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The putative neuropathological roles of astrocytes in the development of Alzheimer's disease

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Astrocytes are known to play pivotal roles in brain signaling and neuroinflammation. Moreover, astrocytes participate in cerebral blood flow regulation by interacting with neurons and the endothelia of microvessels together as "neurovascular units" (NVU). Alzheimer's disease (AD) is being regarded as the most common neurodegenerative form of dementia. Recent research has begun to focus on the vascular aspects of neurodegeneration, as significant number of AD patients exhibit pathological changes in cerebral vasculature in addition to having the classical beta-amyloid (Aβ) deposits. Studies have demonstrated changes in endothelin-1 (ET-1) - an important protein in vasoregulation and vasoinflammation - and its associating receptors in the AD brains. Exposure of neuroblastoma cells to oligomeric Aβ has been shown to upregulate ETconverting enzyme. Analysis of a astrocytic cell line with an ET-1 expression plasmid showed that ET-1 over-expression led to an increase of Aβ(1-42) without altering cell survival. Treatment of wild-type mouse primary astrocyte-enriched cultures with exogenous ET-1 increased the level of Aβ(1-42) dose dependently. Furthermore, cellular viabilities appeared to be enhanced at all ET-1 concentrations. The obtained data demonstrate that Aβ(1-42) is produced in astrocytes upon stimulation by ET-1. Together with the existing literature, our results suggest the existence of a possible astrocytic regulatory mechanism between Aβ processing and the ET system. Furthermore, aberrant ET-1 production as a result of NVU pathology could be an important upstream event contributing to the eventual Aβ accumulation and toxicity. Further studies into the roles of astrocytes in NVU dysfunction associated with the pathogenesis of AD are warranted.

Biography

Andrew C. K. Law received his bachelor degree in pharmacology from The University of Toronto. He then went to The University of Cambridge to read cardiovascular physiology, and pursued his medical education in St. Louis, USA. He then received his doctoral degree in neuroscience from McGill University. He was a recipient of the Doctoral Research Award from The Alzheimer Society of Canada. He returned to The University of Toronto for training in psychiatry. He is a specialist in psychiatry, focusing on geriatric neuropsychiatry. He is also the Director of the Neurodysfunction Research Laboratory at The University of Hong Kong. Research Interest: Cellular mechanisms of neurodegenerative disorders.

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