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Review article

Hippocampal 5-HT$_{1A}$ receptor expression changes in prodromal stages of Alzheimer's disease: Beneficial or deleterious?

Mathieu Verdurand [a], Luc Zimmer [a, b, *]

[a] Université Claude Bernard Lyon 1, CNRS, INSERM, Lyon Neuroscience Research Center, Lyon, France
[b] CERMEP, Hospices Civils de Lyon, Lyon, France

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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.

Contents

* Corresponding author. CERMEP-Imaging Platform, Groupement Hospitalier Est, 59 Boulevard Pinel, F-69673 Bron, France.
E-mail address: luc.zimmer@univ-lyon1.fr (L. Zimmer).

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1. Introduction

Alzheimer's disease (AD) is a neurodegenerative disease associated with specific histopathological markers, including extracellular deposits of amyloid-beta (Aβ), 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 serotoninergic 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.

2. 5-HT_{1A} receptors in normal aging and in AD patients

2.1. 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 ([^{3}H]5-HT, [^{3}H]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 [^{11}C]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.

2.2. 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-HT_6R (Rodriguez et al., 2012). Binding studies of *post-mortem* AD brains, using non-selective 5-HT_{1A}R radioligands like [^{3}H]5-HT (binding to all 5-HT receptors) or the agonist [^{3}H]8-OH-DPAT (binding to 5-HT_{1A}/5-HT_7 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 [^{18}F]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-HT_7 receptors agonist [^{3}H]8-OH-DPAT showed that reduced temporal cortex binding correlated with aggressive behavior (Lai et al., 2003) and