Upregulation of AMPA receptor GluR2 (GluA2) subunits in subcortical ischemic vascular dementia is repressed in the presence of Alzheimer’s disease

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\textbf{A B S T R A C T}

Glutamatergic AMPA receptors are of clinical significance in dementia because of their roles in mediating fast excitatory neurotransmission and other synaptic events relevant to cognition. Reductions in the AMPA receptor GluR2 subunit are well-established in Alzheimer’s disease (AD), but the status of GluR2 in subcortical ischemic vascular dementia (SIVD) and mixed AD/SIVD (MIX) has not been investigated. In this study we measured GluR2 immunoreactivity and mRNA levels in the postmortem neocortex of a longitudinally assessed cohort of SIVD and MIX, together with age-matched controls. We found that GluR2 immunoreactivity and mRNA were up-regulated in SIVD, but remained unchanged in MIX. Furthermore, higher GluR2 immunoreactivity was associated with milder cognitive impairment and lower concentrations of A\textsubscript{β}42 peptide and phosphorylated tau. Our study suggests that GluR2 up-regulation may be an adaptive process in SIVD, and that this process is repressed in the presence of concomitant AD in mixed dementia.

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1. Introduction

Alzheimer’s disease (AD) and vascular dementia are the two most common types of dementia, a neurodegenerative disease characterized clinically by cognitive impairments as well as behavioral disturbances. Neuropathologically, AD is characterized by the presence of neuritic plaques, neurofibrillary tangles, and degeneration of transmitter source nuclei with associated synapse loss and neurochemical alterations (Francis et al., 2010; Selkoe, 2002; Whitehouse et al., 1982). In contrast, patients with vascular dementia have prominent cerebrovascular changes, previous histories of stroke or hypertension, and low plaque and tangle burden (Jellinger, 2002a,b). Of the several subtypes of vascular dementia, subcortical ischemic vascular dementia (SIVD) is clinically homogenous and characterized by executive dysfunction, mild dementia and relatively preserved language, calculation and other higher cortical functions (Rom\text{"{a}}n et al., 2002). Mixed dementia, a condition where AD and vascular dementia occurred concurrently, is increasingly found among the elderly (Jellinger and Attems, 2007). In considering the neurochemical correlates of the clinical and neuropathological features of these diseases, it is important to investigate the glutamatergic system given its status as the major excitatory neurotransmitter system in the CNS and its critical roles both in cognitive functions as well as in excitotoxicity (Baudry and Lynch, 2001; Fonnum, 1984; Francis et al., 1993; Olney et al., 1997). However, while glutamatergic dysfunctions have been fairly well characterized in AD (Francis, 1996, 2003; Francis et al., 1993), their status in vascular and mixed dementias is unclear. It is of particular interest whether differences in glutamatergic alterations may underlie clinical differences in between SIVD and AD (e.g., milder dementia in SIVD).

Glutamatergic neurotransmission is mediated by ligand-gated ionotropic receptors (iGlur) as well as G-protein-coupled metabotropic glutamate receptors (mGlur). The major iGlurS include N-methyl-D-aspartate (NMDA), \alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and kainate receptors. Of the iGlurS, the AMPA receptors consist of heterotetramers of GluR1 – GluR4 (recently renamed GluA1 – GluA4) subunits and display rapid trafficking into and out of post-synaptic domains in their role as regulators of fast excitatory synaptic transmission, synaptic plasticity as well as cognitive processes (Dingledine et al., 1999;