

"No screams and cries will convince us that white is white and black is black", an ode to the defenders of amyloid cascade hypothesis of Alzheimer's disease.

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Since its formulation in 1992 Amyloid Cascade Hypothesis (ACH) has been the most influential theory explaining the pathogenesis observed in Alzheimer's disease. Its paradigms have been subsequently translated to picture the broader spectrum of neurodegenerative disorders. The ACH assumes that minor accumulation of A β is a primary trigger of pathology observed in disease continuum. Recently, linear structure of hypothesis has been rearranged to emphasize central role of oligomeric amyloid species in progressing pathology. Although extensive efforts have been made to figure out effective therapeutic strategy that would follow the ACH principles, no trial has succeeded. Current FDA-approved therapies tune neurotransmitter abnormalities but have no effect on the physiological events that mediate the progression of pathology. For more than 20 years numerous reports have identified various limitations of the ACH. The idea of causative role of amyloid deposition has eroded over time and become modest. Although we can still associate the A β with the secondary effect of dementia in AD, its primary role in expansion of neurodegenerative mechanisms is limited to being a marker of upstream changes. In fact, these changes lead to synaptic losses observed in sporadic AD, while amyloid deposition seems to be a part of adaptive response to stress conditions that exaggerate with age. Recently the "allostatic load" concept that addresses these chronic stressors has been formulated to picture the negative changes observed in late onset sporadic Alzheimer's disease. There is a lot of evidence pointing toward the neurovasculature and its damage as a trigger for AD. The endothelial cells forming the blood brain barrier control the homeostasis of neuronal stem cells involved in neurogenesis in brain segments that are crucial for a memory formation. This phenomenon is principally mediated by brain derived neurotrophic factor (BDNF), a member of neurotrophin family that is downregulated in AD and other neurodegenerative disorders. Its mechanisms of action, potential therapeutic application along with cross-interactions of its biochemical pathways with metal ion homeostasis have been summarized in this review.

Słowa kluczowe

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