

Synaptic Dysfunction and Neuro Inflammation Intracellular Effectors in Alzheimer's and Other Neurodegenerative Disorders

Akari Andro*

Department of Pathology, Institute for Developmental Research, Kasugai, Japan

ABSTRACT

Dynamic processes controlled by regulators of plasticity or morphogenesis of pre and postsynaptic compartments sustain synaptic function. Around the time of disease initiation in neurodegenerative disorders, including Alzheimer's disease (AD), synaptic dysfunction frequently precedes neuronal loss and dysregulated microglia induces prolonged neuro inflammation with serious clinical symptoms. While astrocyte-derived apolipoprotein E4 (ApoE4) impaired amyloid beta (A β) clearance has been considered to be the key contributor to sporadic AD, it has been shown that intracellular effectors, such as cell-adhesion regulatory proteins or lipophilic mediators, regulate synaptic homeostasis and are further involved in controlling chronic inflammatory dissemination during neurodegenerative times. The proteins of the catenin family, such as β -catenin and p120 catenin, control the trafficking of cadherin and cytoskeletal rearrangement. The signalling of aberrant catenin has been shown to play a role in neuronal dysfunction seen in models of AD or Parkinson's disease (PD) with irregular Amyloid Precursor Protein (APP) or oxidative vulnerability processing.

Keywords: Alzheimer's disease; Catenin; Microglia; Neuro inflammation; Presenilinc

DESCRIPTION

Inordertoformsuccessfulneuronalnetworksbasedonsomatosensory inputs or behavioural experiences, synaptic morphogenesis and plasticity are controlled by neuronal activity. Improved neuronal activity activates the reorganisation in presynaptic compartments of the actin cytoskeleton and causes coordinated shifts in applied postsynaptic density with actin dynamics [1]. These processes include various cell-adhesion molecules, and classical cadherins are most characterised and relevant for synaptic formation or dendritic arborisation [2,3]. Several neurotransmission modulators play a role in synaptic plasticity, besides cell-adhesion proteins. For synaptic homeostasis, neuronal activity-dependent processing of Amyloid Precursor Protein (APP) is needed, but excess amyloid β (A β) output may depress synaptic transmission, resulting in cognitive impairment, as seen in early ADD pathogenesis [4]. A β deposition and neurofibrillary tangle formation have been shown to precede synaptic dysfunction in AD model mice containing knockin mutant presenilin 1 (PS1M146V), mutant tau protein (tauP301L), and Swedish APP (APPSwe), simulating the regional effect of $A\beta$ plaques and neurofibrillary tangles observed in AD pathology [5]. The underlying regulatory mechanism of the production of APP by PS1 interacting proteins such as catenin and inflammatory balance in dopaminergic neurons has also been elucidated, and proteins of the catenin family play an important role in pathogenesis of AD and PD with different mechanisms [6-8]. In microglia expressing purinergic receptors that react to extracellular ATP, a similar 2-AG generating mechanism catalysed by PLC and DAGLs is preserved in [9]. MAGL-mediated development of proinflammatory arachidonic acid (AA) is noticeably needed for microglial activation and inflammatory cytokine generation. In inflammatory conditions, such as $A\beta$ accumulation or LPS treatment, microglial MAGL expression is considered to be upregulated and MAGL is involved in the phagocytic activity of activated microglia [10,11]. CB2R is barely detectable in immune cells under normal conditions, but caused by neuronal inflammation, as 2-AG stimulates signalling of CB Receptors (CBR), resulting in microglial migration [12]. Since CB1R signalling modulation causes extreme psychotropic effects, production of CB2R-specific chemicals has been pursued as a therapeutic problem for the resolution of neuro inflammation.

DISCUSSION AND CONCLUSION

Catenin proteins have been shown to mediate various cellular signalling patterns that are both essential for neuronal homeostasis, including synaptic responses and dendritic spine morphology. Improved development of All is shown to impair synaptic efficiency, and is also correlated pathologically with dysfunctional

Correspondence to: Akari Andro, Department of Pathology, Institute for Developmental Research, Kasugai, Japan, E-mail: andro@inst.kek.jp Received: December 30, 2020; Accepted: January 13, 2021; Published: January 20, 2021

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adhesion and adverse effects of ApoE4 mediated by cadherin. In addition, by a mutually restrictive mechanism, PS1 is integrated with cadherin-mediated catenin signalling and cadherin and APP processing control. In addition to influencing APP processing through PS mutations, aberrant γ -secretase activity induced by FAD PS mutations can result in decreased neuronal activity and synaptic depression. AMPA and NMDA-mediated transmission are downregulated by APP mutations followed by MAGL activation, with JZL184-dependent stability restoration previously established in animal AD models involving the latter.

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