Intact cannabinoid CB1 receptors in the Alzheimer's disease cortex

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ARTICLE INFO

Article history:
Received 11 August 2010
Received in revised form 29 September 2010
Accepted 14 October 2010
Available online 27 October 2010

Keywords:
Alzheimer's disease
Dementia
Cannabinoid CB1 receptors
Cortex
Hippocampus
Caudate

ABSTRACT

The cannabinoid CB1 receptor has gained much attention as a potential pharmacotherapeutic target in various neurodegenerative diseases including Alzheimer's disease (AD). However, the relation of CB1 receptors to cognitive function in AD is at present unclear. In this study, postmortem brain tissues from a cohort of prospectively assessed, neuropathologically confirmed AD patients and aged controls were used to measure CB1 receptors by immunoblotting, and a subset of subjects also had [3H]SR141716A binding. Correlational analyses were then performed for the neurochemical and cognitive data. We found that CB1 receptor levels in were unchanged AD in the brain regions assessed (frontal cortex, anterior cingulate gyrus, hippocampus, caudate nucleus). Within the AD group, frontal cortical CB1 immunoreactivity correlated with cognitive scores assessed within a year of death. Our study suggests that CB1 receptors are intact in AD and may play a role in preserving cognitive function. Therefore, CB1 receptors should be further assessed as a potential therapeutic target in AD.

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1. Introduction

Alzheimer’s disease (AD) represents the bulk of neurodegenerative dementia as well as associated healthcare costs in both developed and developing regions of the world (DeKosky and Orgogozo, 2001; Wimo et al., 2006; Kalaria et al., 2008). Neuropathologic features of AD include intercellular β-amyloid (Aβ)-containing neuritic plaques as well as intracellular neurofibrillary tangles in multiple regions of the cortex (Selkoe and Podlisny, 2002). Another salient feature of AD is the perturbation of various neurotransmitter systems and concomitant alterations of associated receptors and synthetic enzymes. For example, AD has been found to manifest neuronal degeneration in the basal forebrain cholinergic system and deficits of choline acetyltransferase (Whitehouse et al., 1982; Wilcock et al., 1983), together with alterations of muscarinic and nicotinic acetylcholine receptors (Nordberg et al., 1992; Flynn et al., 1995; Court et al., 2001; Lai et al., 2001). Besides the cholinergic system, another neurotransmitter system known to be affected in AD is the glutamatergic system which comprises the majority of excitatory pyramidal neurons throughout the neocortex and may mediate the excitotoxicity of AD (Francis, 1996, 2006; Olney et al., 1997). These findings supported the development of acetylcholinesterase inhibitors (AChEIs) and memantine, a non-competitive N-methyl D-aspartate (NMDA) receptor antagonist, in dementia pharmacotherapy (Geerts and Grossberg, 2006; Thomas and Grossberg, 2009). However, such therapeutics have proven to be of limited benefit. Moreover, AChEI administration results in side effects such as nausea, dizziness and diarrhoea (Birks, 2006), while memantine is generally prescribed only for severe AD and has limited pro-cognitive effects (Areosa et al., 2005). Therefore, there is a need to identify and study other potential targets for AD pharmacotherapy.

Recently, the endocannabinoid system has attracted much interest as a novel target for AD and other neurodegenerative diseases due to potentially neuroprotective, anti-inflammatory and neurotrophic effects of certain cannabinoids (Campbell and Gowran, 2007; Basavarajappa et al., 2009). Researchers have shown that certain marijuana components prevent AChE-induced Aβ aggregation and competitively inhibit AChE (Eubanks et al., 2006) as well as Aβ-induced tau hyperphosphorylation in vitro (Esposito et al., 2006), and may therefore amplify the therapeutic effects of AChEIs and have other disease-modifying effects. Neurochemically, the endocannabinoid system plays a significant role in regulating cholinergic and glutamatergic neurotransmission. For example, the Gαi-coupled, presynaptic CB1 receptor is