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β-Amyloid 42/40 ratio and kalirin expression in Alzheimer disease with psychosis

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Abstract

Psychosis in Alzheimer disease differentiates a subgroup with more rapid decline, is heritable, and aggregates within families, suggesting a distinct neurobiology. Evidence indicates that greater impairments of cerebral cortical synapses, particularly in dorsolateral prefrontal cortex, may contribute to the pathogenesis of psychosis in Alzheimer disease (AD) phenotype. Soluble β-amyloid induces loss of dendritic spine synapses through impairment of long-term potentiation. In contrast, the Rho guanine nucleotide exchange factor (GEF) kalirin is an essential mediator of spine maintenance and growth in cerebral cortex. We therefore hypothesized that psychosis in AD would be associated with increased soluble β-amyloid and reduced expression of kalirin in the cortex. We tested this hypothesis in postmortem cortical gray matter extracts from 52 AD subjects with and without psychosis. In subjects with psychosis, the β-amyloid$_{1-42}$/β-amyloid$_{1-40}$ ratio was increased, due primarily to reduced soluble β-amyloid$_{1-40}$, and kalirin-7, -9, and -12 were reduced. These findings suggest that increased cortical β-amyloid$_{1-42}$/β-amyloid$_{1-40}$ ratio and decreased kalirin expression may both contribute to the pathogenesis of psychosis in AD. Published by Elsevier Inc.

Keywords: β-amyloid; Kalirin; Psychosis; Alzheimer disease

1. Introduction

The emergence of psychosis in individuals with late-onset Alzheimer disease (AD) is an indicator of a more severely progressive form of the disease. Psychotic symptoms, delusions and hallucinations, are frequent in AD, with a prevalence of upwards of 40% (Ropacki and Jeste, 2005). Individuals with AD and psychosis (AD+P) decline more rapidly on measures of cognition and function, and are more likely to be institutionalized (Lopez et al., 1999; Scarmeas et al., 2005). AD+P demonstrates familial aggregation (Sweet et al., 2002a, 2010), and the estimated heritability of any occurrence of psychotic symptoms in AD is 30%, increasing to 61% for multiple/recurrent symptoms (Bacanu et al., 2005). The familial and heritable nature of AD+P strongly suggests that it develops from a distinct neurobiological origin.

Findings from neuroimaging studies and postmortem studies have pointed to increased synaptic disruption in the

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neocortex, but not medial temporal cortex, as underpinning the development of psychosis in AD. Structural assessment with magnetic resonance imaging identified reduced gray matter density in frontal and parietal gyri in AD+P subjects in comparison with AD subjects without psychosis (AD−P) (Bruen et al., 2008). Studies of cerebral perfusion with single photon emission computed tomography show hypoperfusion of frontal and parietal lobes (Kotrla et al., 1995), frontal regions (Staff et al., 1999), and dorsolateral frontal and parietal regions (Mega et al., 2000) in AD+P versus AD−P. A positron emission tomography study identified hypometabolism in the frontal lobe of AD+P subjects, compared with AD−P (Sultzer et al., 1995). A magnetic resonance spectroscopy study of synaptic disruption in postmortem tissue identified an excess of membrane breakdown products in several neocortical regions, including the dorsolateral prefrontal cortex (DLPFC), in AD+P (Sweet et al., 2002b). These findings indicate that AD+P is associated with deficits across multiple neocortical regions, however evidence consistently points to frontal regions and the DLPFC in particular.

Evidence of greater neocortical synaptic impairments in AD+P subjects is also consistent with clinical observations that these individuals exhibit a steeper trajectory of cognitive decline than individuals with AD−P (Emanuel et al., 2011; Paulsen et al., 2000; Scarmeas et al., 2005). Loss of synapses is the most robust correlate of degree of cognitive impairment among AD subjects (DeKosky and Scheff, 1990; Scheff and Price, 2006; Terry et al., 1991; Walsh and Selkoe, 2004). The nonspecific presynaptic protein synaptophysin, and the intracortical excitatory bouton selective protein vesicular glutamate transporter VGLUT1, are both reduced in AD neocortex and correlated with cognitive decline (Counts et al., 2006; Kashani et al., 2008; Terry et al., 1991). Similarly, dendritic spines, the postsynaptic components of the majority of synapses in the cortex (Rakic et al., 1986), and the dendritic spine associated proteins synaptopodin and drebrin, are reduced in neocortex of subjects with AD, and correlated with cognitive impairment (Counts et al., 2006; Grutzendler et al., 2007; Reddy et al., 2005).

Soluble β-amyloid (Aβ) oligomers have emerged as the most likely cause of dendritic spine deficits observed in AD. Normally, enhanced synaptic efficacy, dendritic spine enlargement, and spine persistence are correlated phenomena mediated by long-term potentiation (LTP) (Matsuzaki, 2007). Soluble, oligomeric Aβ isolated from AD brains inhibits LTP and induces spine loss (and as a consequence the synapses onto them) in rodent hippocampus, while insoluble plaque cores do not have the same effects unless solubilized first (Shankar et al., 2008). Studies of transgenic mouse models of AD have demonstrated that well before plaque deposition, increased soluble (nonfibrillar) Aβ concentration is associated with changes in dendritic length and shape (Wu et al., 2004), reductions in synaptic density (Mucke et al., 2000), and impaired synaptic transmission (Hsia et al., 1999). Application of naturally secreted Aβ oligomers inhibits hippocampal LTP in vivo (Walsh et al., 2002) and in vitro (Wang et al., 2002), and induces dendritic spine loss in vitro (Shankar et al., 2007).

The excess synaptic disruption in AD+P could be driven simply by increased concentrations of soluble Aβ leading to greater inhibition of LTP and resultant spine loss. Alternatively, reductions in proteins which serve to mediate the effects of LTP on dendritic spines could independently lead to excess spine and synapse loss in AD+P. One such mediator is kalirin, a guanine nucleotide exchange factor (GEF) which activates the Rho family of GTP binding proteins (Alam et al., 1997; Cerione and Zheng, 1996). Four major isoforms generated through alternative splicing of the kalirin gene are expressed in adult central nervous system (CNS) (kalirin-5, -7, -9, -12) (Johnson et al., 2000). In the cortex, kalirin is necessary for LTP-induced dendritic spine enlargement and controls expression of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors at the synapse (Xie et al., 2007). In the hippocampus however, other GEFs that are not highly expressed in the cortex may substitute for kalirin, as kalirin knockout mice have reduced dendritic spine densities in the cortex but not hippocampus (Cahill et al., 2009). Kalirin messenger RNA and protein expression is lower in AD hippocampus compared with cognitively normal controls (Youn et al., 2007a, 2007b). However, kalirin expression in the neocortex of AD subjects, and in relationship to psychosis status of AD subjects, has not been evaluated. Considering the integral function kalirin has in activity-dependent mechanisms of spine enlargement and glutamatergic transmission, reduction in kalirin could play a role in rendering synapses to be more vulnerable in AD+P.

We therefore undertook to evaluate soluble Aβ and kalirin expression in the cerebral cortex of subjects with AD+P in comparison with AD−P subjects. We hypothesized that susceptibility to AD+P may result from a deficit in kalirin, from an increase in Aβ, or their combined effect; more Aβ drive acting on vulnerable synapses may lead to greater loss of synapses in AD+P.

2. Methods

2.1. Subjects

Fifty-two subjects (Table 1) underwent neurologic, neuropsychologic, and psychiatric diagnostic evaluations at successive time points as part of their participation in the Clinical Core of the Alzheimer Disease Research Center (ADRC), with methods previously described (Sweet et al., 2000, 2001).

The presence or absence of delusions and hallucinations were indicated as part of semistructured examinations conducted by research psychiatrists and rated on the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) Behavioral Rating Scale (Tariot et al., 1995).