Relevance of 5-HT4Rs Modulation in Memory Disorders

Subjects: Pathology

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Multilevel alterations of hippocampal function have been identified as a common denominator of memory impairments in a number of psychiatric and neurodegenerative diseases. For many years, the glutamatergic and cholinergic systems have been the main targets of therapeutic treatments against these symptoms. Type 4 serotonin receptors (5-HT4Rs) is a new therapeutic target for memory disorders. To date, much of the researched information gathered by scientists from both animal models and humans converge on pro-mnesic and anti-amnesic properties of 5-HT4Rs activation.

5-HT4Rs serotonin hippocampus memory disorders therapeutic target synaptic plasticity cognition

1. Introduction

Memory impairments are a core symptom of a number of neurodegenerative diseases, such as Alzheimer's disease (AD) [1] and Parkinson's disease (PD) [2], but are also common to several psychiatric pathologies such as major depressive disorder (MDD) [3] and schizophrenia (SCZ) [4]. Whether or not this is the core symptom of these pathologies, alterations of memory function always have a severely disabling effect on a patient's everyday life. Indeed, memory function is a fundamental process which allows human beings to adapt from previous experiences and to progressively construct their unique identity [5].

Unfortunately, memory impairments remain therapeutically poorly apprehended. Over the past 30 years, only four drugs were approved to treat cognitive disorders. Initially developed in the context of AD—as the most prominent neurodegenerative disorder—the application domain of these drugs was thereafter extended to a larger number of pathologies. Among these drugs, three are acetylcholine esterase (Ach-E) inhibitors and the last is an N-methyl-D-aspartate receptor (NDMA-Rs) antagonist [6]. Regardless of their mechanism of action, they all show a limited efficacy and tolerance profile, leading to insufficient medical benefit. This contrasts with the large number of new therapeutic drug candidates tested in the field of preclinical studies, some demonstrating promising results. In 2008, over 172 drug development failures were registered in the field of AD [6]. Further, the only drug approved since 2003 was approved only very recently, with a use restricted to the United States [7].

2. Episodic Memory Function and the Hippocampal Formation

From the second half of the 20th century, case studies of patients with amnesia, as well as the development of a large number of animal models with memory disorders, enabled major breakthroughs in the understanding of the brain memory system—or how the brain stores different kinds of information. The idea of the existence of different forms of memory stems from this wealth of clinical work and fundamental studies. Often viewed as the most sophisticated, episodic memory is characterized by the capacity to re-experience a past personal event, situation or experience in the context in which it originally occurred [8]. A characteristic feature of episodic memory resides in the ability to bind together various interrelated stimuli and their spatial, temporal and conceptual relationships, to build up coherent memory representations [9]. Unfortunately, episodic memory shows the largest degree of decline in age-related cognitive impairments such as in AD [1] or even in several psychiatric contexts, such as MDD [3].

2.1. The Hippocampal Formation

Lying deep in the medial temporal lobe (MTL), the hippocampus sits at the top of a hierarchy of cortical systems in which later stages integrate information from previous ones. This allows it to build complex representations and to influence earlier stages of operations through back projections—the proper definition of episodic memory [8]. Such consideration fuels the broad consensus that the hippocampus and surrounding MTL structures play a critical role in the encoding and subsequent retrieval of new long-term episodic memories.

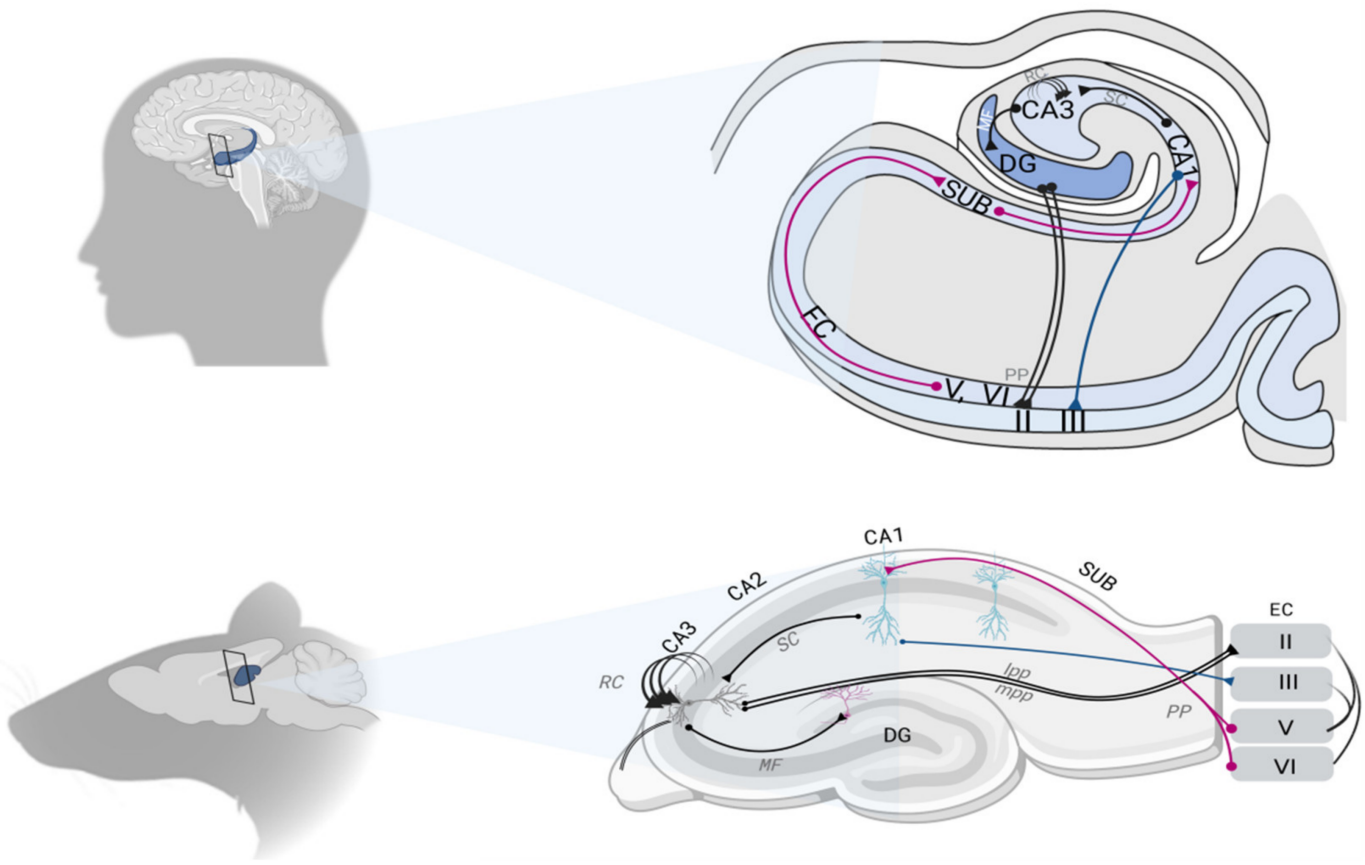
A turning point in cognitive neurosciences came from patient case studies with hippocampal damage. One of the most famous examples comes from the post-surgery follow-up of patient H.M. (Henry Molaison) that enabled the role played by the hippocampus in episodic memory to be highlighted [10]. Following these clinical observations, several animal models with lesions of distinct brain structures, notably the hippocampus, were developed. First in rodents [11][12] and then in a non-human primate species [13], all models highlighted the hippocampus as having a core role in memory function. Since then, the sheer number of studies performed in experimental models of amnesia has demonstrated the role of the hippocampus in episodic memory [14][15][16] and demonstrated its anatomo-functional specialization. Thus, the ventral (or anterior) and the dorsal (or posterior) part of the hippocampus (in rodents and primate, respectively) differ markedly in their afferences/efferences and consequently in their dedicated role [17]. The ventral hippocampus (VH) has robust efferent connections to the rostral hypothalamus and amygdala and is mostly involved in the emotional components of memory processes [18]. Hence the ventral part of the hippocampus attracts much of the work on memory impairment related to psychiatric disorders, such as anxiety-induced depression and post-traumatic stress disorder. Conversely, the dorsal hippocampus (DH) is mainly involved in spatial memory processing [19], with outputs primarily projecting to the dorsal lateral septum and the mammillary body [17]. Further, the discovery of place cells (within the CA1) [20]—which activate specifically when a person is in a precise location (spatial information)—reinforced the theory of an anatomo-functional segregation within the hippocampus.

2.2. The Hippocampal Formation Circuitry

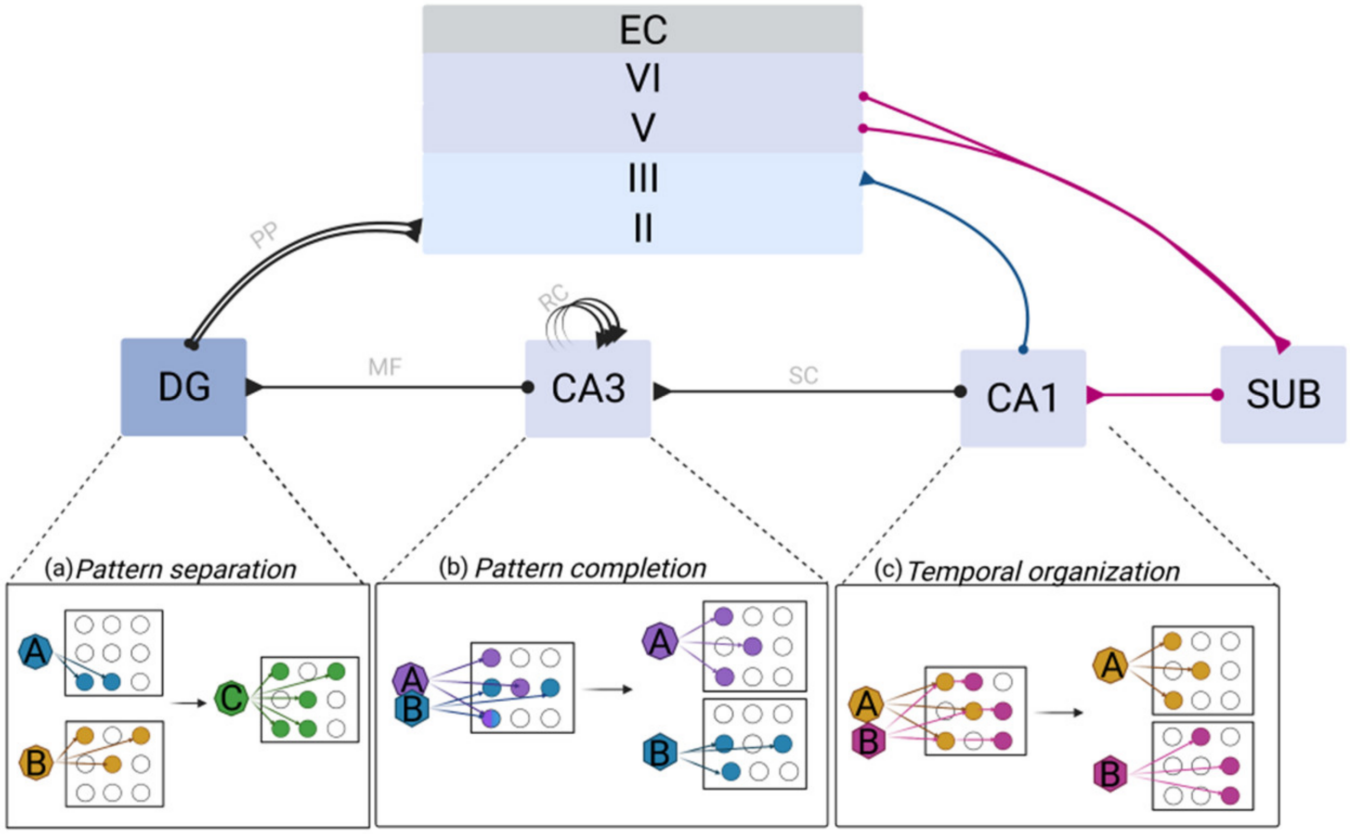
Composed of three cyto-architectonically distinct regions, i.e., the dentate gyrus (DG), the subiculum and the cornus ammonis (CA) with its three subfields (CA1, CA2 and CA3), the hippocampal formation forms a trisynaptic

loop. The entorhinal cortex (EC) is the major source of both input and output of information within the hippocampus [21].

Before being projected into the hippocampal formation through the EC, information may arise either from the parahippocampal gyrus or the perirhinal cortex, respectively encoding spatial and object representations. Mostly concentrated within the superficial layers (II-III) of the EC, this flow of information can reach the pyramidal neurons of the CA1 area by two distinct pathways. Indeed, the apical shafts of the CA1 area can be reached either directly (1/6 synapses) thus constituting the perforant path (PP), or using a tri-synaptic pathway, i.e., first passing by the DG, then the CA3 (through mossy fiber projections, MF), to finally reach CA1 through the Schaffer collateral pathway (SC). Finally, CA1 pyramidal neurons send their axons to the subiculum which flows information out to the EC, within its deep layers (V-VI) [21] (**Figure 1**A).



(**A**)



(B)

Figure 1. (**A**) Schematic representation of the location of hippocampal formation in both humans and rodents (left). Circuitry organization of the hippocampal formation in both species is depicted (right). Main inputs to the hippocampus are provided by superficial layers of the EC. Inputs converge to the CA1 through both the tri-synaptic pathway (DG, CA3 and CA1) and monosynaptic pathway, directly to the CA1 through the layer II of the EC. Recurrent collaterals (RC) of the CA3 contact other CA3 neurons and form the auto-associative network. The CA1 connection with the subiculum provides the main hippocampal outflow back to the deep layers of the EC (adapted from Small et al. 2011). (**B**). Representation of the functional specialization of each hippocampal subfield. The DG–CA3 axis is assigned to pattern separation (a), a function allowing it to disambiguate sensory inputs from similar experiences. Two similar inputs (A) and (B) are thus represented as two non-overlapping inputs. The pattern-separated signals from the DG are then projected onto the CA3 via the mossy fibers (MF) pathway. The CA3 is specialized in pattern completion (b), a process by which a partial or degraded subset (A) and (B) of the initial input can re-activate the retrieval of the whole context through a generalization process (C). The CA1 performs temporal organization of sequentially activated place cells (c). During spatial navigation, temporally close events (A→B) activate place cells in sequences that are then played out separately on a compressed time scale as a specific theta sequence (A/B). Abbreviations: CA1, CA3: cornus ammonis 1,3; DG: dentate gyrus; EC: entorhinal cortex; lpp, lateral perforant path; MF: mossy fibers; mpp, medial perforant path; PP, perforant path; SC, schaffer collateral pathway; RC: recurrent collaterals; SUB: subiculum.

2.3. Synaptic Plasticity as a Correlate of Hippocampal Memory

The unraveling of mechanisms by which the hippocampus encodes and stores information has a long history. Efforts made over the past decades of research on this topic have progressively lead to the now widely accepted synaptic plasticity and memory hypothesis: "*activity-dependent synaptic plasticity is induced at appropriate synapses during memory formation, and is both necessary and sufficient for the encoding and trace storage of the type of memory mediated by the brain area in which that plasticity is observed*" [22]. Indeed, a defining characteristic of the hippocampus is this incredible ability to undergo activity-dependent functional and morphological remodeling via plasticity mechanisms. Over a century ago, Ramón y Cajal raised the idea that the dynamics of neural circuits (i.e., the changes in the efficacy of synapse transmission) would serve memory function. He was the first to propose the cellular theory of memory storage as an anatomical change in synaptic functional connections. This foreshadowed the Hebbian theory "*cells that fire together wire together*" that led to the assumption that associative memories are formed by synaptic plasticity, driven by temporal contiguity of pre- and post-synaptic activity [23]. This appealing cellular basis for learning and memory was further supported by the discovery of long lasting potentiation of synaptic strength, now known as long term potentiation (LTP). The characteristics of LTP (cooperativity, associativity, input specificity, as well as its durability) serve as non-trivial explanations for the great capacity, rapid acquisition and stability of memory [24].

Bliss and Lomo were the first to demonstrate the existence of LTP in the hippocampus following brief trains of high-frequency stimulation (HFS-100 Hz) [25]. Following this pioneering work, thousands of papers have been published on ex vivo hippocampal LTP, using different sets of stimulating protocols [26], such as theta-burst stimulation (TBS-5 Hz). As a matter of fact, the potentiation effects have a deep relationship with rhythmic bursts of activity that mimic naturally occurring brain oscillations [27]. Respectively described as gamma -γ- (30–100 Hz) rhythms for HFS and theta -θ- (4–12 Hz) rhythms for TBS, these oscillatory frequencies are observed during spatial and contextual learning [20][28][29]. Importantly, phase-amplitude coupling between theta and gamma oscillations has been reported across species, including mice, rats, and humans. Additionally, this phase-amplitude coupling is known to play a critical role in hippocampus-dependent memory processes [30].

Further, performance in hippocampal-dependent memory tasks has been associated with changes in LTP [31][32]. Inhibitors of hippocampal LTP were found to block both learning and retention when assessed in spatial memory tasks [31][32]. Additionally, several biochemical changes that occur after induction of LTP also arise during memory acquisition [33]. Since then, LTP has become a prototypical experimental model for the assessment of basic mechanisms involved in learning and episodic-like memory formation [26].

The induction of hippocampal LTP—in almost all of its subfields—is dependent on NMDA-Rs (with the exception of the MF-CA3 which can also display a form of LTP independent of NMDA-Rs) [33]. Therefore, the critical event leading to induction of LTP is the influx of calcium ions into the postsynaptic spine upon NMDA-Rs activation. Subsequent to calcium entry is the increase in calmodulin kinase II (CaMKII) activity that contributes to enhanced AMPA conductance and new addressing to the membrane. In addition, two other major pathways that involve different protein kinases, cyclic adenosine-monophosphate (cAMP)-dependent protein kinase (PKA) and

extracellular regulated kinase (ERK), have also been identified as triggered by NMDA-Rs activation [33]. Downstream extracellular signals, including brain-derived neurotrophic factor (BDNF) have further been proposed to support the long lasting changes in synaptic function [33][34].

Nevertheless, hippocampal synaptic plasticity does not resume to LTP. Depotentiation (DP)—the reversal of LTP—and long term depression (LTD), which denotes the weakening of synapses, were also described in the hippocampus [34]. Both are necessary to specific forms of memory—also termed flexibility—that requires extinction of the obsolete memory traces, such as in the novelty recognition task [35]. These two synaptic plasticity processes are induced by low-frequency stimulation (LFS-1 Hz), which ranges around the hippocampal delta frequency band (0.5-4 Hz). Otherwise, both synaptic plasticity processes seem to rely upon similar mechanisms to LTP at a molecular level [36].

2.4. Neurotransmission Systems in the Hippocampus

Cellular events supporting learning and memory are the result of complex interactions between various neurotransmission systems. Most knowledge regarding these processes stems from the observation of the dysfunction of these systems in pathological conditions or from experiences of pharmacological manipulation [33][37]. The neurotransmitters and neuromodulators systems involved in hippocampal memory function are incontestably numerous. Of most interest, the serotonergic one is known to play a crucial role in memory processes.

3. Relevance of 5-HT$_4$Rs Modulation in Memory Disorders

5-HT$_4$Rs belong to excitatory Gαs (stimulatory alpha subunit) protein-coupled receptors (GPCR). Their activation exerts a stimulatory effect through the activation of adenylate cyclase (ADC) as a primary mode of signal transduction on cAMP concentration. This second messenger interacts with various other proteins including PKA, which is known to modulate the activation of gene expression modifying transcription factors, such as the cAMP response element-binding protein (CREB) [38]. Additionally, an intriguing aspect of metabotropic 5-HTRs is their ability to elicit non-canonical pathways that can be G-protein independent. With regard to 5-HT$_4$Rs, their activation can initiate phosphorylation of their associated non-receptor tyrosine kinase Src, which activates mitogen-activated protein kinases (MAPK) including the extracellular signal-regulated kinases (ERK) [38][39]. Quite interestingly, these molecular actors also appear to be involved in LTP. Moreover, cAMP/signaling and BDNF expression were found to be disrupted in a number of animal models of neurological disorders [40][41] and found to be enhanced after 5-HT$_4$Rs activation [40][41] (**Figure 2**). Altogether, this raises the interest of 5-HT$_4$Rs-targeting in plasticity-related memory enhancement.

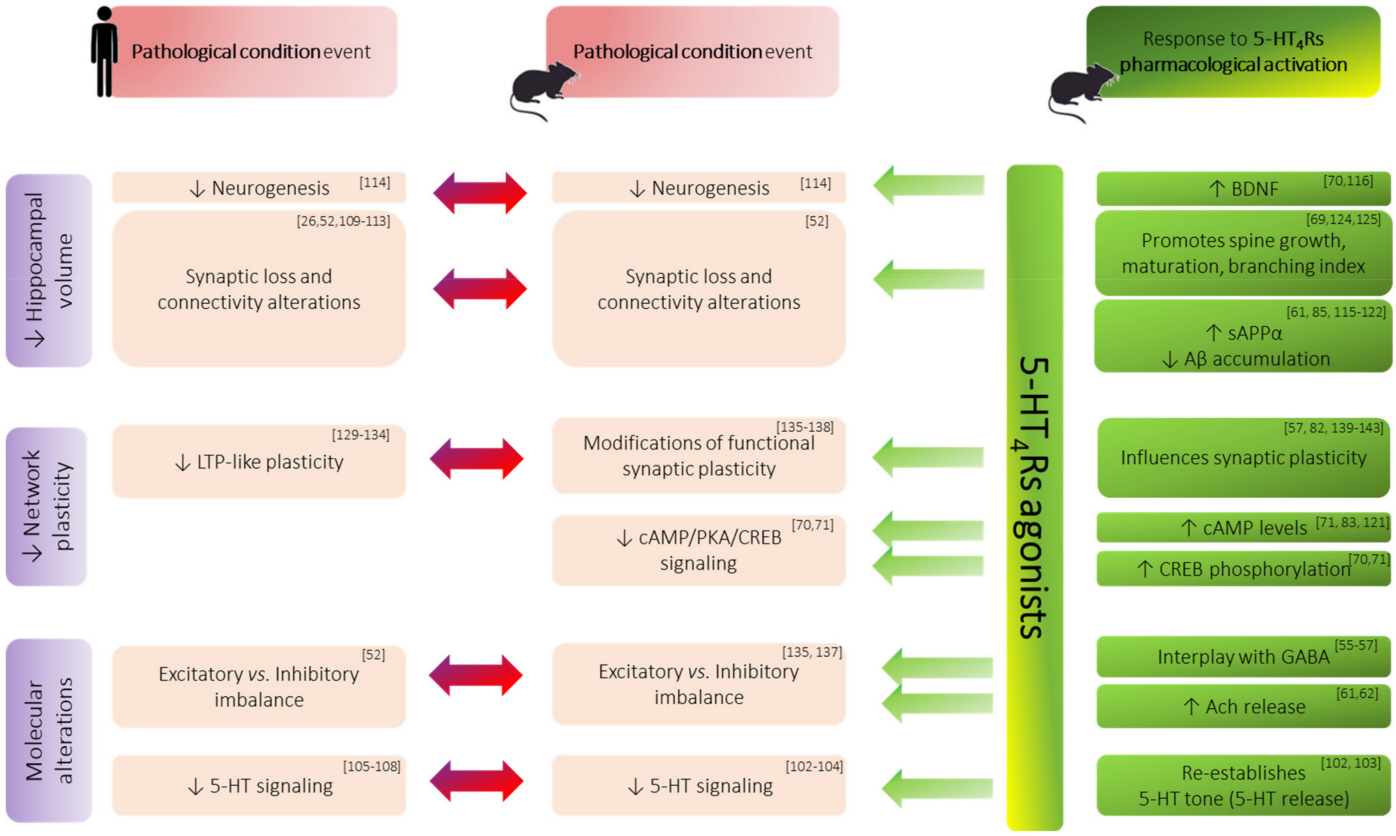


Figure 2. Summary of major hippocampal alterations (purple boxes) associated with memory impairments in both human and animal models of amnesic condition (red boxes). The beneficial effects of 5-HT$_4$Rs pharmacological activation are represented at each level of alteration (green boxes). ↑ denotes an increase; ↓ denotes a decrease. Abbreviations: Aβ: beta-amyloid peptide; Ach: acetylcholine; BDNF: brain derived neurotrophic factor; cAMP: cyclic adenosine monophosphate; CREB: cAMP response element-binding protein; GABA: gamma-aminobutyric acid; LTP: long-term potentiation; PKA: protein kinase A; sAPPα: soluble alpha-amyloid precursor protein; 5-HT: serotonin; 5-HTR: serotonin receptor.

3.1. Insights from Animal Behavior Investigations

The idea that 5-HT$_4$Rs agonists are promising drug candidates for memory impairments—especially those related to hippocampal dysfunction—was firstly supported by behavioral studies on different animal models [42][43]. On one hand, cognitive impairments were often reported following antagonism (either pharmacologic agent or optogenetic construct) of 5-HT$_4$Rs [44]. Surprisingly, the genetic ablation of 5-HT$_4$Rs did not alter learning and memory capacities in mice. However, the deleterious effect of scopolamine (a cholinergic antagonist) on long term memory was enhanced in 5-HT$_4$Rs KO mice [45]. On the other hand, a very large number of preclinical studies reported consensual data supporting the beneficial effects of 5-HT$_4$Rs activation on memory performance. Overall, administration of 5-HT$_4$Rs agonists increased the learning rate in a hippocampus-dependent spatial task, such as the MWM [46] and the object recognition test [47][48][49]. 5-HT$_4$Rs agonists also restored memory impairments in animals treated with cholinergic antagonists [50][51][52], in aged animal [47][53] and in transgenic models of neurological diseases [54][55]. Additionally, it was recently reported that intra-hippocampal injection of a 5-HT$_4$Rs

agonist reduced sleep deprivation-induced memory impairments [56]. These behavioral effects of 5-HT$_4$Rs modulation were extensively reviewed [43][57]. Likewise, chronic 5-HT$_4$Rs activation was found to counterbalance learning and memory deficits induced by stress-induced depression [3].

Additionally, 5-HT$_4$Rs have also been considered as an associative target of choice. Indeed, given the multidimensional and complex aspect of the pathogenesis of memory disorders, a new approach has emerged that consists of the simultaneous modulation of more than one target. After having proved the efficacy of 5-HT$_4$Rs stimulating activity in co-administration protocols with different AchE inhibitors [48][58], the first multi-target drug ligand (MTDL) associating both activities has been designed. Named as Donecopride, this drug candidate was mainly developed for application in the field of AD [59]. Indeed, these promising results argue for the development of other MTDLs combining 5-HT$_4$Rs agonistic activity with a different secondary target (other than AchE inhibitor) to be used for different medical application [60].

These observations constitute the first line of evidence for an interest in 5-HT$_4$Rs activation in disorders related to hippocampal dysfunction. However, a limitation of preclinical research has certainly been the lack of investigation of 5-HT$_4$Rs' functional and/or expression alteration in animal models that display memory deficits [61]. In order to clarify if 5-HT$_4$Rs changes are causative or involved in the etiology of diseases, their expression pattern needs to be assessed on a cellular level in preclinical models.

3.2. Distribution of 5-HT$_4$Rs in CNS and Memory Disorders

The distribution of 5-HT$_4$Rs within the brain is mainly restricted to the limbic system, thus intimately tied to memory function. The highest 5-HT$_4$Rs mRNA levels and densities are found in caudate, putamen, accumbens, and in the hippocampal formation [62][63][64]. Within the hippocampal formation, the highest expression is found in the granule cell layer of the DG, followed by the pyramidal cell layer of the CA. Further, 5-HT$_4$Rs exhibit a layered distribution within CA subfields, with the highest densities identified in the stratum oriens and stratum radiatum. This suggests a localization of receptors at both basal and apical dendritic fields of pyramidal cells. Radio-ligand assays also show strong labelling in the stratum lucidum of the CA3 area, probably reflecting the presence of 5-HT$_4$Rs on MF [65][66].

Ligand binding studies also help to reinforce the idea that 5-HT$_4$Rs play a pivotal role in memory function. In fact, the hippocampal density of 5-HT$_4$Rs was found to be inversely correlated with episodic memory test performance in healthy subjects [67]. Further, it has also been observed that a striking feature of aging is the dramatic decrease in 5-HT$_4$Rs density that occurs [63][68]. Likewise, the loss of 5-HT$_4$Rs expression was also observed in different cohorts of patients suffering from memory deficits [61][69] and was correlated with the stage of the disease. For instance, a post-mortem brain analysis in AD patients reported a 70% decrease in hippocampal 5-HT$_4$Rs [70], a change that was positively correlated to amyloid beta peptide load [68]. Additionally, reduced 5-HT$_4$Rs binding was observed in the hippocampus in an animal model of depression [71] (**Figure 2**).

Moreover, it has been proposed that improvement of memory performance in patients who suffer from memory disorders is supported by up-regulation of 5-HT$_4$Rs, which in turns stimulates hippocampal 5-HT release as shown

in rodents [72][73] (**Figure 2**). Indeed, there is now a large body of preclinical data showing a dynamic positive correlation between central 5-HT levels and 5-HT_4Rs densities. For instance, 5-HT_4Rs KO mice have diminished tissue levels of 5-HT (and its main metabolite, 5-HIAA) [74]. Hence, 5-HT_4Rs activation could enhance 5-HT global tone through the positive feedback loop projecting from the prefrontal cortex to the DRN and thus, to the hippocampus [61]. If so, this could account for the variation of 5-HT_4Rs expression observed in AD. Indeed, an upregulation of 5-HT_4Rs expression occurs at the pre-clinical stage of the disease and continues along with dementia progressing (up to mild stage), as if a compensatory strategy was put in place (in response to decrease in interstitial 5-HT levels), until exhaustion [68]. Indeed, the loss of serotonergic cells in AD patients can reach above 70% in the DRN and MRN [75] and can even be reduced to undetectable levels [76][77]. This ultimately contributes to a decrease in hippocampal 5-HT neurotransmission, which has been identified as a correlate of cognitive impairment [78] (**Figure 2**). Altogether, the changes in 5-HT_4Rs density may reflect the abnormal range of 5HT levels required for memory functioning. Hence, the clinical stage of the disease during which 5-HT_4Rs may be used appears critical.

3.3. Morphological/Structural Alterations of Hippocampal Formation in Memory Disorders

Although a host of brain changes are likely to be responsible for cognitive decline, structural and functional hippocampal alterations were identified as one major correlate. Therefore, magnetic resonance imaging (MRI) scan has become one of the most common markers associated with cognitive scales performed in aging studies or in clinical practice to measure brain disease burden [79]. Whilst hippocampal atrophy is an important imaging correlate of memory impairments observed in numerous brain disorders, its pattern of alteration may vary according to the disease and the stage of the disorder.

For instance, within hippocampal formation, the EC appears to be most resistant to the effects of normal aging, as changes are mainly restricted to the DG and CA3. In contrast, the EC is most vulnerable to AD while the DG and CA3 remain relatively preserved. With regard to the CA1 area and the subiculum, they are mainly affected in SCZ and MDD respectively. Unlike AD, no prominent cell loss has been identified in aging, SCZ and MDD, suggesting rather, functional alterations such as connectivity dysfunction [79]. Consistently, an MRI-based study using diffusion tensor imaging to detect dendritic integrity revealed age-related alterations of DG and CA3 dendrites in aged patients [80] (**Figure 2**). Nevertheless, the measure of hippocampal volume was found to be sensitive enough to aging and to neurodegenerative and psychiatric disorders. For instance, after the age of 70, total hippocampal volume is believed to decrease at a rate of ~1.5% a year [81]. Additionally, hippocampal volume loss has been shown to reach 10 to 15% in mild cognitive impaired (MCI) patients [81]. Patients suffering from schizophrenia, PD or depression also exhibit hippocampal volume reduction of 4–6% relative to healthy subjects [82][83][84].

Of most interest, several lines of evidence now support that 5-HT_4Rs agonists could limit such hippocampal deterioration at different levels, notably in AD context.

First, the above reported hippocampal volume loss—either due to aging or pathological condition—can be compensated, at least partly, through neurogenesis boost, which is altered in various neurological and psychiatric diseases [85]. However, it has been shown that sub-chronic treatment with 5-HT_4Rs agonists induced an increase in

BDNF expression in the CA1 (72%) as well as in the DG (52%), this latter demonstrating a neuro-proliferative activity [40]. Further, increased levels of other neurotrophic factors have also been reported after 5-HT_4Rs agonist treatment, such as the soluble (non-amyloidogenic) form of the amyloid precursor protein alpha (sAPPα) (**Figure 2**). The functions of sAPPα include—but are not limited to—proliferation, neuroprotection, synaptic plasticity, memory formation, neurogenesis and neuritogenesis in cell culture and animal models. Quite interestingly, sAPPα production was found to be promoted following acute [86] and chronic 5-HT_4Rs activation in various conditions that include cell lines overexpressing 5-HT_4Rs (50% increase) [87][88][89][90][91] as well as neuroblastoma cell line [87], and cultured neurons from a mouse model of AD [55][92][93][94]. A similar effect was observed in vivo both in healthy mice (2-fold increase) [86] and in AD mice models (1.5-fold increase) [54][55]. In the context of AD, the effects of 5-HT_4Rs activation on sAPPα production would confer an additional benefit though a reduction in amyloid load (31–55% in a mouse model of AD [54][55]) by limiting the amyloidogenic pathway. Indeed, accumulation of neurotoxic Aβ in key hippocampal regions appears to be the primary cause of neuronal death leading to hippocampal atrophy [95] (**Figure 2**).

Second, additional data supporting the putative role of 5-HT_4Rs in preserving hippocampal integrity come from studies focusing on dendritic spines hosting excitatory synapses. The latter are dynamic structures, whose formation, shape, volume and collapse depend on neural activity. Therefore, they influence (but also can in return be influenced) the learning processes and memory performance [15]. In mice, pharmacological activation of 5-HT_4Rs was shown to selectively potentiate the learning-induced dendritic spines' growth (+6%) within the hippocampal CA1 (**Figure 2**). This was not found in other brain structures that are not as much implicated in memory processing (i.e., primary visual cortex) [39]. Moreover, in a recent study using high resolution time lapse FRET imaging on neuronal dendrites, 5-HT_4Rs activation was found to prompt maturation of synaptic connections via the 5-HT_4R/G13/RhoA signaling cascade [96]. By activating PKA and BDNF/TrkB signaling pathways, 5-HT_4Rs activation also promoted total dendritic length, number of primary dendrites and branching index in vitro [97]. Since spines represent potential sites of postsynaptic excitatory input, boosting their growth and maturation may translate into an increase in the number of excitatory synapses.

Finally, it is worth mentioning that reactive astrocytes are found both in human AD patients and AD mice models. Post-mortem morphological brain studies demonstrate close interaction between astrocytes and Aβ deposition in AD patients. In fact, reactive astrocytes are thought to be involved in Aβ production by upregulating β-secretase activity and APP in the diseased brain [98]. In this way, any strategy that would participate in a reduction in astrogliosis may substantially contribute to a reduction in Aβ load and subsequent neuronal loss. IL-1β and MCP-1 are two key pro-inflammatory mediators involved in glial reactivity whose levels have been found to be reduced by 30% to 45% following chronic 5-HT_4Rs activation in an early onset mouse model of AD [54]. Consequently, astrogliosis and microgliosis were reduced by 50–60% and 57% respectively in the EC, an area of the hippocampal formation that is particularly susceptible to degeneration in AD, as previously discussed [54][55]. Of note, astrogliosis reduction was even more pronounced with a longer duration of 5-HT_4Rs agonist treatment [55]. Hence, 5-HT_4Rs modulation could modify AD pathogenesis by targeting inflammatory pathways in glial cells.

The demonstration of such beneficial effects of 5-HT_4Rs ligands holds promise for the development of disease-modifying drugs, which represents a yet unmet medical need. Of course, upstream correction of the pathological drivers of the disease is crucial to significantly improving the downstream symptoms and to prevent progressive cognitive deterioration. To date, preclinical studies that showed beneficial effects of 5-HT_4Rs on hippocampal function have been mainly performed in either non-pathological conditions or in experimental models of the disease (cell lines or animal models). However, it seems important to stress that the pathology of AD shares a number of hippocampal alterations with ageing, SCZ, MDD and PD as discussed above. This ultimately raises the hope for potential translation of such beneficial effects of 5-HT_4Rs in a large number of brain diseases.

3.4. Functional Synaptic Plasticity Impairments

Considered as the cellular support of memory, LTP has received much attention in the search for a better understanding of the mechanisms involved in memory disorders. Veritably, impairment of hippocampal synaptic function is often considered as an early detectable feature of aging and/or pathological stage, well before the first memory symptom appearance or before the observation of hippocampal atrophy.

Downregulation of plasticity-related proteins such as cAMP and CREB have, for instance, been observed in the hippocampus of both animal models of AD, and AD patients [99]. In this regard, there is accumulating evidence for a beneficial action of 5-HT_4Rs agonists on cAMP/CREB signaling. Consistently, increases in both cAMP and CREB levels as well as the phosphorylated form (active form) of CREB (pCREB) were found both in healthy rats [40] and the neuroblastoma cell line [93] following 5-HT_4Rs activation.

However, the effects of 5-HT_4Rs modulation on synaptic plasticity have been little studied, with only eight studies performed between 2001 and present, and results varying according to the hippocampal subfield investigated (**Table 1**).

Table 1. Compilation of electrophysiological investigations of synaptic plasticity in rodents after pharmacological 5-HT_4Rs activation.↑ denotes an increase; ↓ denotes a decrease; = denotes no change. Abbreviations: CA1, CA3: cornus ammonis 1,3; DG: dentate gyrus; DP: depotentiation; HFS: high frequency stimulation; LTD: long term depression; LTP: long term potentiation; LFS: low frequency stimulation; SUB: subiculum; TBS: theta burst stimulation.

Method	Hippocampal Area	Plasticity	Conditioning Stimulus	5-HT_4Rs Agonist	Effects of 5-HT_4Rs Activation on Plasticity	Reference
In vivo	DG	LTP	HFS (200 Hz)	RS67333	↓	Kulla and Manahan-Vaughan.2002

Method	Hippocampal Area	Plasticity	Conditioning Stimulus	5-HT_4Rs Agonist	Effects of 5-HT_4Rs Activation on Plasticity	Reference
		LTP	HFS (200 Hz)	5-Methoxytryptamine	=	
		LTP	HFS (10 × 400 Hz)	RS67333	Transient ↑ and curtailed	Marchetti et al. 2004
		LTP	HFS (200 Hz)	RS67333	Curtailed	Twarkowski et al. 2016
		DP	LFS (5 Hz)	RS67333	Blocked	
		LTD	LFS (1 Hz)	RS67633	↓	
	CA3	LTP	HFS (4 × 100 Hz)	RS67333	↓	Twarkowski et al. 2016
		LTD	LFS (1 Hz)	RS67333	↓	
		LTP	HFS (5 × 400 Hz)	SC53116	↑	Matsumoto et al. 2001
	CA1	LTP	HFS (4 × 100 Hz)	RS67333	=	Kemp and Manahan-Vaughan 2005
		LTD	LFS (1 Hz)	RS67333	↓	
Ex vivo	CA1	LTP	HFS (1 × 100 Hz)	RS67333	=	Lecouflet et al. 2020

Method	Hippocampal Area	Plasticity	Conditioning Stimulus	5-HT$_4$Rs Agonist	Effects of 5-HT$_4$Rs Activation on Plasticity	Reference
		LTP	TBS (4 × 5 Hz)	RS67333	↓	
	SUB	LTP	HFS (4 × 100 Hz)	RS67333	=	
		LTD	LFS (1 Hz)	RS67333	↑	Wawra et al. 2014

These data support the fact that 5-HT4Rs, through their modulatory effects on synaptic plasticity processes, will enable the hippocampus to ensure its filtering role of information during acquisition and more variable changes in the downstream areas. This perspective seems consistent with clinical data that suggest that an increased signal-to-noise ratio within the hippocampus improves the encoding accuracy, a function which is thought to be mainly supported by the DG, where 5-HT4Rs are most abundantly expressed [102].

4. Concluding Remarks and Future Perspectives

Overall, arguments to consider 5-HT4Rs as a target of choice for the treatment of memory impairments mainly stem from preclinical evidence. In fact, only a few experiments were performed on humans.

Nonetheless, quite recently, SUVN-D4010, a novel, potent, highly selective 5-HT4Rs partial agonist intended for the treatment of cognitive disorders, was found to be safe and well tolerated in healthy human subjects, even in elderly population (Suven Life Sciences, NCT02575482 and NCT03031574). Lastly, the results published last year regarding prucalopride dose also got our interest. Indeed, while already approved by the FDA in 2018 to treat chronic idiopathic constipation, prucalopride was investigated in a battery of cognitive tests related to hippocampal functions. In healthy human subjects, prucalopride showed beneficial effects on learning and memory performance (NCT03572790) [100] and is currently under investigation for its role in depression. Evidence for improved memory performance after 5-HT4Rs activation in humans was extended by a very recent fMRI study. Following prucalopride intake, hippocampal activity during memory recall was significantly increased compared with volunteers receiving a placebo [101].

The use of 5-HT4Rs ligands in the treatment of memory deficits is still an ongoing challenge but has long been—and still unfortunately is, restricted to AD and MCI. However, a number of functional and morphological changes within the hippocampus are a common denominator of a broader range of both normal ageing and neurological

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diseases (such as PD, MDD, SCZ). A large amount of data from both animal models and humans have now reached a consensus on the fact that 5-HT4Rs activation can attenuate some of these hippocampal dysfunctions. This ultimately raises the exciting potential of restoring—or at least limiting—memory decline in these pathologies. Nevertheless, a deeper understanding of the mechanisms at work is still needed and would help further development. In this view, studies that investigate 5-HT4Rs effects on hippocampal function in a more integrated view should provide substantial insights.

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