Temporal lobe proteins implicated in synaptic failure exhibit differential expression and deamidation in vascular dementia

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1. Introduction

Vascular dementia is a potentially fatal condition that occurs following interruptions in blood supply to specific areas of the brain following a stroke or microinfarcts (Shih et al., 2013). VaD is the second most common form of dementia after Alzheimer’s disease (AD) (Gorelick et al., 2011; Kalaria et al., 2008), and exhibits a pathology that is at least partially reversible (McVeigh and Passmore, 2008), indicating potential for new drug treatments if the underlying molecular mechanisms can be defined and suitable targets identified. At the cellular level, dementia syndromes are characterized by progressive synaptic failure among cortical neurons, which contributes to their common clinical manifestations; disorientation, defects in long-term memory, mood disorders and executive dysfunction (Herbert et al., 2014; Wesnes and Edgar, 2014). Synaptic degeneration begins with disrupted vesicular trafficking in presynaptic boutons, and progresses toward structural malformations in the postsynaptic dendrite arborization, preceding eventual loss of neurons in the affected cortical areas (Bolay et al., 2002; Chang et al., 2013; Mufson et al., 2012). While this process is in itself well documented, the molecular mediators of these events have yet to be identified (Muresanu et al., 2014; Yao, 2004). Synaptic failure strongly correlates with the cognitive impairments manifest in VaD and AD, even when the presence of characteristic senile plaques cannot be established (DeKosky and Scheff, 1990; Overk and Masliah, 2014; Terry et al., 1991). Moreover, synaptic failure is the pathological feature most commonly shared by VaD and AD patients (Iadecola, 2013; Kalaria, 2000, 2002), consistent with the concept that loss of synapse function is a key event in the pathogenesis of dementia syndromes.

A B S T R A C T
Progressive synaptic failure precedes the loss of neurons and decline in cognitive function in neurodegenerative disorders, but the specific proteins and posttranslational modifications that promote synaptic failure in vascular dementia (VaD) remain largely unknown. We therefore used an isobaric tag for relative and absolute proteomic quantitation (iTRAQ) to profile the synapse-associated proteome of post-mortem human cortex from vascular dementia patients and age-matched controls. Brain tissue from VaD patients exhibited significant down-regulation of critical synaptic proteins including clathrin (0.29; p < 1.0·10^{-3}) and GDH1 (0.51; p = 3.0·10^{-3}), whereas SNAP25 (1.6; p = 5.5·10^{-3}), bassoon (1.4; p = 1.3·10^{-3}), excitatory amino acid transporter 2 (2.6; p = 9.2·10^{-1}) and Ca^{2+}/calmodulin dependent kinase II (1.6; p = 3.0·10^{-2}) were substantially up-regulated. Our analyses further revealed divergent patterns of protein modification in the dementia patient samples, including a specific deamidation of synapsin1 predicted to compromise protein structure. Our results reveal potential molecular targets for intervention in synaptic failure and prevention of cognitive decline in VaD.

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Abbreviations: iTRAQ, isobaric tag for relative and absolute quantitation; VaD, vascular dementia; AD, Alzheimer’s disease; BA21, Brodmann area 21; PTM, post-translational modification; SV, synaptic vesicle; SNARE, soluble NSF attachment protein receptors family; RMSD, root mean square deviation; SEM, standard error of the mean; PDL, protein database; LTP, long-term potentiation; CBF, cerebral blood flow; CNS, central nervous system; PTM, protein posttranslational modification; IsoAsp, isoaspartic acid; Asp, aspartic acid; Asn, asparagine; GLN, glutamine; ERLIC, electrostatic repulsion–hydrophobic interaction chromatography; TEB, triethylammonium bicarbonate; HPLC, high-performance liquid chromatography; LC–MS/MS, liquid chromatography–tandem mass spectrometry; MDLC, multidimensional liquid chromatography; TM-score, template modeling score; FDR, false discovery rate; CME, clathrin-mediated endocytosis.

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