, suggesting that 5-HT and 5-HTR represent important pharmacological targets for cognition enhancement and restoration of impaired cognitive performance in neuropsychiatric disorders.

Keywords

• Alzheimer's disease • Cognitive function • Receptors • Schizophrenia • Serotonin

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1. Introduction

Cognitive functions represent a spectrum of mental abilities and complex processes related to attention, memory, judgment and evaluation, problem-solving and decision-making, as well as to comprehension and language synthesis. As normal aging is frequently associated with a decline in memory and cognitive abilities, cognitive impairment is one of the major challenges of our rapidly aging society. Moreover, cognitive deficits are prominent features of many psychiatric and neurodegenerative disorders including schizophrenia and Alzheimer's disease (AD). In spite of extensive research, the neurobiological underpinnings of cognitive flexibility in both healthy subjects and neuropsychiatric patients are still unclear. A great deal of attention has been directed towards the role of serotonin (5-hydroxytryptamine, 5-HT) in various emotional states and mood disorders. More recently, studies have focused on 5-HT as one of the possible cognition-related biomarkers. This mini-review assesses the literature on the involvement of 5-HT receptors (5-HTR) in multiple aspects of cognitive performance and particularly emphasizes 5-HTRs potential for therapeutic intervention of cognitive deficits in AD and schizophrenia.

2. 5-HT and cognition

As a neurotransmitter, 5-HT not only regulates many important physiological processes such as body temperature, sleep, appetite, pain and motor activity [1], but also modulates higher brain functions, including cognition and emotional behaviour [2]. Widespread distribution of serotonergic (5-HTergic) neurons allows modulation of various neuronal networks located in distant brain regions whose coordinated activity is required for most cognitive functions [3]. A high density of 5-HTergic projections in the hippocampus and prefrontal cortex [4-6] underlines the anatomical and neurochemical linkage of the 5-HTergic system with brain areas most commonly associated with learning and memory [7]. While the 5-HTergic system in the hippocampus is involved in different memory processes, spatial navigation, decision making and social relationships [8-10], in the prefrontal cortex 5-HT plays a major role in working memory, attention, decision-making and reversal learning [11,12].

The neuromodulatory action of 5-HT on cognitive functions in both physiological and pathological states largely depends on the action of enzymes, transporters, and specific subtypes of expressed receptors (5-HTR), and their localization, which regulate local 5-HT

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* *E-mail: dsvob@irb.hr*

concentration and neurotransmission [13,14]. In addition, part of 5-HT's role in the neurobiology of learning and memory might be attributed to complex interactions between the 5-HTergic system and other neurotransmitters such as acetylcholine, dopamine, GABA and glutamate [15]. Preclinical and clinical studies suggest that the activity of the 5-HTergic system is associated with short- and long-term memory and cognitive performance, during aging [16] as well as in many psychiatric (schizophrenia, depression, alcoholism) and neurological (AD, epilepsy) disorders [4,17,18].

Cognitive-attentional dysfunction is one of the key features of schizophrenia and it is related to poor psychosocial outcomes [19]. Major cognitive dimensions affected in schizophrenia include speed of processing, working memory, vigilance, attention, reasoning and problem solving, sound cognition, as well as both visual and verbal learning and memory [20]. In schizophrenia, ascending 5-HTergic pathways from the dorsal raphe nuclei to the substantia nigra and from the rostral raphe nuclei to the neocortex, limbic regions, and basal ganglia are upregulated, leading to dopaminergic hypofunction [21]. It is believed that the symptoms of schizophrenia are at least in part due to this interconnectivity between 5-HTergic and dopaminergic systems [22]. On the other hand, the disruption of serotonergic / cholinergic / GABAergic interactions in the frontal cortex [23], as well as synaptic disorganization in the hippocampus [24], suggests that synchronization of neural activity between the prefrontal cortex and the hippocampus might be crucial for the complex cognitive behaviour in schizophrenia [3].

The most pronounced symptom of AD is the progressive decline of various cognitive domains, primarily affecting episodic, semantic and working memory, but also executive functions such as attention, linguistic and visio-spatial skills [25]. The hippocampus, the most affected brain area in AD, is involved in cognitive changes and impaired memory observed in the disease [26]. A reduced numbers and activity of 5-HTergic neurons [27,28], associated with a decrease in the concentration of 5-HT and its main metabolite 5-hydroxyindoleacetic acid (5-HIAA) in the *post-mortem* brain [29], cerebrospinal fluid [30], and blood platelets [31], suggest extensive serotonergic denervation in AD [32]. The association of 5-HT signalling with accumulation of amyloid-β (Aβ) plaques [27,33], and expression or processing of amyloid precursor protein (APP), as well as the improvement of cognitive functions following treatment with 5-HT modulators [32,34,35], indicate that the 5-HTergic system is a potential target for AD therapy. The alterations in the 5-HTergic system could be also associated with the development of non-cognitive symptoms in AD, called behavioural and psychological symptoms of dementia (BPSD), which affect up to 90% of dementia patients [36], and include aggressive behaviour, depression, psychotic symptoms (hallucinations, delusions), apathy, as well as changes in sleep and appetite [37].

3. Serotonin receptors (5-HTR)

A variety of 5-HTergic functions is accomplished by the release of 5-HT in targeted areas and its action via at least 14 different pre- and postsynaptic 5-HTR [38]. As shown in Tables 1 and 2, 5-HTR are subdivided according to their distribution, molecular structure, cell

Table 1. Classification, distribution and function of 5-HTR.

Receptor family	Subtype	Distribution	Mechanism	Cellular response
5-HT_1	1A, 1B, 1D, 1E, 1F	CNS, blood vessels	Adenylate cyclase	Inhibitory
5-HT_2	2A, 2B, 2C	CNS, PNS, platelets, blood vessels, smooth muscle	Phospholipase C	Excitatory
5-HT_3	3A, 3B	CNS, PNS; GI tract	Ligand-gated ion channel	Excitatory
5-HT_4		CNS, PNS	Adenylate cyclase	Excitatory
5-HT_5		CNS	Adenylate cyclase	Inhibitory
5-HT_6		CNS	Adenylate cyclase	Excitatory
5-HT_7		CNS , GI tract, blood vessels	Adenylate cyclase	Excitatory

Abbreviations: CNS = central nervous system; PNS = peripheral nervous system, GI tract = gastrointestinal tract.

Table 2. 5-HTR in the brain.

Receptor family	Distribution in the brain
5-HT_1	Pituitary gland, rostral raphe nuclei, hippocampus, prefrontal cortex cerebellum, basal ganglia, amygdala, globus pallidus, putamen, caudate nucleus
5-HT_2	Cerebral cortex, basal ganglia, amygdala, choroid plexus, hypothalamus, hippocampus, caudate nucleus, putamen, globus pallidus, substantia nigra
5-HT_3	Area postrema, tractus solitarius, limbic system, hippocampus, cerebral cortex
5-HT_4	Prefrontal cortex, caudate nucleus, putamen, globus pallidus, hippocampus, substantia nigra
5-HT_5	Cerebral cortex, amygdala, cerebellum, hypothalamus, hippocampus
5-HT_6	Dentate gyrus, hippocampus, olfactory tubercle, nucleus accumbens, amygdala, cerebellum
5-HT_7	Thalamus

response and function into seven groups from 5-HTR$_1$ to 5-HTR$_7$ [39, 40]. Except 5-HTR$_3$ which are ligand-gated ion channels, all other 5-HTR are G-protein-coupled receptors influencing different transduction pathways [39].

Although 5-HTR are widespread in the central nervous system (CNS) and to a lesser extent in some peripheral organs, the prefrontal cortex and hippocampus are the two main targets of 5-HTergic neurons and express almost all 5-HTR [41, 42]. 5-HTR subtypes found in these brain regions include 5-HT$_1$, 5-HT$_2$, 5-HT$_3$, 5-HT$_4$, 5-HT$_5$, 5-HT$_6$, and 5-HT$_7$ class of receptors [43, 44]. The activation of different 5-HTR subtypes through the action of distinct neuronal networks, within the same brain region, or even within the same local synapse can have opposite outcomes [13, 45]. The changes in the 5-HTR related to cognition are given in Table 3. Since both agonists and antagonists of specific 5-HTR affect cognitive processes, 5-HTR emerged as attractive potential drug targets for the treatment of cognitive deficits.

Table 3. Changes in the 5-HTR related to cognition.

Receptor	Findings reported	Reference
5-HT$_{1A}$	Decrease in receptor activity and density with aging in healthy subjects	54
	Stimulation of receptors by antipsychotics increase prefrontal cortical dopamine release	61
	Negative correlation between receptor binding potential and cognitive function in healthy persons	55
	Decreased receptor number or density in elderly with MCI and AD	57
	Relationship between receptor number and BPSD	58
	No correlation between receptor binding potential and cognitive function in healthy persons	56
	Receptors affect declarative and non-declarative memory functions via glutamatergic, cholinergic and GABAergic neurons	49
	Receptors regulate different kinases and immediate early genes implicated in memory formation	49
	Decreased receptor binding in amygdala of patients with schizophrenia	60
	Increased receptor binding in prefrontal cortex of patients with schizophrenia	60
	No change in brain receptor binding in patients with schizophrenia	60
	Activation of postsynaptic receptors in rodents impairs emotional memory through attenuation of neuronal activity	53
	Activation of presynaptic receptors reduces 5-HT release and exerts pro-cognitive effects on passive avoidance retention	53
	Potential of 5-HTR$_{1A}$ and DR$_2$ heterodimers in the frontal cortex for cognitive enhancement	62
5-HT$_{1B}$	Receptor agonist reduces cognitive function in experimental animals	66
	Decrease in receptor binding potential with aging in healthy subjects	65
	Role of receptor inverse agonists and antagonists in treatment of damaged memory and cognitive processes	66
	Decrease in receptor density in frontal and temporal cortex associated with cognitive dysfunction in patients with AD	67
	Decrease in receptor binding in brain stem associated with good response to psychotherapy in depressive patients	69
	Positive correlations between creative ability, a measure of divergent thinking, and average receptor availability in grey matter	64
	Increased receptor mRNA levels in the hippocampal formation in patients with schizophrenia	70
	Receptor agonists induce potentiation of latent inhibition, a characteristic of antipsychotics	71
5-HT$_{2A}$	Decreased receptor number in hippocampus and frontal cortex with aging correlates with cognitive decline	27
	Severity of cognitive impairment in AD patients correlates with the decrease in receptor binding	77,78
	Receptor antagonism improves cognition in schizophrenia	85
	Receptor antagonist improves working memory function in young and aged monkeys	82
	Receptor low affinity of the atypical antipsychotics is more beneficial for cognition and social function than high affinity	87
	Decrease in receptor density with aging correlates with cognitive decline	73
	Conflicting results in vivo studies of receptor binding on schizophrenia patients	83,84
	Changes in receptor expression associated with pathological and progressive accumulation of Aβ in animal model of AD	79
	Decrease in brain receptor density in patients with AD	74-76
	Decrease in number of prefrontal receptors in brain of schizophrenia patients	60
	Receptor activation with high affinity agonist enhanced working memory in rats	80
	Intrahippocampal injections of receptor antagonist increase rat spatial learning and memory	81
5-HT$_{2C}$	Receptor agonism, rather than antagonism has beneficial effects on cognitive functions in schizophrenia	99
	Both receptor agonists and antagonists may have positive effects on cognitive functions in schizophrenia	90
	Reducing receptor activity facilitates reversal learning in mouse by reducing influence of previously non-rewarded associations	92
	Receptor agonist treatment ameliorated impairments in cognitive flexibility and reversal learning in the mutant mice	94
	Administration of selective receptor antagonist, prior to environmental stress, prevented tau hyperphosphorylation and repaired defects in hippocampal LTP and spatial memory	93
	Stimulation with receptor agonist in vitro and *in vivo* reduces Aβ production	95,96
	Increase of receptors in NK-cells linked with cognitive deficits in AD	

Receptor	Findings reported	Reference
5-HT$_3$	Ondansetron blocked scopolamine-induced learning deficits in learning	104
	Ondansetron improved radial arm maze performance in MK801-impaired rats	103
	Antagonist itasetron showed memory-enhancing effects	105
	Receptor antagonists improve memory	102
	Receptor antagonists provide improvement in cognitive symptoms of schizophrenia	115
	Ondansetron as potential adjunctive treatment for schizophrenia particularly for negative symptoms and cognitive impairments	116-118
	Improvements in verbal memory after tropisetron therapy	119
	Link between gene variant of the 5-HTR$_{3E}$ subunit and sustained attention in schizophrenic patients	114
	Blockade of receptors protects neurons against Ab-induced neurotoxicity by inhibition and stimulation of glutamate and acetylcholine release, respectively	106,107, 108
	Neuroprotective effects of synthetic compounds targeting 5-HTR$_3$ with acetylcholinesterase or with alpha-7 nicotinic receptor activity	110-112
5-HT$_4$	Decreased receptor number in hippocampus and cortex from AD patients	58,140
	Receptor agonists and antagonists modulate short-term and long-term memory in rats	128
	Beneficial effects of receptor activation on cognition in rodents and primates	122,129, 130
	Receptor agonists acutely improved performance on learning and memory tests	132-134
	Receptor agonists reversed age-related or pharmacologically-induced cognitive deficits	86,135-137
	Chronic partial agonist improved memory performance in mice	138
	Receptor agonists stimulate acetylcholine release, regulate memory performance, have neuroprotective and neurotrophic effects	141-143
	No change in the receptor number during aging in humans	139
	Receptor role in cognitive processes and expression of genes that regulate synaptic plasticity	131
	Receptor agonists decrease production of neurotoxic Aβ	142-144
	Receptor expression not changed in schizophrenic patients	146
	Receptor gene haplotype associated with schizophrenia	147
5-HT$_5$	Receptor blockade impairs short- and long-term memory, while its stimulation facilitate it	150
	Receptor antagonist improves positive symptoms and cognitive impairment in animal models of schizophrenia, aged rats and mice with memory deficit	151,152
5-HT$_6$	Decreased receptor density in temporal and frontal cortex in AD patients	67
	Decrease in the number of neurons expressing receptors in AD patients	74
	Receptor antagonists enhance cognitive performance	158,159
	Receptor agonists and antagonists regulate learning and memory	153-155
	High affinity receptor compounds are investigated *in vitro* or in pre-clinical and clinical trials for the improvement of cognitive functions in AD	155-157
	Recruitment of mammalian target of rapamycin (mTOR) by receptors in the prefrontal cortex (PFC) contributes to perturbed cognition in schizophrenia	162
	Compounds with high receptor affinity are enrolled in preclinical and clinical investigations	155-157
	Improvements following administration of receptor antagonists in preclinical tests for episodic memory, social cognition, executive function, working memory	163
	Receptor antagonist in the AD mouse model counteracts memory impairment by attenuating the generation of Aβ	160
	Receptor agonism facilitate the emotional learning by promoting the neuronal plasticity in caudate putamen, hippocampus, and PFC	161
	Combination of receptor antagonist with low doses of prazosin enhances memory and demonstrates potential in treatment of schizophrenia	164
5-HT$_7$	Receptors associated with hippocampus-dependent cognitive processes	166
	Increase in recognition memory and antipsychotic efficacy of receptor antagonist	182
	Receptor agonists could be useful in the treatment of memory decline in AD	175,176
	Decrease in the receptor number in hippocampus and prefrontal cortex of schizophrenia patients	178,179
	Association between receptor gene haplotype and schizophrenia	180
	Increase in the receptor number in rats treated with typical antipsychotic haloperidol	178
	High affinity of several atypical antipsychotics for receptors	178,181
	Receptor antagonism have procognitive effects	167
	Receptor antagonist attenuated phencyclidine (PCP) and scopolamine-induced learning deficits and improved reference memory	168-171
	Receptor antagonist attenuated MK-801, scopolamine and PCP-induced impairments in learning and memory	172,173
	Receptor antagonism facilitates memory retention	53
	Selective receptor agonist rescues alterations in motor coordination, spatial reference memory and synaptic plasticity in mouse model of Rett syndrome	174

3.1. 5-HT$_{1A}$ receptors

The 5-HTR type 1A (5-HTR$_{1A}$), probably the most investigated 5-HT receptor class, are highly abundant in cortical and limbic brain regions, associated with cognitive functions [46]. The involvement of 5-HTR$_{1A}$ autoreceptors in cognitive performance has been underlined by their important role in the regulation of the activity of the entire 5-HTergic system. 5-HTR$_{1A}$ autoreceptors, located on the soma of 5-HTergic neurons, are key components of the negative feedback loop that inhibits neuronal signalling and 5-HT release [47]. 5-HTR$_{1A}$ heteroreceptors located on postsynaptic 5-HTergic and non-5-HTergic neurons [39], particularly those in the limbic system, are involved in the control of cognitive functions, mood and emotional states [48]. 5-HTR$_{1A}$ can affect declarative and non-declarative memory functions by exerting their influence on the activity of glutamatergic, cholinergic and GABAergic neurons in the cerebral cortex, hippocampus and the septohippocampal projection [49]. Moreover, 5-HTR$_{1A}$ activation increases dopamine release in the medial prefrontal cortex, striatum, and hippocampus [50, 51]. In addition to cooperation with other neurotransmitter systems [52], 5-HTR$_{1A}$ regulate the G-protein dependent and independent signalling pathways that target immediate early genes implicated in memory formation [49].

In rodents, activation of postsynaptic 5-HTR$_{1A}$ impairs emotional memory through attenuation of neuronal activity, whereas presynaptic 5-HTR$_{1A}$ activation reduces 5-HT release and exerts pro-cognitive effects on passive avoidance retention [53]. Human studies as well as experimentation in animals both suggest an association of 5-HTR$_{1A}$ with cognition. In healthy subjects during aging the activity and density of 5-HTR$_{1A}$ declines 10% every ten years [54]. Positron emission tomography (PET) studies have found a negative [55] or a lack of [56] correlation between 5-HTR$_{1A}$ binding potential and cognitive function in healthy individuals. The discrepancies are probably due to the differences in specificity and sensitivity of cognitive tests and in methodologies that were used, as well as ethnic diversity of the subjects [56].

A progressive decline in the density of 5-HTR$_{1A}$ in the hippocampus and dorsal raphe has been found in elderly subjects with mild cognitive impairment (MCI) and AD [57]. A relationship between the number of 5-HTR$_{1A}$ in the temporal cortex and aggressive behaviour [58] suggests their role in development of BPSD. In addition, results from behavioural and pharmacological studies with antagonists or inverse agonists imply that 5-HTR$_{1A}$ could be an important target for the new compounds used in AD treatment [59].

In addition to the association of the 5-HTR$_{1A}$ and cognitive processes, reported in animal models, healthy subjects, and patients with MCI and AD, there are also data regarding their role in schizophrenia. Although *in vivo* imaging studies of 5-HTR$_{1A}$ distribution in schizophrenia patients showed inconsistent results, it appears that ligand binding to 5-HTR$_{1A}$ is enhanced in the cortical areas, while it is diminished or unchanged in the amygdala [60]. In addition, a recent meta-analysis study has reported a significant increase in *post-mortem* 5-HTR$_{1A}$ binding in the prefrontal cortex of patients with schizophrenia [60]. Direct stimulation of 5-HTR$_{1A}$ increases prefrontal cortical dopamine release. It is therefore possible that the antipsychotic effects of clozapine, ziprasidone and aripiprazole are in part due to their agonist effects on 5-HTR$_{1A}$ [61]. The recent detection of 5-HTR$_{1A}$ and dopamine receptors type 2 (DR$_2$) heterodimers in the frontal cortex and their potential for cognitive enhancement, has implications for the development of improved pharmacotherapy for schizophrenia or other disorders [62].

3.2. 5-HT$_{1B}$ receptors

Activated presynaptic 5-HTR type 1B (5-HTR$_{1B}$) inhibit the release of 5-HT and other neurotransmitters (GABA, glutamate, noradrenaline), while modulating the release of acetylcholine [63]. Postsynaptic 5-HTR$_{1B}$ are found on non-5-HTergic neurons within the basal ganglia, striatum, hippocampus and cortex [39]. Positive correlations between creative ability, a measure of divergent thinking, and average 5-HTR$_{1B}$ levels in the grey matter have been reported in the study of Varrone *et al*. [64]. A moderate age-related decline in the brain's 5-HTR$_{1B}$ binding potential of 8% every 10 years has also been observed in healthy subjects [65]. The suggested role of 5-HTR$_{1B}$ in memory and learning is consistent with the findings that 5-HTR$_{1B}$ agonists reduce cognitive function in experimental animals [66].

Post mortem analysis of brains from AD patients showed a reduced density of 5-HTR$_{1B}$ in the frontal and temporal cortex, associated with cognitive dysfunction [67]. Since these receptors inhibit acetylcholine release [68], when they are in a heteroreceptor context, lower expression of 5-HTR$_{1B}$ observed in AD [67] might represent a compensatory mechanism aimed to repair downregulated acetylcholine levels. These results suggest that disrupted cognition in AD might be improved by the administration of inverse agonists and antagonists of 5-HTR$_{1B}$ [66]. The suggested importance of 5-HTR$_{1B}$ in cognition has been confirmed in a recent clinical PET study in patients with major depressive disorders before and after psychotherapy [69]. Increased 5-HTR$_{1B}$ mRNA levels in the hippocampal formation were also observed in patients with schizophrenia [70]. The up-regulation of 5-HTR$_{1B}$ in concert with the downregulation of 5-HTR$_{2A}$, could lead to a reduction in GABAergic activity and consequently enhanced hippocampal glutamatergic output in schizophrenia [70]. On the other hand, agonists of 5-HTR$_{1B}$ might provide an alternative therapeutic approach for schizophrenia, as they induce potentiation of latent inhibition, which is a characteristic of many effective antipsychotics [71].

3.3. 5-HT$_{2A}$ receptors

5-HTR type 2A (5-HTR$_{2A}$) are located mostly in different parts of the cortex, basal ganglia and slightly less in the hippocampus [39], where they enhance the release of dopamine, glutamate and GABA, and inhibit the release of noradrenaline [72]. An age-dependent decrease in the number of 5-HTR$_{2A}$ was found in the hippocampus and frontal cortex of healthy individuals [27]. The observed 12% reduction in the density of 5-HTR$_{2A}$ every decade, also correlates with cognitive decline [73].

Imunohistochemical [74], post-mortem [75] and imaging [76] studies revealed reduced brain 5-HTR$_{2A}$ density in patients with AD. The severity of cognitive impairment in AD patients seems to also correlate with the decrease in neocortical temporal 5-HTR$_{2A}$ [77, 78]. Studies on the AD mouse model that overexpresses Aβ and has high age-dependent levels of amyloid plaques [79], suggested that changes in 5-HTR$_{2A}$ expression are associated with the pathological and progressive accumulation of Aβ.

Various animal studies investigated the effects 5-HTR$_{2A}$ agonists or antagonists on cognitive performance. The activation of 5-HTR$_{2A}$ with the high affinity agonist TCB-2 enhanced working memory in rats [80], while intrahippocampal injections of ritanserin (5-HTR$_{2A/2C}$ antagonist) increased spatial learning and memory, also in rats [81]. Improved working memory was also observed in younger and older monkeys following treatment with 5-HTR$_{2A}$ antagonist EMD 281014 [82].

The role of 5-HTR$_{2A}$ in the most common cognitive deficits in schizophrenia, such as attention, executive functions, and spatial working memory is not clear [83]. A recent meta-analysis [60] found a reduced number of prefrontal 5-HTR$_{2A}$ in the *post-mortem* brain of schizophrenia patients. On the other hand, *in vivo* studies of 5-HTR$_{2A}$ binding reported conflicting results [83, 84]. The observed discrepancies might be due to the fact that *post-mortem* studies included patients treated with antipsychotics - 5-HTR$_2$ antagonists, which may decrease the density of 5-HTR$_{2A}$. Although 5-HTR$_{2A}$ antagonism was reported to improve cognition in schizophrenia [85], the adverse side effects of 5-HTR$_{2A}$ antagonists, such as atypical antipsychotics olanzapine and clozapine, limit their clinical use to short-term treatment of BPSD in patients with most severe symptoms [86]. However, some studies suggest that 5-HTR$_{2A}$ affinity plays an important role in the modulation of the cognitive effects of atypical antipsychotics, indicating that low affinity to 5-HTR$_{2A}$ is more beneficial for cognitive and social performance than high affinity [87]. Further development of highly selective 5-HTR$_{2A}$ ligands is essential for elucidating the critical involvement of these receptors in different cognitive functions [88].

3.4. 5-HT$_{2C}$ receptors

5-HT activity in different brain regions is modulated by 5-HTR type 2C (5-HTR$_{2C}$), which are found throughout the CNS [89]. RNA editing generates at least 14 functionally distinct 5-HTR$_{2C}$ isoforms, any of which could be a potential target for improved therapeutic and side effect profiles [90]. Moreover, the negligible presence of 5-HTR$_{2C}$ in cardiac and vascular tissues makes these receptors ideal targets for treatment of brain disorders, due to their limited peripheral side effects [91].

In various animal models, 5-HTR$_{2C}$ antagonism seems to improve cognitive flexibility. 5-HTR$_{2C}$ blocking with the antagonist SB242084 promoted reversal learning in mice [92], whereas administration of the selective 5-HTR$_{2C}$ antagonist RS-102,221 prevented tau hyperphosphorylation and repaired the defects in hippocampal long-term potentiation and spatial memory [93], suggesting a beneficial effect on disrupted hippocampal synaptic plasticity. Treatment with the 5-HTR$_{2C}$ agonist CP809,101 improved impairments in cognitive flexibility and reversal learning in mutant mice with a genetically engineered 5-HT-synthesizing enzyme (tryptophanhydroxylase-2) [94]. Pharmacological stimulation of 5-HTR$_{2C}$ with another agonist dexnorfenfluramine *in vitro* [95] and *in vivo* [96] enhanced secretion of the APP metabolite and reduced Aβ production, suggesting that one of the strategies for AD therapy development could be to target 5-HTR$_{2C}$. The significant increase of 5-HTR$_{2C}$ in NK-cells has been linked with cognitive deficits in AD [97], suggesting that it may serve as a biomarker for diagnosing dementia.

The presence of 5-HTR$_{2C}$ in the limbic system, frontal cortex, and hippocampus suggests their possible involvement in schizophrenia [98]. Preclinical data revealed that 5-HTR$_{2C}$ modulation of cognitive symptoms might have beneficial effects in schizophrenia, as well [99]. Several studies indicated that both 5-HTR$_{2C}$ agonists and antagonists may have positive effects on cognitive functions in schizophrenia [for review see 90]. Further research focused on the 5-HTR$_{2C}$ modulation is necessary to assess whether 5-HTR$_{2C}$ agonism or antagonism improve cognitive defects in schizophrenia [90].

3.5. 5-HT$_3$ receptors

In contrast to all other 5-HTR, 5-HTR type 3 (5-HTR$_3$) are ligand-gated channels that regulate permeability to sodium, potassium and calcium ions in the CNS and peripheral nervous system. These receptors induce rapid membrane depolarization and consequently the release of 5-HT, acetylcholine, dopamine, GABA and peptides [100]. While the location of 5-HTR$_3$ on presynaptic neurons in cortical regions, amygdala and striatum, and on postsynaptic neurons in the hippocampus [39], suggest a potential role in cognition, studies investigating the involvement of 5-HT$_3$ receptors in cognitive functions are few.

The 5-HTR$_3$ antagonists, such as ondansetron, are mainly used for the treatment of chemotherapy-induced emesis [101]. However, they have been also shown to improve cognition in different models of memory impairment [102]. Boast *et al*. [103] reported that ondansetron improves radial arm maze performance in MK801-impaired rats, suggesting its cognition enhancing properties. Ondansetron also blocked scopolamine-induced learning deficits [104], whereas another 5-HTR$_3$ antagonist itasetron showed memory-enhancing effects [105].

Several pharmacological studies suggested the role of 5-HTR$_3$ in AD. 5-HTR$_3$ antagonists MDL72222 and Y25130 reduced Aβ protein-induced neurotoxicity in cultured rat cortical neurons [106]. Moreover, the inhibition of 5-HTR$_3$ with tropisetron alleviated the spatial memory deficit in the rat model of AD. It also protected neurons from Aβ-induced inflammation and neurotoxicity by inhibiting and stimulating glutamate and acetylcholine release, respectively [107,108], or by inhibiting calcineurin activity in the hippocampus (107). Other 5-HTR$_3$ antagonists which interact with multiple targets have also been investigated [109]. Synthetic dual action compounds targeting 5-HTR$_3$ (antagonist) and acetylcholinesterase activity (inhibitor) [110, 111], or 5-HTR$_3$ (inhibitor) and alpha-7 nicotinic receptor (activator) [112] had neuroprotective effects. 5-HTR$_3$ antagonists could therefore be used as building blocks in the development of new neuroprotective drugs.

While no significant changes in the number and affinity of 5-HTR$_3$ in amygdala of schizophrenic patients have been observed in one *post-mortem* study [113], another report noted a link between a coding variant of the

5-HTR$_{3E}$ subunit and sustained attention in schizophrenic patients [114], suggesting the involvement of 5-HTR$_3$ in cognitive deficits in schizophrenia. Several recent studies also found that 5-HTR$_3$ antagonists can provide significant amelioration of cognitive symptoms of schizophrenia [115]. Ondansetron has shown some promise in treatments for schizophrenia, particularly for negative symptoms and cognitive impairments [116, 117]. Akhondzadeh *et al*. [116] and Levkovitz *et al*. [118] reported improved visio-spatial learning and memory following treatment with ondansetron, whereas Zhang *et al*. [119] observed improvements in verbal memory after tropisetron therapy. These findings suggest that 5-HTR$_3$ antagonists possibly have therapeutic potential for the management of cognitive deficits in both AD and schizophrenia.

3.6. 5-HT$_4$ receptors

5-HTR type 4 (5-HTR$_4$) have been found in different brain regions such as the hypothalamus, hippocampus, nucleus accumbens, ventral pallidum, amygdala, basal ganglia, olfactory bulbs, frontal cortex and substantia nigra [120, 121]. These receptors are cleary highly expressed in brain structures involved in memory processes, including cell bodies and nerve endings of GABA neurons in the limbic system, as well as cholinergic neurons in the cortex where they modulate acetylcholine release [122]. In addition to acetylcholine [123, 124], activation of 5-HTR$_4$ increases the release of dopamine [125, 126] and 5-HT [127].

Both 5-HTR$_4$ agonists and antagonists modulate short-term and long-term memory in rats [128]. Various studies reported beneficial effects of 5-HTR$_4$ activation on cognition in rodents and primates [122, 129, 130]. 5-HTR$_4$ have also been implicated in the expression of genes that regulate synaptic plasticity [131]. 5-HTR$_4$ agonists, administered acutely, improved performance on learning and memory tests [132-134], and reversed age-related or pharmacologically-induced cognitive deficits [86, 135-137]. Chronic activation of 5-HTR$_4$ also seems promising strategy for the treatment of memory deficits, as long-term administration of the partial agonist RS-67333 improved recognition memory in mice (138).

Although some studies reported that aging does not change the number of 5-HTR$_4$ in the human brain [139], reduced levels of 5-HTR$_4$ have been measured *post-mortem* in the hippocampus and cortex of AD patients [58,140]. Both, *in vivo* and *in vitro* studies imply that activation of 5-HTR$_4$ by agonists like 5-HT itself has a beneficial effect in AD. 5-HTR$_4$ agonists have been shown to stimulate acetylcholine release [141], regulate memory performance and have neuroprotective and neurotrophic effects [142, 143]. Additionally, they stimulate the non-amyloid-forming metabolism of APP and thus decrease the production of neurotoxic Aβ, involved in the AD etiology [142-144].

Since they modulate cognitive functions, 5-HTR$_4$ receptors are attractive target candidates for therapeutic strategies aimed at curbing cognitive symptoms of schizophrenia [145]. 5-HTR$_4$ expression does not appear to change in schizophrenic patients [146], but 5-HTR$_4$ gene variants have been associated with schizophrenia [147]. Overall, selective 5-HTR$_4$ ligands may provide novel approaches for the development of new cognitive enhancers, which would be useful for treatments of both AD and schizophrenia [138].

3.7. 5-HT$_5$ receptors

5-HTR type 5 (5-HTR$_5$) are expressed in different brain regions like the cerebral cortex, hippocampus, nucleus accumbens, amygdala, and hypothalamus [148, 149]. A preclinical study demonstrated that blocking and stimulation of 5-HTR$_{5A}$ might impair and facilitate short- and long-term memory, respectively [150]. On the other hand, the 5-HTR$_{5A}$ antagonist ASP5736 improved positive and cognitive symptoms in a schizophrenia mouse model as well as in aged rats and mice with scopolamine-induced working memory deficit [151, 152]. These data suggest that ASP5736 may be used in the treatment of cognitive defects in schizophrenic patients. As far as we know, no data are yet available on 5-HTR$_5$ and AD.

3.8. 5-HT$_6$ receptors

5-HTR type 6 (5-HTR$_6$) are located on postsynaptic 5-HT neurons in the basal ganglia, cortex and limbic system and on cholinergic and GABAergic neurons in the striatum [39]. Preclinical studies on 5-HTR$_6$ suggest their role in regulation of learning and memory, mediated probably by stimulation of glutamatergic and cholinergic transmission [153-155].

The density of 5-HTR$_6$ in the temporal and frontal cortex [67], as well as the number of neurons expressing 5-HTR$_6$ [74], are reduced in AD patients, suggesting that these receptors might also be a good target for anti-dementia medication. Several compounds with high affinity to 5-HTR$_6$, especially 5-HTR$_6$ antagonists, have been synthesized and are currently being investigated *in vitro* or are in different phases of pre-clinical and clinical trials for the improvement of cognitive functions in AD [155-157]. 5-HTR$_6$ antagonists were shown to enhance cognitive performance in different learning and memory tests performed on rodents and primates [158, 159]. For instance, in the AD mouse model, the 5-HTR$_6$ antagonist, SB271036, counteracts memory deficiencies probably by reducing Aβ formation via the inhibition of γ-secretase activity and the inactivation of astrocytes and microglia [160]. 5-HTR$_6$ agonism has also been reported to facilitate emotional learning by promoting the neuronal plasticity in the caudate putamen, hippocampus, and prefrontal cortex [161].

In animal models of schizophrenia, the activation of 5-HTR$_6$ was associated with the stimulation of the mTOR (mammalian Target of Rapamycin) signalling pathway in prefrontal cortex. Rapamycin, the mTOR inhibitor, prevented cognitive deficits induced by 5-HTR$_6$ agonists [162]. Improvements in episodic memory, social cognition, executive function, and working memory were also observed following administration of 5-HTR$_6$ antagonists in preclinical trials [163]. There are also reports showing that the combination of 5-HTR$_6$ antagonist PRX-07034 with low doses of prazosin enhances memory which could be used for the treatment of schizophrenia [164].

3.9. 5-HT$_7$ receptors

5-HTR type 7 (5-HTR$_7$) are the most recently discovered 5-HTR. They are located mostly in the hippocampus, hypothalamus and thalamus, and somewhat less in the cortex, as well as in the amygdala and the dorsal raphe nucleus [39, 165]. Although 5-HTR$_7$ are associated with hippocampus-dependent cognitive processes [166], their role in memory and cognition is still unclear, mainly due to the lack of selective agonists and antagonists. Most studies are therefore done with partially specific drugs that also target other receptors.

Preclinical data show pro-cognitive effects of a 5-HTR$_7$ antagonist, alone or in combination with antidepressants, indicating that 5-HTR$_7$ antagonist represent new targets for the treatment of cognitive deficits in stress-related neuropsychiatric disorders [167]. The 5-HTR$_7$ antagonist SB-269970 attenuated PCP and scopolamine-induced learning deficits [168-170], and improved reference memory [171]. Another antagonist, lurasidone, attenuated MK-801, scopolamine and PCP-induced impairments in learning and memory [172,173].

In the mice model of Rett syndrome, treatment with LP-211, a selective 5-HTR$_7$ agonist, improved motor coordination, spatial reference memory, and synaptic plasticity, suggesting a potential therapeutic potential of 5-HTR$_7$ agonism in therapies for this neurological disorder [174]. Recent findings in rodents suggested that antagonism of the 5-HTR$_{1A}$ assists memory retention, likely through activation of 5-HTR$_7$, which facilitate emotional memory [53].

In addition, preclinical study proposed that 5-HTR$_7$ agonists could be useful in the treatment of impaired memory associated with aging or AD [175]. Therapeutic effects of 5-HTR$_7$ agonists on cognitive symptoms in AD have also been examined in clinical trials [176]. It therefore seems that promnesic or anti-amnesic effects of both 5-HTR$_7$ agonists and antagonists depend on whether the basal performance is normal or impaired [177].

The lower expression of 5-HTR$_7$ in the hippocampus and prefrontal cortex of schizophrenia patients [178, 179], a positive association between a 5-HTR$_7$ gene haplotype and the incidence of schizophrenia [180], the affinity of several atypical antipsychotics for 5-HTR$_7$ [178, 181], and the increase of the 5-HTR$_7$ number in rats treated with typical antipsychotic haloperidol [178], all suggest the involvement of these 5-HTR in the neurobiological alterations in schizophrenia. In line with the potential contribution of 5-HTR$_7$ to cognitive dysfunction in schizophrenic patients, a preclinical study suggested an improvement in recognition memory and antipsychotic efficacy after treatment with a 5-HTR$_7$ antagonist in animal model of psychosis and cognition [182].

4. Conclusion

Evidence from the literature suggests that the 5-HTergic system plays a significant role in cognitive performance. Pro-cognitive and neuroprotective effects of 5-HT have been observed in both humans and animals [183-186]. The involvement of 5-HTR in learning and memory is consistent with high expression of those receptors in limbic areas, the prefrontal cortex and basal ganglia, which are all brain regions involved in the regulation of various cognitive processes [187] and are innervated by 5-HTergic projections from the raphe nuclei [5]. Modulatory effects of different 5-HTR on cognition are additionally mediated by interactions with other neurotransmitter systems such as cholinergic, dopaminergic, GABAergic and glutamatergic.

Although agonists and/or antagonists of 5-HTR$_{1A/1B}$, 5-HTR$_{2A/2C}$, 5-HTR$_3$, 5-HTR$_4$, 5-HTR$_6$ and 5-HTR$_7$ have a potential for the treatment of cognitive deficits in healthy elderly people and patients with AD and schizophrenia [187], results of studies attempting to identify individual 5-HTergic targets for cognitive enhancement have been somewhat disappointing.

Contradictory findings might be due to variability in the choice of protocols for training/testing, behavioral tasks and animal models, as well as drugs that were used. Moreover, dysfunction in distinct cognitive areas, observed during aging or in diseases such as schizophrenia and AD, might have different underlying mechanisms. This might suggest that subjects with different cognitive impairments could benefit from customized therapeutic strategies. As the effects of a drug on a single 5-HTR could be counterbalanced by changes in the other receptors in order to maintain homeostasis, the development of medications which act on multiple 5-HTergic targets may be more promising for treatments of cognitive impairments caused by 5-HTergic dysfunction.

An example of such a multitarget drug is the antidepressant vortioxetine [188, 189], which modulates various 5-HTergic components, acting as a 5-HTR$_3$, 5-HTR$_7$, and 5-HTR$_{1D}$ antagonist, and a 5-HTR$_{1B}$ partial agonist, a 5-HTR$_{1A}$ agonist and also a 5-HT transporter inhibitor. It produces more robust effects on cognitive function by activation of multiple neurotransmitter systems (noradrenergic, dopaminergic, cholinergic, histaminergic, etc.), or possibly some other factors such as brain-derived neurotrophic factor (BDNF), which are critical for neural plasticity and cognitive processing [13].

Overcoming the big challenges in the development of these drugs, is an extremely worthy endeavor as it would result in the substantial improvement of the quality of life of patients with age-related cognitive impairments and other diseases with a significant component of memory dysfunction, such as AD and schizophrenia. New pharmacological, genetic and epigenetic tools, including selective 5-HTR antagonists and agonists, as well as novel transgenic, molecular and neuroimaging techniques might offer important insights into the role of 5-HTergic system in cognitive performance including memory formation, amnesia, or related behavioral/psychiatric alterations. Investigating changes in the 5-HTergic and other neurotransmitter systems at a circuit level, as well as potential neurobiological markers (5-HTR protein or mRNA expression, signaling cascades, etc.) may prove particularly valuable in elucidating normal and impaired cognition and exploring the full potential of 5-HTergic drugs as cognition enhancers.

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