Decreased rabphilin 3A immunoreactivity in Alzheimer's disease is associated with Aβ burden

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ABSTRACT

Synaptic dysfunction, together with neuritic plaques, neurofibrillary tangles and cholinergic neuron loss is an established finding in the Alzheimer’s disease (AD) neocortex. The synaptopathology of AD is known to involve both pre- and postsynaptic components. However, the status of rabphilin 3A (RPH3A), which interacts with the SNARE complex and regulates synaptic vesicle exocytosis and Ca2+–triggered neurotransmitter release, is at present unclear. In this study, we measured RPH3A and its ligand Rab3A as well as several SNARE proteins in postmortem neocortex of patients with AD, and found specific reductions of RPH3A immunoreactivity compared with aged controls. RPH3A loss correlated with dementia severity, cholinergic deafferentation, and increased β-amyloid (Aβ) concentrations. Furthermore, RPH3A expression is selectively downregulated in cultured neurons treated with Aβ25–35. Our data suggest that presynaptic SNARE dysfunction forms part of the synaptopathology of AD.

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1. Introduction

Alzheimer’s disease (AD) is the predominant cause of dementia in aging populations and is characterized by the neuropathologic hallmarks of extracellular senile plaques, intracellular neurofibrillary tangles, and degeneration of neurons in transmitter source nuclei, including cholinergic neurons located in the medial septum and nucleus basalis of Meynert (Coyle et al., 1983; Selkoe, 2001; Whitehouse et al., 1982). The resultant cholinergic deafferentation (as indicated by loss of presynaptic choline acetyltransferase and acetycholinesterase activities) correlated with dementia severity, thus supporting a role for cholinergic dysfunction in the cognitive features of AD (Bartus et al., 1982). These neurochemical findings were subsequently expanded to include glutamatergic, serotonergic and other neurotransmitter systems (Francis et al., 2010). Contemporaneous to the neurochemical studies were reports that the major constituents of senile plaques were fibrillar forms of 40–42 amino-acids β-amylloid peptide (Aβ). Excessive production or impaired clearance of Aβ, which is derived from proteolytic processing of the larger amyloid precursor protein (APP) was thought to initiate further neurotoxic and neuropathologic events such as tangle formation and neuronal degeneration, thus establishing itself as the central pathogenic factor in AD (Hardy and Allsop, 1991). There is also increasing recognition that neuronal loss is preceded by alterations in synapse proteins and synaptic function (Selkoe, 2002). Aβ is known to have neurotoxic and synapticotoxic properties (Klyubin et al., 2012; Williams and Serpell, 2011), and cortical Aβ burden correlated with cognitive decline in AD (Naslund et al., 2000) as well as with loss of synaptic marker synaptophysin in AD and APP transgenic mice (Lue et al., 1999; Mucke et al., 2000). Taken together, these studies indicate that the synaptopathology of AD may be related to Aβ burden.

One critical function of the presynapse is the release of neurotransmitters stored in synaptic vesicles into the synaptic cleft in response to depolarization and Ca2+ influx. This is mediated by exocytosis of synaptic vesicles in a process catalyzed by complexes of several soluble N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) proteins (Jahn et al., 2003). It is now known that Ca2+ evoked synaptic vesicle exocytosis and neurotransmitter release are regulated by four isoforms of GTP-binding...