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Synaptic plasticity, Dementia and Alzheimer's Disease

Neuroplasticity is both a substrate of learning and memory and a mediator of responses to neuronal cell attrition and injury. It is a continuous process in reaction to neuronal activity and injury, death, and genesis, involving modulation of structural/functional processes of axons, dendrites, and synapses. Structural elements that embody plasticity include long-term potentiation (a cellular correlate of learning and memory), synaptic efficacy, synaptic remodeling, synaptogenesis, neurite extension including axonal sprouting and dendritic remodeling, and neurogenesis and recruitment. As research on human neurodegeneration has moved from descriptive phenomenology to mechanistic analysis, it has become increasing apparent that the morphological lesions long used by neuropathologists to confirm a clinical diagnosis after death might provide an experimentally tractable handle to understand causative pathways. For example, Alzheimer disease (AD) is an aging-dependent neurodegenerative disorder characterized neuropathologically by deposition of insoluble amyloid β-peptide (Aβ) in extracellular plaques and aggregated tau protein, which is found largely in the intracellular neurofibrillary tangles. We now appreciate that mild cognitive impairment in early AD may be due to synaptic dysfunction caused by accumulation of non-fibrillar, oligomeric Aβ, well before widespread synaptic loss and neurodegeneration become evident. Soluble Aβ oligomers can adversely affect synaptic structure and plasticity at extremely low concentrations, although the molecular substrates by which synaptic memory mechanisms are disrupted remain to be fully elucidated. A primary locus of excitatory synaptic transmission in the mammalian central nervous system is the dendritic spine. Loss of spine density has been linked to cognitive and memory impairment in AD. We will review current knowledge on the bases of synaptic dysfunction in neurodegenerative diseases, with a focus on AD, and will cover both amyloid- and non-amyloid-driven mechanisms. Consideration will also be given to emerging data which point to potential therapeutic approaches for ameliorating the cognitive and memory deficits associated with these disorders.

Speaker Biography

Stephen Skaper received a PhD in biochemistry from the University of South Dakota and Laurea in chemistry from the University of Padua, Italy. He is currently Adjunct Professor in the Department of Pharmaceutical and Pharmacological Sciences (section on Pharmacology and Anesthesiology) at the University of Padua. Previously he was a Senior Group Leader for Neurodegeneration Research, Neurology Centre of Excellence for Drug Discovery, GlaxoSmithKline Research and Development Limited, United Kingdom, and also held academic research positions in the Departments of Medicine and Biology at the University of California, San Diego. Skaper has authored/co-authored over 300 research papers, as well as having guest-edited journal thematic issues and two volumes of Methods in Molecular Biology on neurotrophic factors. He is Editor-in-Chief of CNS & Neurological Disorders Drug Targets, a Councilor of the International Association of Neurorestoratology, and a member of Sigma XI, Phi Lambda Upsilon, and the Society for Neuroscience.

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