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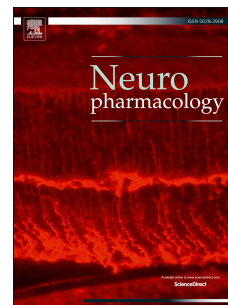
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Neuropharmacology

Hippocampal 5-HT_{1A} receptor expression changes in prodromal stages of Alzheimer's disease: beneficial or deleterious?

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Short title: 5-HT_{1A} receptors in early stages of Alzheimer's disease

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ABSTRACT

There is increasing evidence that the serotonergic system is highly dysfunctional in Alzheimer's disease (AD), and this could be related to cognitive impairments associated with dementia. Of the various serotonin receptors, 5-HT_{1A} receptors are relevant to AD as they are highly expressed in the human hippocampus and are known to be involved in the regulation of memory processes. This review will discuss the involvement of 5-HT_{1A} receptors in AD at several levels (*post-mortem*, *in-vivo* imaging, animal models). The involvement of this receptor subtype in AD pathophysiology will be reviewed particularly in terms of the modulation of its expression in the hippocampal region. Hypotheses involving 5-HT_{1A} receptors will be developed, from two points of view: 5-HT_{1A} receptors expression regulation as being beneficial and needing to be pharmacologically stimulated; and 5-HT_{1A} receptors expression modulation as deleterious and needing to be limited. Finally, we will propose perspectives for future experiments that should weigh in favor of one or the other of the two hypotheses.

Keywords: 5-HT_{1A} receptors, hippocampus, serotonin, Alzheimer's disease, reactivity, PET, fMRI, animal model, prodromal.

INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative disease associated with specific histopathological markers, including extracellular deposits of amyloid-beta ($A\beta$), intraneuronal accumulation of neurofibrillary tangles composed of abnormal hyperphosphorylated tau filaments (Duyckaerts et al., 2009), synaptic loss and neuronal death. AD-related neurodegeneration severely affects the neurochemistry of the brain. Although AD primarily affects the cholinergic system, other neurotransmitter systems are also implicated, including norepinephrine (NE), dopamine (DA) and serotonin (5-HT) (Dringenberg, 2000; Lai et al., 2002). Drugs that enhance cholinergic function have only modest success in treating cognitive deficits associated with AD, further implicating the involvement of other neurotransmitter systems. There is increasing evidence that the serotonergic system is highly dysfunctional in AD, and this could be related to several clinical symptoms of dementia (Ramirez et al., 2014).

Serotonin 5-HT_{1A} receptors (or 5-HT_{1A}R) are particularly relevant to AD as they are highly expressed in the human hippocampus and are known to be involved in the regulation of memory processes (Ogren et al., 2008). The role of serotonin (5-HT) in the memory deficits mediated by hippocampal function in AD is of ongoing relevance in view of the central role of 5-HT in control of cognition and the primary influence of 5-HT_{1A}R in controlling serotonergic neurotransmission. In line with hypotheses of 5-HT_{1A}R involvement in cognitive processing, particularly in AD (Bowen et al., 1994), 5-HT_{1A}R antagonists have been developed with the therapeutic aim of enhancing cognitive capacity, although no positive results have been reported in clinical trials (Schechter et al., 2005). While one study reported benefit of 5-HT_{1A}R agonists in treating non-cognitive symptoms in patients with dementia (Sato et al., 2007), converging preclinical and clinical results are still awaited to confirm the therapeutic promise of 5-HT_{1A}R targeting in AD (Ramirez et al., 2014; Rodriguez et al., 2012). Indeed, discordant evidence points to both a beneficial and a deleterious role of 5-HT_{1A}R. Multiple drugs with serotonergic properties are currently being clinically tested in AD patients (Declercq et al., 2016). Examples include selective serotonin reuptake inhibitors (SSRIs), which have indirect 5-HT_{1A}R agonist properties (Declercq et al., 2016), and more recent drugs such as the antipsychotic brexpiprazole, and the antidepressant vortioxetine, both of which possess direct 5-HT_{1A}R agonist properties. The

question of whether 5-HT_{1A}R activation is desirable or to be avoided is, therefore, of considerable current relevance.

The present article will discuss the involvement of 5-HT_{1A}R in AD at several levels (*post-mortem*, *in-vivo* imaging, animal models). The goal is, firstly, to describe how this receptor subtype is implicated in AD pathophysiology and, secondly, to put forward suggestions for how its particular expression modulation in the hippocampal region can be studied in greater detail. We will develop hypotheses implicating 5-HT_{1A}R expression regulation, from two points of view: that 5-HT_{1A}R regulation of expression is beneficial, and needs to be encouraged; and that modifications of 5-HT_{1A} expression are deleterious, and need to be inhibited. Finally, we will set out perspectives for future experiments that should weigh in favor of one or the other of the two hypotheses.

5-HT_{1A} RECEPTORS IN NORMAL AGING AND IN AD PATIENTS

Normal aging

Alterations of the 5-HT system in normal aging occur at multiple levels including changes in (i) density of 5-HT neurons in the raphe nuclei, (ii) 5-HT metabolism, (iii) density of 5-HT projections, (iv) expression of 5-HT uptake transporter and (v) expression of 5-HT receptors (Meltzer et al., 1998). *In vitro* autoradiographic studies that reported age-related decrease in 5-HT_{1A}R density in human brain used radioligands ([³H]5-HT, [³H]8-OH-DPAT) that were not solely specific to 5-HT_{1A}R (Dillon et al., 1991; Marcusson et al., 1984) which makes their interpretation less conclusive regarding 5-HT_{1A}R. *In vivo* PET studies using the selective 5-HT_{1A}R antagonist [¹¹C]WAY100635 as radioligand found either an age-related decline in 5-HT_{1A}R binding potential (Tauscher et al., 2001) or no changes (Parsey et al., 2002). Despite some discrepancies in part attributable to methodological differences, the general tendency is toward a global age-related decline in 5-HT_{1A}R (including hippocampus), making careful age-matching recommended for any studies looking at 5-HT_{1A}R level of expression.

AD patients

In addition to a reduced number of 5-HT neurons in the raphe nuclei and compromised 5-HT neurotransmission, AD-related changes in several 5-HT receptors has been observed including 5-HT_{1A}R, 5-HT_{1B}R, 5-HT_{1D}R, 5-HT_{2A}R and 5-HT₆R (Rodriguez et al., 2012). Binding studies of *post-mortem* AD brains, using non-selective 5-HT_{1A}R radioligands like [³H]5-HT (binding to all 5-HT receptors) or the agonist [³H]8-OH-DPAT (binding to 5-HT_{1A}/5-HT₇ receptors), reported either no AD-related changes in temporal cortex, neocortex and the hippocampus (Lai et al., 2003; Tsang et al., 2010) or an increase in the frontal cortex (Lai et al., 2002). Focusing specifically on 5-HT_{1A}R in AD patients, immunohistochemical studies reported specific decreases in 5-HT_{1A}R in the hippocampus (Mizukami et al., 2011) and in the dorsal raphe nucleus (Yeung et al., 2010). These studies supported earlier suggestions that 5-HT_{1A}R are affected at the late-stage of AD pathology (Cross et al., 1984), since severe decrease in 5-HT_{1A}R immunoreactivity were observed only in patients at late Braak stages V-VI for both studies (Mizukami et al., 2011; Yeung et al., 2010) (**Table 1**). *In vitro* autoradiography of AD brain specimens with [¹⁸F]MPPF, a selective 5-HT_{1A}R antagonist, showed up to 60% decreases of binding sites in the hippocampus in comparison to the control group (Kepe et al., 2006). AD patients with pronounced decrease in their hippocampal 5-HT_{1A}R density had more severe disease progression as measured by mini mental state examination (MMSE) (Kepe et al., 2006). Binding studies using 5-HT_{1A}/5-HT₇ receptors agonist [³H]8-OH-DPAT showed that reduced temporal cortex binding correlated with aggressive behavior (Lai et al., 2003) and reduced hippocampal binding correlated with depressive symptoms in AD patients (Lai et al., 2011). Despite some inconsistencies, the majority of studies assessing 5-HT_{1A}R status in *post-mortem* brains of AD patients reported decreased 5-HT_{1A}R density. Other receptors do not show a decline in density like 5-HT_{1A}R and reinforce the argument that the observed 5-HT_{1A}R effects are pathophysiologically significant (Nordberg, 1992).

Post-mortem studies were either looking at AD patients at advanced stages of dementia or the neuropathological status of the patients was not systematically taken into account. Our lab has taken a slightly more advanced approach with the aims of (i) looking at 5-HT_{1A}R in *post-mortem* brains of different groups of patients representing the continuum of progression towards AD, and (ii) assessing, in these patients, the level of expression of different sub-groups of 5-HT_{1A}R thanks to the use of complementary radioligands. As G-protein-coupled receptors (GPCR), 5-HT_{1A}R have been shown to exist in different states (Mongeau et al., 1992): a high-affinity state for

agonists, (effective receptor/coupled G-protein, supposedly active), and a low affinity state (uncoupled G-protein, non-functional). Our neuropharmacological hypothesis was that an agonist radiotracer (like [^{18}F]F15599 or [^{18}F]F13640), that preferentially labels functional G-protein-coupled 5-HT_{1A}R, would detect a different profile of 5-HT_{1A}R modifications during AD in comparison to an antagonist radiotracer (like [^{18}F]MPPF) which labels the entire 5-HT_{1A}R population (functional and non-functional receptors). These studies revealed an early (Braak I-II-III) hippocampal cornu amonnis 1 (CA1) decrease in functional 5-HT_{1A}R when the entire 5-HT_{1A}R population was not affected yet. It was proposed that the coupling state of 5-HT_{1A}R was altered before the loss of receptors themselves in AD (Becker et al., 2014). Another observation was that, at early stages (Braak I-II), when functional 5-HT_{1A}R were under-expressed in CA1, there was a concomitant overexpression of the entire 5-HT_{1A}R population in the dentate gyrus (DG) that was correlated with an increased neuronal density (reflected by NeuN counting) (Vidal et al., 2016). These results pointed to early pathophysiological mechanisms in the course of disease progression towards AD that are affecting the 5-HT_{1A}R in specific sub-regions of the hippocampus (**Table 1**).

In vivo PET studies using [^{18}F]MPPF in AD patients at mild to severe dementia stage were mostly consistent with AD-related decreases in 5-HT_{1A}R binding sites in raphe nuclei and the hippocampus (Kepe et al., 2006; Truchot et al., 2007). Concerning the prodromal MCI stage of the disease (approximately corresponding to Braak stage III-IV (Markesbery, 2010)), three PET imaging studies with [^{18}F]MPPF reported divergent alterations in 5-HT_{1A}R binding sites (Kepe et al., 2006; Truchot et al., 2008; Truchot et al., 2007). The initial report demonstrated a decrease in hippocampal 5-HT_{1A}R binding sites (Kepe et al., 2006). Subsequent studies by Truchot and colleagues demonstrated either an increase in hippocampal 5-HT_{1A}R binding sites when applying partial volume effect correction (Truchot et al., 2007), or an increase tendency that did not reach significance when using a statistical parametric mapping (SPM) analysis with hippocampal atrophy as covariate (Truchot et al., 2008). Due to limited spatial resolution (~ 4-5 mm *in vivo*), the accuracy of binding potentials measured by PET imaging techniques can be affected by partial volume effects. Partial volume effect is thus particularly important in the case of AD which is associated with severe cortical and hippocampal atrophy. It is likely that the difference between the reported studies may be due to inclusion of a partial volume effect correction to compensate for hippocampus atrophy (Truchot et al., 2007). In addition, the

members of the control group used in the initial PET study (Kepe et al., 2006) were of a younger age compared to the patients with MCI, which may account for the difference between studies, especially in view of the previously reported age-associated decreases in hippocampal 5-HT_{1A}R binding (Dillon et al., 1991; Marcusson et al., 1984) (**Table 1**).

5-HT_{1A} RECEPTORS IN ANIMAL MODELS OF AD

Transgenic mouse models of AD

In old (15 months) Tg2576 mice, *in-vitro* autoradiography using [¹⁸F]Mefway, a 5-HT_{1A}R antagonist radioligand, reported a decrease in 5-HT_{1A}R in the hippocampus and cortex (Saigal et al., 2007) in comparison to wild-type age-matched mice. *In-vitro* autoradiography using [¹⁸F]Mefway in triple transgenic (3xTg) AD mice found a progressive decline in 5-HT_{1A}R in the hippocampus, starting as early as 1 or 2 months of age and peaking at 18 months (Saigal et al., 2007). No changes were apparent in the cortex at 1 or 2 months, but decreases were observed at 18 months (Saigal et al., 2007). This decrease in 5-HT_{1A}R expression is in accordance with results obtained in AD patients at the dementia stage. However, preclinical *in-vitro* autoradiography studies targeting 5-HT_{1A}R status in these transgenic mice models of AD did not find the early serotonergic hyperactivity observed in human MCI patients *in-vivo* and *in-vitro* (Kepe et al., 2006; Truchot et al., 2008; Truchot et al., 2007; Vidal et al., 2016). It is possible that finer sub-regional 5-HT_{1A}R changes were not detected by these studies because they only looked at global hippocampal variation (**Table 1**).

A β -injected rat model of AD

Using a rat model of AD, we demonstrated that A β 40 fibrils stereotaxically injected in rat hippocampus were able to trigger a transient overexpression of 5-HT_{1A}R on *in-vitro* [¹⁸F]MPPF autoradiography (Verdurand et al., 2011; Verdurand et al., 2016). This effect was accompanied by a moderate rate of neuronal death of granular neurons (NeuN immunostaining), no change in neurogenesis (DCX immunostaining), and moderate astroglial reaction (GFAP immunostaining) (Verdurand et al., 2016). Injecting the more neurotoxic isoform A β 42 fibrils (Klein et al., 1999) increased neuronal death, decreased neurogenesis and strengthened astroglial reaction, but did not trigger any modifications in 5-HT_{1A}R, although a decreased expression could have been expected

as an indirect measure of neuronal death (Verdurand et al., 2016). This absence of decreased 5-HT_{1A}R expression after A β 42 fibril injection could be interpreted as a balance between compensating overexpression of 5-HT_{1A}R and strong neurotoxic effects. Overall, our studies revealed a transient 5-HT_{1A}R overexpression that resemble the hippocampal 5-HT_{1A}R increased expression observed in the prodromal phase of AD patients (MCI) *in vivo* (Truchot et al., 2008; Truchot et al., 2007) and *in vitro* (Vidal et al., 2016) (**Table 1**).

A POTENTIAL LINK BETWEEN 5-HT_{1A}R EXPRESSION AND NEURONAL ACTIVITY IN AD?

In AD patients

As mentioned above, several authors focusing on 5-HT_{1A}R status observed early hippocampal overexpression at the MCI stage, followed by loss of receptors at advanced stages of the disease. Interestingly, functional magnetic resonance imaging (fMRI) studies have shown early hippocampal activity in the prodromal stages of AD that parallels *in-vivo* PET studies of 5-HT_{1A}R. The fMRI blood oxygen level dependent (BOLD) signal is an indirect reflection of neuronal activity (both excitatory and inhibitory) that depends in a complex way on combined physiological changes in blood flow and oxygen metabolism. Several fMRI studies reported elevated hippocampal activation under a number of conditions that entail risk of AD, including cognitively normal carriers of the Apo ϵ 4 allele (Bookheimer et al., 2000; Dennis et al., 2010), presymptomatic carriers of genetic mutations for familial AD (Quiroz et al., 2010), patients with amnesic mild cognitive impairment (aMCI), although patients with late aMCI and early AD showed reduced hippocampal activity (Ewers et al., 2011). In early aMCI, in which memory is poorer than expected for a person of the same age, it was suggested that this increased hippocampal activation has a beneficial compensatory function by recruiting additional neural resources. An alternative view is that excess activation directly contributes to memory impairment and may be tied to widespread degenerative processes in prodromal AD (Putcha et al., 2011). A link can be made between hippocampal activation and 5-HT_{1A} heteroreceptors located in this areas, known to inhibit the firing rate of both excitatory glutamatergic granule (DG) and pyramidal (CA1, CA3) neurons and GABAergic inhibitory interneurons. Activation of

5-HT_{1A}R in the hippocampus would thus result in contrasting effects; (i), direct inhibition of glutamatergic neurons resulting in overall reduction of hippocampal network activity but also (ii), indirect excitation of glutamatergic cells, through disinhibition of GABAergic neurotransmission and resulting in overall increase in hippocampal network activity. Moreover, given that the fMRI BOLD signal is sensitive to both excitatory and inhibitory neuronal activity, 5-HT_{1A}R modulation could result in fMRI BOLD signal increase or decrease at the hippocampal network level.

In animal models of AD

In 2006, high levels of A β were shown to elicit epileptiform activity and non-convulsive seizures in neocortical and hippocampal networks of human amyloid precursor protein (hAPP) transgenic mice (Palop et al., 2007). Epileptiform activity was also observed in hAPP/PS1 doubly transgenic mice (Minkeviciene et al., 2009). These A β effects may relate closely to the increased incidence of epileptic seizures seen in patients with AD (Palop and Mucke, 2009). Using two-photon calcium imaging microscopy to monitor the activity of neuronal populations in the hippocampal CA1 region of AD transgenic mice (APP23xPS45) *in-vivo*, significant alterations in hippocampal activity were observed in the presence of A β plaques (6-7 months of age), in comparison to wild-type (WT) mice (Busche et al., 2012). Notably, hyperactive neurons were mainly found near plaques, consistent with previous findings in the cortex (Busche et al., 2008). In young (1-2 months old) transgenic mice, a marked increase in hippocampal activity was observed before onset of A β plaques. Experimental evidence suggested that this hyperactivity was directly promoted by soluble A β (Busche et al., 2012). Similarly, in 3xTg AD transgenic mice, episodic-like memory deficit could be due to the development of an abnormal hyper-excitable state in the hippocampal formation (Davis et al., 2014). Using a multi-site electrode recording approach (Kloosterman et al., 2004) in the DG and CA1 of 3xTg AD mice, DG and CA1 excitability was shown to be higher than in controls, particularly in young mice (4-6 months) at the age at which intracellular hippocampal A β starts to be detected. In the 3xTg AD model, early deficit in episodic-like memory developed slightly by 3 months and fully by 6 months of age (Davis et al., 2013), when pronounced intracellular accumulation of A β was observed (Oddo et al., 2003). This behavioral deficit coincided with subtle abnormalities in neuronal excitability in the DG and CA1 regions, without degradation of the hippocampal fiber pathway, suggesting that intracellular A β accumulation mediates the observed effects, at least in young mice.

HIPPOCAMPAL 5-HT_{1A}R EXPRESSION REGULATION IN PRODROMAL AD: BENEFICIAL OR DELETERIOUS?

In prodromal stages of AD, modulation of 5-HT_{1A}R expression is constituted by (i), an early increase in total 5-HT_{1A}R count in the DG observed in *post-mortem* (Vidal et al., 2016) and *in-vivo* PET studies (when using partial volume effect correction) (Truchot et al., 2007) and reproduced in an animal model of AD *in-vitro* (Verdurand et al., 2016); and (ii), an early decrease in functional 5-HT_{1A}R count in the CA1 region observed in *post-mortem* studies (Vidal et al., 2016). Given that the fMRI BOLD signal is sensitive to both excitatory and inhibitory neuronal activity, our hypothesis is that the modulation of 5-HT_{1A}R expression (increase or decrease, activation or inhibition) may result in modifications of fMRI BOLD signal in the hippocampal network. In MCI, memory is poorer than expected for a subject of the same age. This is a stage showing increased hippocampal activation, which has been hypothesized to have a beneficial compensatory function by recruiting additional neural resources to compensate for memory-related dysfunction. A different hypothesis is that excess activation directly contributes to memory impairment and may be bound to widespread degenerative processes in prodromal AD (Putcha et al., 2011). As discussed below, several arguments are in favor of either hypothesis.

Evidence in favor of a beneficial effect of early changes in 5-HT_{1A}R expression

Sprouting. Neuronal sprouting refers to the growth of axons or dendrites from a damaged neuron or from an intact neuron that projects to an area denervated by damage to other neurons. It is thus a beneficial compensatory mechanism following neuron lesion, restoring neuronal function. But how does neuronal sprouting relate to 5-HT_{1A}R expression? In our animal model with intra-hippocampal infusion of A β , neuronal death was observed at the injection site in the hippocampus (DG), concomitant with 5-HT_{1A}R overexpression. It is thus possible that 5-HT_{1A}R are carried by neurons that have undergone axon or dendrite growth from damaged neurons in the hippocampus. If the animal model is considered as reproducing the 5-HT_{1A}R overexpression observed in patients (*post-mortem* and *in-vivo*), it is also possible that neuronal sprouting accounts for 5-HT_{1A}R overexpression in MCI patients. Interestingly, early sprouting of 5-HT neurons (at 3 months) has been demonstrated in a 3xTg AD mouse model (Noristani et al., 2011).

In this study, it was hypothesized that serotonergic axon sprouting was directly related to an increase in serotonin transporter (SERT) terminal density that may act as a compensatory mechanism in maintaining overall synaptic efficacy. This increased serotonergic input might be an intrinsic neuroprotection response to counteract A β -induced neurotoxicity and altered hippocampal glutamatergic circuitry, as revealed by the decrease in synaptic density, accounting for the early behavioral changes and later onset of severe permanent cognitive and memory impairment in AD (Noristani et al., 2011). However, despite the presence of 5-HT terminals in the hippocampus, 5-HT_{1A}R are known to be heteroreceptors in this projection area, and thus located on non-serotonergic neurons. The changes in 5-HT_{1A}R expression are thus probably not due to homotypic 5-HT sprouting but to heterotypic sprouting of glutamatergic or GABAergic neurons bearing 5-HT_{1A}R. Notably, in an APP23 transgenic mice model, plaques in the entorhinal cortex were demonstrated to trigger sprouting of glutamatergic neurons in the hippocampus (Phinney et al., 1999). It is thus possible that changes in 5-HT_{1A}R expression reflects glutamatergic sprouting in the hippocampus, acting as a compensatory mechanism aimed at maintaining overall synaptic efficacy. Concerning GABAergic sprouting, studies have shown that increased epileptic activities, reported in a subset of AD patients, can trigger downstream alterations including GABAergic sprouting and increased synaptic inhibition in hippocampal circuits (Li et al., 2016). These alterations are characterized as compensatory inhibitory mechanisms to ameliorate neuronal over-excitation and keep the normal neuronal excitation.

Neuroprotective mechanisms. One explanation for total 5-HT_{1A}R overexpression in the DG at early prodromal stages of AD could be that it is overexpressed by newly generated neurons in the hippocampus, compensating for A β -induced cell loss. New neurons formed in the hippocampus are known to become incorporated into the granule cells of the adult dentate gyrus (Gould et al., 1999). Pathologically elevated A β levels trigger a multitude of cellular events, including not only cell death but also structural and functional changes at synapse level and intense astrogliosis (Mucke and Selkoe, 2012). Although still under debate, it has been postulated that astroglial cells may express 5-HT_{1A}R (Hirst et al., 1998; Patel and Zhou, 2005). Alternatively, reactive astrocytes present in the vicinity of A β plaques have been shown to induce an increase in serotonergic axon sprouting (Olabarria et al., 2010; Verdurand et al., 2011; Verdurand et al., 2016). Reactive astrocytes are able to increase their release of S100 β , a neurotrophic factor that is produced, stored and released by astrocytes and promotes the outgrowth of 5-HT fibers (Azmitia,

2001). Also, transgenic mice with increased S100 β expression display an increase in the number of S100 β -positive astrocytes, associated with increased serotonergic fiber density in the hippocampus (Shapiro et al., 2010). However, as mentioned above, 5-HT_{1A}R in the hippocampus are known to be located on non-serotonergic neurons. Thus, even if 5-HT sprouting does occur, it would not lead directly to 5-HT_{1A}R overexpression. Indirect overexpression of 5-HT_{1A}R located on post-synaptic glutamatergic or GABAergic neurons following 5-HT pre-synaptic sprouting remains a possibility.

Procognitive mechanisms. 5-HT_{1A}R knock-out (KO) mice present an anxiety (Toth, 2003) phenotype and have memory impairment demonstrating that 5-HT_{1A}R are involved in memory processes (Wolff et al., 2004). Carli and collaborators observed that 5-HT_{1A}R-targeting drugs showing presynaptic stimulatory effects (5-HT_{1A} autoreceptor agonists) and/or post-synaptic blocking effects (5-HT_{1A} heteroreceptor antagonists) alleviated memory problems due to cholinergic dysfunction (Carli et al., 1997, 1998). Thus a decrease in “5-HT tone” improves cholinergic neurotransmission and thus memory function. In prodromal AD, we mentioned that overall changes in 5-HT_{1A}R do not solely comprise total 5-HT_{1A}R overexpression in the hippocampus (DG), but also decreased functional 5-HT_{1A} levels in CA1, as demonstrated in *post-mortem* studies (Vidal et al., 2016). A decrease in functional 5-HT_{1A}R density in CA1 has the same “functional” consequences as using an antagonist on these receptors. Thus, the decrease in functional 5-HT_{1A}R in CA1 could be a compensatory mechanism restoring normal cognitive function. A decrease in 5-HT_{1A}R functionality may reflect a compensatory mechanism balancing compromised cholinergic (and maybe also glutamatergic) neurotransmission. 5-HT_{1A}R antagonists have given promising results in preclinical studies in rodents and non-human primates, and in clinical trials with AD patients (Luttgen et al., 2005; Millan et al., 2004; Schechter et al., 2005). Regarding other symptoms, 5-HT_{1A}R agonists have proved useful in treating non-cognitive aspects of AD, including behavioral and psychological symptoms of dementia (Sato et al., 2007).

Evidence in favor of a deleterious effect of early changes in 5-HT_{1A}R expression

MCI is the stage showing changes in 5-HT_{1A}R expression (increase in total and decrease in functional receptors) and an increase in hippocampal activation. As the fMRI BOLD signal is an indirect measure of neuronal activity that depends on physiological changes of blood flow and

oxygen metabolism, an increase or a decrease in 5-HT_{1A}R can both produce fMRI BOLD signal changes (up or down) at the hippocampal network level. Moreover, the fMRI BOLD signal is not specific enough to determine which neuronal population is activated or inhibited. The serotonergic system, as any other neurotransmission system implicated in hippocampus regulation, could be responsible for the increase in fMRI BOLD signal observed in the hippocampus of patients at prodromal stages of AD. An alternative view to beneficial compensatory changes in 5-HT_{1A}R expression and hippocampal activation at early stages of AD is that they could directly contribute to memory impairment and may be tied to widespread degenerative processes (Putchá et al., 2011). It was recently argued that increased hippocampal activation in MCI may be a dysfunctional condition rather than a beneficial functional compensation (Bakker et al., 2012; Tahmasian et al., 2015). Supporting the possibility of adverse consequences, studies in a rodent model of age-related memory loss demonstrated that abnormally elevated neural activity occurs specifically in the CA3 region of the hippocampus when neurons are unable to encode new information (Wilson et al., 2006). Additionally, treatments targeting excess CA3 activity in the same animal model, including low doses of certain antiepileptic drugs (AED), improved memory performance (Koh et al., 2010). Consistent with these findings, recent evidence from high-resolution fMRI in humans indicated that greater hippocampal activation in aMCI localizes to the DG/CA3 regions (Yassa et al., 2010), suggesting similar network dysfunction. Taken together, these findings support the concept that reducing excess activity could have benefit in aMCI. Bakker and colleagues tested this hypothesis, using the FDA-approved AED levetiracetam to lower excess hippocampal activity. Levetiracetam treatment of hyperactivity in human patients with MCI and in mice with pathological levels of A β reduced hippocampal activity and improved memory (Bakker et al., 2012; Sanchez et al., 2012).

A “consecutive” hypothesis: deleterious neuronal hyperactivation followed by compensatory 5-HT_{1A}R expression modulation

To unify these two hypotheses of beneficial and/or deleterious effects of 5-HT_{1A}R modulation of expression and neuronal activation, the two might occur consecutively. Early A β deposits or intraneuronal A β would induce glutamatergic hyperactivity in the hippocampus. This hyperactivity would translate into hippocampal dysfunction. As 5-HT_{1A}R receptors are coupled

to Gi/o proteins for signal transduction, their activation in the hippocampus results in adenylyl cyclase inhibition and G protein-coupled inwardly-rectifying potassium channel (GIRK) activation, strongly inhibiting neuronal firing and excitability. In the hippocampal CA1 region, early loss of 5-HT_{1A}R receptor functionality was observed in postmortem brains of early Braak-stage patients (Vidal et al., 2016). This aspect of 5-HT_{1A}R reactivity could indirectly contribute to greater and potentially harmful hippocampal activity. However, in the DG, 5-HT_{1A}R overexpression could act as a mechanism compensating hippocampal hyperactivity, lowering neuronal activation. Thus, at early stages of AD (MCI), therapeutics with a 5-HT_{1A}R agonistic profile at hippocampal heteroreceptors might be useful, compensating for 5-HT_{1A}R CA1 loss and encouraging 5-HT_{1A}R DG overexpression.

PERSPECTIVES

In the early MCI prodromal stage of AD, memory is poorer than would be expected for a person of the same age. This is also the stage showing increased hippocampal activation with changes in 5-HT_{1A}R expression. We reviewed how these changes in 5-HT_{1A}R expression and hippocampal hyperactivation might serve a beneficial compensatory function in MCI by recruiting additional neural resources to compensate for memory-related dysfunction. We also reviewed how they might contribute directly to memory impairment and may be linked to widespread degenerative processes in prodromal AD. Finally, we raised the possibility of a sequence whereby A β -induced neuronal hyperactivation triggers compensatory 5-HT_{1A}R overexpression (DG), limiting the deleterious effects of hippocampal hyperactivation.

In order to determine whether changes in 5-HT_{1A}R expression are temporally correlated with neuronal activation or if the two appear consecutively, the recent arrival of hybrid PET-MRI cameras could allow simultaneous *in-vivo* studies, targeting 5-HT_{1A}R receptors by PET and BOLD neuronal activation by fMRI, in patients representing the continuum of AD (aged controls, patients at risk, MCI, AD, at rest and/or under memory task).

Neuronal hyperactivity in presymptomatic and prodromal stages of AD has been documented by several groups, and 5-HT_{1A}R modulation of expression in the prodromal stages has been reported *in vitro* and *in vivo* in patients and animal models. The relationship between 5-HT_{1A}R and

hippocampal activity needs to be studied in more detail. For example, electro-encephalography (EEG) recording under drugs that specifically target 5-HT_{1A}R in the hippocampus would be of great interest. EEG recordings of animal models of AD showing cognitive impairment would also provide valuable insights. Conducting PET-MRI experiments in these animal models would also be useful.

Therapeutics targeting 5-HT_{1A}R in these animal models would provide valuable information. It was seen above that 5-HT_{1A}R can inhibit both principal (glutamatergic) neurons and GABAergic interneurons. Inhibition of GABAergic interneurons can be expected to disinhibit principal cells and thus counteract the direct effects of 5-HT_{1A}R expressed on principal neurons. It was also seen, in the literature, that therapeutics with 5-HT_{1A} autoreceptor agonist and/or heteroreceptor antagonist properties should be particularly effective in improving memory. Therefore, selectively targeting 5-HT_{1A}R may not be an optimal strategy for modulating hippocampal function, unless these receptors could be targeted in a regional or cell-specific manner (Newman-Tancredi et al., 2009). The recent concept of “biased agonism” holds that highly selective agonists can preferentially direct receptor signaling to specific intracellular responses (Kenakin, 2012). 5-HT_{1A}R are known to interact with G_{αi3} in the dorsal raphe, G_{α0} and G_{αi3} in the cortex, and G_{α0}, G_{αi1}, G_{αi3} and G_{αz} in the hypothalamus (Mannoury la Cour et al., 2006). Besides this regional heterogeneity in G-subtype protein coupling, another “downstream” 5-HT_{1A}R signaling response, phosphorylation of extracellular signal-regulated kinase (ERK1/2), also exhibits brain region-specificity (Buritova et al., 2009). This opens up the possibility of identifying drugs that target 5-HT_{1A}R in specific brain regions and may therefore be more therapeutically effective (Becker et al., 2016).

Finally, the extent of 5-HT_{1A}R G-protein coupling may provide original information shedding light on the mechanisms underlying neurotransmission impairment in AD. Fluorinated PET 5-HT_{1A}R radioligands are directly transferable to *in-vivo* PET imaging: the antagonist [¹⁸F]MPPF is a widely-used PET radiopharmaceutical and the agonist radiotracer we developed, [¹⁸F]F13640, will soon be available for human studies, its first-in-man study being currently underway (EU Clinical Trials Register, EudraCT number #2016-00016-15). Comparing the binding profiles of a PET agonist and an antagonist to determine *in vivo* the extent of G-protein coupling of 5-HT_{1A}R and to follow the evolution of functionality during the neurodegenerative process represents a

new and promising neuropharmacological concept for nuclear medicine that we have already started to apply in animal studies (Becker et al., 2016).

ACCEPTED MANUSCRIPT

FINANCIAL DISCLOSURES

The authors declare that they have no conflict of interest.

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Table 1. Summary of 5-HT_{1A} receptor studies in AD (clinical and preclinical)

		Subject	Stage	Mean Age	Number	Regions	Results/Effects			Methodology	References
							Decrease	No Change	Increase		
<i>Human</i>	<i>postmortem</i>	AD	nr	nr	nr	Frontal cortex	-52%			[³ H]5-HT	(115)
		AD	nr	79 y.o.	n=12	Frontal cortex	-85%			[³ H]5-HT	(35)
		AD	nr	81 y.o.	n=33	Frontal cortex		=		[³ H]8-OH-DPAT	(32)
		AD	nr	82 y.o.	n=17	Frontal cortex			↑	[³ H]8-OH-DPAT	(8)
		AD	nr	79 y.o.	nr	Parietal cortex	-74%			[³ H]5-HT	(116)
		AD	nr	79 y.o.	n=12	Amygdala	-48%			[³ H]5-HT	(35)
		AD	nr	79 y.o.	n=12	Temporal cortex	-53%			[³ H]5-HT	(35)
		AD	nr	78 y.o.	n=13	Temporal cortex		=		[³ H]5-HT	(30)
		AD	nr	81 y.o.	n=33	Temporal cortex		=		[³ H]8-OH-DPAT	(32)
		AD	nr	82 y.o.	n=35	Temporal cortex		=		[³ H]8-OH-DPAT	(33)
	AD	nr	79 y.o.	n=12	Hippocampus	-60%			[³ H]5-HT	(35)	
	AD	nr	82 y.o.	n=24	Hippocampus	-50%			[³ H]8-OH-DPAT	(37)	
	AD	nr	77 y.o.	n=8	Hippocampus		=		[³ H]5-HT	(31)	
	prodromal	Braak I/II	84 y.o.	n=5	Hippocampus (CA1)	-19%			[¹⁸ F]F13640	(42)	
	prodromal	Braak III/IV	84 y.o.	n=10	Hippocampus (CA1)	-23%			[¹⁸ F]F13640	(42)	
	prodromal	Braak I/II/III	75 y.o.	n=6	Hippocampus (CA1)		=		[¹⁸ F]MPPF	(41)	
	AD	nr	nr	n=2	Hippocampus (CA1)	-60%			[¹⁸ F]MPPF	(36)	
	AD	Braak V/VI	76 y.o.	n=10	Hippocampus (CA1)	-33%			[¹⁸ F]MPPF	(42)	
	AD	Braak V/VI	76 y.o.	n=10	Hippocampus (CA1)	-36%			[¹⁸ F]F13640	(42)	
	AD	Braak IV/V/VI	82 y.o.	n=8	Hippocampus (CA1)		=		[¹⁸ F]MPPF	(41)	
prodromal	Braak I/II/III	75 y.o.	n=6	Hippocampus (DG)	-40%			[¹⁸ F]F15599	(41)		
prodromal	Braak I/II	84 y.o.	n=5	Hippocampus (DG)		=		[¹⁸ F]F13640	(42)		
prodromal	Braak I/II/III	75 y.o.	n=6	Hippocampus (DG)		=		[¹⁸ F]MPPF	(41)		
prodromal	Braak I/II	84 y.o.	n=5	Hippocampus (DG)			+26%	[¹⁸ F]MPPF	(42)		
AD	Braak IV/V/VI	82 y.o.	n=8	Hippocampus (DG)	-50%			[¹⁸ F]F15599	(41)		
AD	Braak V/VI	76 y.o.	n=10	Hippocampus (DG)	-40%			[¹⁸ F]F13640	(42)		
AD	Braak V/VI	76 y.o.	n=10	Hippocampus (DG)		=		[¹⁸ F]MPPF	(42)		
AD	Braak IV/V/VI	82 y.o.	n=8	Hippocampus (DG)		=		[¹⁸ F]MPPF	(41)		
<i>in vivo PET</i>	prodromal	nr	77 y.o.	n=6	Hippocampus	-13%			[¹⁸ F]MPPF	(36)	
	prodromal	nr	73 y.o.	n=11	Hippocampus			+59%	[¹⁸ F]MPPF	(43)	
	prodromal	nr	73 y.o.	n=11	Hippocampus			↑	[¹⁸ F]MPPF	(44)	
	AD	nr	75 y.o.	n=8	Hippocampus	-27%			[¹⁸ F]MPPF	(36)	
	AD	nr	70 y.o.	n=10	Hippocampus	-35%			[¹⁸ F]MPPF	(43)	
	AD	nr	70 y.o.	n=10	Hippocampus		↓		[¹⁸ F]MPPF	(44)	
	AD	nr	70 y.o.	n=10	Hippocampus				[¹⁸ F]MPPF	(44)	
<i>Animal</i>	<i>transgenic mice</i>	Tg2576	NA	15 months	nr	Hippocampus	-90%			[¹⁸ F]Mefway	(49)
		3xTg AD	NA	1 month	nr	Hippocampus	-23%			[¹⁸ F]Mefway	(49)
			NA	2 months	nr	Hippocampus	-37%			[¹⁸ F]Mefway	(49)
			NA	15 months	nr	Hippocampus	-90%			[¹⁸ F]Mefway	(49)
			NA	18 months	nr	Hippocampus	-90%			[¹⁸ F]Mefway	(49)
<i>fibril-injected rats</i>	Ab40 in hipp	NA	7 days p.i.	n=8	Hippocampus (DG)			+42%	[¹⁸ F]MPPF	(50)	
	Ab40 in hipp	NA	7 days p.i.	n=6	Hippocampus (DG)			+41%	[¹⁸ F]MPPF	(51)	
	Ab42 in hipp	NA	7 days p.i.	n=6	Hippocampus (DG)		=		[¹⁸ F]MPPF	(51)	
	Ab40 in hipp	NA	7 days p.i.	n=8	Hippocampus		=		[¹⁸ F]F15599	(50)	

Abbreviations: AD = Alzheimer's disease; y.o. = years old; nr = not reported; NA = not applicable; p.i. = post-injection

- The serotonergic system is highly dysfunctional in Alzheimer's disease (AD) and this could be related to cognitive impairments associated with dementia.
- Of the various serotonin receptors, 5-HT_{1A} receptors are particularly relevant to AD, being involved in the regulation of memory processes.
- The implication of this receptor subtype is examined, particularly in terms of "reactivity" in the hippocampal region.
- Two hypotheses are discussed: 5-HT_{1A} overexpression is beneficial and needs to be pharmacologically stimulated; 5-HT_{1A} overexpression is deleterious and needs to be limited.