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Invited critical review

Drebrin and cognitive impairment

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ABSTRACT

The kinetics of cytoskeletal networks, with actin as a key factor, play a key role in regulating the morphology and function of dendritic spines. Drebrin is a neuron growth and brain development-related actin-binding protein and is present in 70% of the dendritic spines of excitatory synapses. It regulates the development and formation of dendritic spines and well-developed dendritic spines pave the way for presynaptic elements. Well-developed and mature synapses are prerequisite for maintaining nervous system physiology. Abnormal morphology of dendritic spines and loss of synapses are seen in many neurologic diseases associated with cognitive decline. However, the mechanisms governing these pathologic changes and their correlation with drebrin remain unclear. Exploring the relationship between drebrin and cognitive function may provide insight into the early prevention of cognitive impairment and in the diagnosis and treatment of Alzheimer's disease.

Contents

1. Introduction . . . 0
2. Sources and activities of drebrin . . . 0
3. Drebrin and cognitive dysfunction . . . 0
3.1. Studies conducted in AD patients . . . 0
3.2. Animal model . . . 0
3.3. Cellular and molecular levels . . . 0
4. Mechanisms governing the effects of drebrin on cognition . . . 0
4.1. Effect of drebrin on the formation of dendritic spines and synapses . . . 0
4.2. Effect of drebrin on the remodeling of dendritic spines and synapses . . . 0
4.3. Drebrin-regulating molecules . . . 0
5. Perspectives . . . 0
6. Uncited reference . . . 0
Conflict of interest . . . 0
Acknowledgments . . . 0
References . . . 0

1. Introduction

Alzheimer's disease (AD) is a degenerative disease of the nervous system, marked by insidious onset and slow progression. Its main clinical manifestations include mental changes such as progressive memory impairment, cognitive dysfunction, personality changes, and behavioral disorders, which can seriously lower the quality of life in elderly individuals [1]. Loss of synapses has been found in the brains of AD patients, and the loss of synapses was closely correlated with the severity of dementia [2]. Further studies have demonstrated changes in nervous tissues in the early stage of cognitive dysfunction and that development regulation brain protein (drebrin), a developmentally regulated brain protein, plays key roles in regulating the morphology and remodeling of dendritic spines and synapses. While research has

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shown that the loss of synapses is related to drebrin, the specific mechanisms governing the pathological changes of synapses in the brains of AD patients and the potential correlation between drebrin and synapses remain unclear. In this article, we will review the roles of drebrin in the occurrence and development of cognitive dysfunction.

2. Sources and activities of drebrin

Synapses are functional connections between neurons, and the biological signals are passed from the presynaptic membrane to the postsynaptic membrane. Dendritic spines are tiny protrusions on dendritic shafts. As one of the postsynaptic elements, they contain structures such as an actin cytoskeleton, postsynaptic density, and neurotransmitter receptors, which can maintain the fundamental morphology and functions of the synapses. Drebrin is a neuron growth and brain development-related actin-binding protein [4,5] and is present in 70% of the dendritic spines of excitatory synapses. It has two subtypes: E and A. Drebrin E is mainly found during early brain development, and drebrin A specifically localizes at dendritic spines and is the predominant form in immature neurons [6]. The amino-terminal domain of drebrin A has high-affinity binding sites for actin, and the carboxyl-terminal has affinity binding sites for profilin. Drebrin can regulate the morphology of dendritic spines and synaptic plasticity by act in filament (F-actin) polymerization and fibrous actin binding or dissociation [7]. Interestingly, Roppongi RT found that decreased drebrin and F-actin can occur at the dendritic spines without morphologic changes [8]. Drebrin regulates neuroblast migration in the postnatal mammalian brain [9] and plays a role in inducing long-term potentiation (LTP), promoting the migration of neurons and their repair.

3. Drebrin and cognitive dysfunction

Cognition is a reflection of the complex and sophisticated functions of the cerebral cortex. Any direct or indirect factors that may cause chronic impairment of cerebral cortex structure and function can result in cognitive dysfunction via different mechanisms. The hippocampus is involved in learning and memory formation, and the synaptic plasticity in this region is the neurobiological basis for learning and memory. Neuronal dendritic spine-based drebrin, together with F-actin, can regulate the plasticity of dendritic spines [5]. Previous studies in humans and animal models and those at cellular and molecular levels have shown that drebrin is associated with cognitive dysfunction.

3.1. Studies conducted in AD patients

Drebrin is closely related to cognitive function, as demonstrated in many AD patients. AD is a disease of synaptic dysfunction. Autopsies of clinical AD patients have shown significantly decreased drebrin in the cerebral cortex and hippocampus [10,11]. Golgi staining has shown that the number of neuronal dendritic spines in the hippocampus was decreased in AD [12]. Furthermore, the drebrin level was also significantly decreased in the entire cerebral cortex. In patients with mild cognitive impairment, the expression of drebrin in the temporal lobe was also significantly lower [13]. Drebrin was reduced by approximately 40% in the hippocampus of mild cognitive impairment (MCI) and AD compared to normal subjects [14]. Thus, the decreased drebrin level may contribute to the reduced plasticity of dendritic spines. By affecting dendritic spine morphology and structure, drebrin can cause synaptic changes, blocking the connections among many functional pathways in the brain causing dysfunction. Thus, disordered synaptic plasticity due to the depletion or decrease of drebrin is one of the pathological contributors to AD [10,15,16].

The main pathological changes of AD include the deposition of senile plaques after the aggregation of β-amyloid protein (Aβ) outside cortical and hippocampal neurons, the formation of neurofibrillary tangles due to the abnormal aggregation of Tau protein in neurons, and the loss of neurons. The accumulation of Aβ is central to AD pathogenesis, and the aggregation and oligomerization of Aβ can occur in the neurons in dementia-affected brains [17]. The Aβ oligomers can selectively aggregate at dendrites and synapses [18,19], and the increased Aβ causes AMPA receptor-mediated endocytosis on the cellular surface and protrusions, resulting in NMDA receptor loss and eventually morphological changes and decreased number of drebrin-positive dendritic spines [16].

3.2. Animal model

Animal studies have been conducted in drebrin A knockout rats, APP/PS1transgenic AD mice, and Tg2576 mice. The drebrin located on the neural spines regulates the morphological changes and plays a key role in controlling synaptic plasticity. The drebrin knockout rats are more susceptible to schizophrenia-related behaviors such as stubbornness and increased activity, as well as impaired pre-pulse inhibition and increased sensitivity to mental stimulants, suggesting that the decreased drebrin can impair cognitive function by weakening the function of synaptic spines [20].

In AD transgenic mouse models, the dendrites of hippocampal neurons developed deformations and disturbances [21], and the dendritic spine density clearly decreased [22]. Quantitative immunoelectron microscopy studies showed that the percentage of drebrin-positive dendritic spines in the cerebral cortex was significantly lower in AD transgenic mice models than in wild-type mice [6]. As shown in the above literature, drebrin expression level declines in the early stage of AD, accompanied by morphological changes in dendritic spines.

3.3. Cellular and molecular levels

The cytoskeleton constitutes the dynamic and morphological foundations of cellular differentiation/migration, synapse formation, and neural network formation [23], with F-actin being the main protein in the cytoskeleton. The actin-binding proteins include tropomyosin, drebrin, gelsolin, α-actinin, and α-myosin. Drebrin can inhibit the F-actin-binding activity of tropomyosin and α-actin. By competitively binding with F-actin [24], drebrin can regulate the plasticity of the actin network and the dynamics of actin cytoskeleton network, thus changing the morphology of dendritic spines.

In vitro culture of the B104 neuroblastoma cells showed that overexpression of drebrin in neurons resulted in increased neurite length; in contrast, when the drebrin expression inside cells was inhibited, the growth of cell axons slowed. Therefore, drebrin may regulate intracellular F-actin assembly and thus be involved in the formation of dendrites and axons during neuronal development [25]. Molecular biological studies have found that the drebrin mRNA level was decreased in the brains of AD patients, and drebrin mRNA expression was correlated with drebrin protein expression and sim2. The down-regulation of drebrin mRNA expression played a key role in AD and was closely correlated with disease progression [26].

4. Mechanisms governing the effects of drebrin on cognition

The kinetics of cytoskeletal networks, with actin as a key factor, play a key role in regulating the morphology and function of dendritic spines. Physiologically, drebrin regulates the development and formation of dendritic spines, and well-developed dendritic spines pave the way for the development of presynaptic elements. Well-developed and mature synapses are a prerequisite for maintaining the physiological function of the nervous system. Pathologically, abnormal morphology of dendritic spines and loss of synapses are seen in many neurological diseases associated with cognitive decline. However, the specific mechanisms governing the pathological changes of synapses in the brains of AD patients and the potential correlation between drebrin and synapses

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