IDENTIFYING CHANGES IN CALCIUM-REGULATED PROTEINS IN AD AND RELATED TAUOPATHIES

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Introduction: Increasing evidence suggests a role for aberrant regulation of neuronal calcium in the development and/or progression of Alzheimer's disease (AD) and related tauopathies. However, the mechanisms underlying calcium-associated neurodegeneration are not fully understood.

Aim: Our aim is to elucidate key proteins that play an important role in the molecular mechanisms underlying abnormal calcium homeostasis in AD.

Methods: The amounts and subcellular localisation of calcium-associated proteins in post-mortem human brain and in APP-overexpressing transgenic (Tg2576) mouse brain was assessed on western blots. Calcium imaging and biochemical analyses of primary cortical cultures were employed to explore the mechanism by which soluble oligomeric β-amyloid (Aβ) elevates intraneuronal calcium. Live imaging of fluorescently tagged neuronal calcium sensors was used to investigate their subcellular localisation following exposure of neurons to Aβ.

Results: Calpain activity was increased in human brain samples AD, frontotemporal dementia, progressive supranuclear palsy and corticobasal degeneration. The elevated calpain activity in AD was associated with increased calpain-mediated cleavage of sodium-calcium exchanger-3 (NCX3), indicating its inactivation. Biochemical analyses revealed increased NCX3 cleavage in Tg2576 cortex, together with altered sub-cellular distribution of DREAM (calsenilin/KChIP3), a neuronal calcium sensor that negatively regulates NCX3 expression. Finally, experiments in primary rat cortical neurons revealed that transient receptor potential cation channel-2 (TRPM2), appears to play an important role in mediating the responses of calcium-activated proteins to Aβ.

Conclusions: These results identify calcium-associated proteins, including NCX3, DREAM and TRPM2, that could play important roles in aberrant calcium signalling in AD and related tauopathies.