Mini Review

The current model of the neurodegenerative processes involving Alzheimer disease (AD); the amyloid cascade hypothesis, maintains that it is oligomeric (consists of a few monomers) soluble Aβ that is the key driver of the pathogenic changes found in AD and those neurodegenerative changes are facilitated (at least to a certain degree) by the changes in tau protein [1-5]. In a recent review by Roland Brandt and Lidia Bakota, Department of Neurobiology, University of Osnabruck, Osnabruck, Germany, it was illustrated that microtubules are directly and indirectly involved in the three pathways of the neurodegenerative triad: synaptic impairment, dendritic simplification (loss of dendritic spines on the dendrite), and neuron cell death [6]. These three hidden connections will be briefly reviewed.

Synaptic Impairment

Synaptic impairment associated with the loss of dendritic spines, which is correlated with impairment in long-term potentiation, appears to be amid the initial events in the AD neurodegenerative cascade [6]. Two studies; one using microtubule tip-tracking protein EB3 and the second using stable isotope labeling to measure the turnover of tubulin, support that abnormal functioning in microtubules may directly lead to a loss of dendritic spines [7,8]. Dendritic spines are found on many cortical neurons and form excitatory synapses. Thus the loss of dendritic spines would be associated with a decrease in synaptic strength.

Dendritic Simplification

Microtubule stability may be coupled with the progression of dendritic simplification. This is supported by a seminal study involving cerebellar Purkinje cells [9]. Subsequent research demonstrates two main themes to further support the involvement of microtubule stability to the progression of dendritic simplification. First, the up-regulation of MAP1A and MAP2 are potentially involved in the stability of dendritic microtubules resulting in more stabilized branches [10,11]. Secondly, the deletion of MAP1A and MAP2 disrupts microtubule spacing which results in decreased dendritic arbor complexity (or dendritic branching) [12,13]. Hence, decreases in dendritic complexity result in less potential excitatory synaptic connections.

Cell Death

Cell death that is caused by the disturbance of axonal transport may be due, in part, to microtubule disruption. This possibility is supported by experimental evidence, using line imaging of fluorescent protein-tagged organelles, that demonstrates Aβ oligomers interrupt axonal transport [14] and that abnormal axonal transport is correlated to microtubule destabilization; which may be caused by mitochondrial dysfunction and deficiencies in the carriage of brain-derived neurotrophic factor [15,16]. Thus defective transport results in the products that are vital to the survival of the neuron to not be delivered. This ultimately results in cell death and is considered an early pathologic event in AD [14].

Conclusion

Microtubule dynamics are important in AD, as they are involved during the early pathological stages seen in AD and also during the process of cell death; as they play pivotal roles in axon transport, the structural integrity of the neurons, and neuronal plasticity. In the review by Brandt and Lidia Bakota [6], it is apparent that researchers should not underestimate the role that microtubule dynamics may play in AD as it is evident, now, that they are involved in various degrees in the three pathways of the neurodegenerative triad.

References


