Effects of amyloid-β peptides on the serotonergic 5-HT$_{1A}$ receptors in the rat hippocampus

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Abstract

A recent [$^{18}$F]MPPF-positron emission tomography study has highlighted an overexpression of 5-HT$_{1A}$ receptors in the hippocampus of patients with mild cognitive impairment compared to a decrease in those with Alzheimer’s disease (AD) [Truchot, L., Costes, S.N., Zimmer, L., Laurent, B., Le Bars, D., Thomas-Antérion, C., Croisile, B., Mercier, B., Hermier, M., Vighetto, A., Krolak-Salmon, P., 2007. Up-regulation of hippocampal serotonin metabolism in mild cognitive impairment. Neurology 69 (10), 1012–1017]. We used in vivo and in vitro neuroimaging to evaluate the longitudinal effects of injecting amyloid-β (Aβ) peptides (1–40) into the dorsal hippocampus of rats. In vivo microPET imaging showed no significant change in [$^{18}$F]MPPF binding in the dorsal hippocampus over time, perhaps due to spatial resolution. However, in vitro autoradiography with [$^{18}$F]MPPF (which is antagonist) displayed a transient increase in 5-HT$_{1A}$ receptor density 7 days after Aβ injection, whereas [$^{18}$F]F15599 (a radiolabelled 5-HT$_{1A}$ agonist) binding was unchanged suggesting that the overexpressed 5-HT$_{1A}$ receptors were in a non-functional state. Complementary histology revealed a loss of glutamatergic neurons and an intense astroglial reaction at the injection site. Although a neurogenesis process cannot be excluded, we propose that Aβ injection leads to a transient astroglial overexpression of 5-HT$_{1A}$ receptors in compensation for the local neuronal loss. Exploration of the functional consequences of these serotonergic modifications during the neurodegenerative process may have an impact on therapeutics targeting 5-HT$_{1A}$ receptors in AD.

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1. Introduction

Alzheimer’s disease (AD) is the most common cause of dementia in the elderly. In addition to amyloid plaques and neurofibrillary tangles, the loss of neurons and associated neurochemical alterations represent a pathological hallmark of AD. Although dysfunction of the cholinergic system is usually considered as the most prominent neurotransmitter abnormality, cognitive, behavioural and neuropsychiatric symptoms have been linked to changes in other transmitter systems (Assal and Cummings, 2002).

In particular, several postmortem studies support the involvement of the serotonin system in AD (Meltzer et al., 1998). Reductions of serotonin (Reinikainen et al., 1990), serotonin synthesizing neurons (Aletrino et al., 1992; Curcio and Kemper, 1984; Halliday et al., 1992; Zweig et al., 1988) and serotonin reuptake sites (Chen et al., 1996; Cross, 1990; D’Amato et al., 1987) have been reported in the raphe nuclei and cortical areas of AD brains. More specifically, a decreased number of tryptophan hydroxylase immunoreactive cells in the rostral and caudal dorsal raphe nuclei have been found (Lee and Kowall, 1989).

A substantial number of postmortem studies have evaluated the expression levels of serotonergic receptors. Levels of 5-HT$_{2A}$ (Cross et al., 1986; Lai et al., 2005; Lorke et al., 2006; Reynolds et al., 1984) and 5-HT$_{6}$ (Lorke et al., 2006) receptors are reported as being reduced in AD, and levels of