Synaptic dysfunction and disruption of the postsynaptic drebrin-actin complex: the study of neurological disorders accompanied by cognitive deficits

Nobuhiko Kojima and Tomoaki Shirao

Department of Neurobiology and Behavior, Gunma University Graduate School of Medicine, Maebashi 371-8511, Japan

Abstract

Many neurological disorders accompanied by cognitive deficits, including Alzheimer's disease (AD) and Down syndrome, exhibit abnormal dendritic spine morphology. Actin-based cytoskeletal network dynamics are critical for regulation of spine morphology and function. Recent experimental data from an AD animal model reveal that defects in intracellular signaling cascades related to accumulation of amyloid β (Aβ) cause disruption of postsynaptic actin-regulatory machinery, including cofilin and drebrin. The amount of postsynaptic drebrin, a major F-actin binding protein in dendritic spines, correlates well with the severity of cognitive impairment. We propose that imbalanced regulation of actin-regulatory machinery (loss of drebrin and associated increase in dephosphorylated cofilin) results in synaptic dysfunction underlying the cognitive impairment of neurological disorders and normal aging.

Keywords: Alzheimer's disease; Amyloid β peptide; Cognitive deficits; Dendritic spines; Actin cytoskeletal network; Drebrin; Glutamate receptors

1. Introduction

Dendritic spines are small dendritic protrusions at the postsynaptic side of excitatory synapses. Within these spines are neurotransmitter receptors, ion channels, scaffolding proteins, actin cytoskeletal proteins, and intracellular signaling molecules. Abnormal spine morphology is observed in many neurological disorders accompanied by cognitive deficits, such as Alzheimer's disease (AD), Down syndrome, and fragile X syndrome (Fiala *et al*., 2002), suggesting that spine morphology is closely related to spine function and that abnormal regulation of spine morphology causes neurological symptoms of such disorders.

Actin filaments, which consist of actin molecules and actin-binding proteins, form cytoskeletal networks within dendritic spines and play critical roles in spine morphogenesis, maintenance, and plasticity (Matus, 2000; Carlisle and Kennedy, 2005; Tada and Sheng, 2006). In addition to extracellular senile plaques and intracellular neurofibrillary tangles, another prominent feature of AD is the presence of pathologic rod-shaped inclusions in neuronal processes called Hirano bodies, inclusions that contain actin and several actin-binding proteins (Galloway *et al*., 1987).

Immunohistological evidence shows that cofilin, which binds and severs F-actin, is a major component of Hirano bodies (Maciver and Harington, 1995). Hirano bodies also show strong diffuse immunostaining for fractin, a caspase-cleaved actin fragment (Rossiter *et al*., 2000). These findings suggest that a defect in the actin-regulatory machinery is an underlying factor in dendritic and synaptic dysfunction in AD. In contrast to increased cofilin (Zhao *et al*., 2006), another actin-binding protein, drebrin, is substantially decreased in AD (Harigaya *et al*., 1996; Hatanpaa *et al*., 1999).

2. Drebrin as a key regulator of spine morphology and function

Drebrin is an F-actin-binding protein highly expressed in the brain (Hayashi *et al*., 1996). Drebrin regulates the dynamics of actin cytoskeletal networks by inhibiting actin-myosin interactions (Hayashi *et al*., 1996; Cheng *et al*., 2000) and by competing for F-actin binding with other actin-binding proteins, such as tropomyosin and α-actinin (Ishikawa *et al*., 1994).

Drebrin A is a neuron-specific isoform (Kojima *et al*., 1988) and is prevalent within spines located postsynaptic only to excitatory synapses (Aoki *et al*., 2005).

Overexpression of drebrin A elongates spines in mature neurons (Hayashi and Shirao, 1999) and changes filopodia into aberrantly enlarged megapodia in immature neurons (Mizui *et al*., 2005). Conversely, suppression of drebrin A expression reduces spine density and results in the formation of thin immature spines (Takahashi *et al*., 2006). These findings indicate that the drebrin-actin complex plays a pivotal role in the regulation of spine morphology.

In addition to its role in spine morphology, drebrin A and its accumulation within spines is required for facilitating the accumulation of a glutamate receptor scaffolding protein, PSD-95, at postsynaptic sites *in vitro* (Takahashi *et al*., 2003). Furthermore, a relationship between drebrin and NMDA receptors has been recently demonstrated: Activation of NMDA receptors induces the translocation of drebrin from spines to their parent dendrite (Sekino *et al*., 2006); and drebrin A is necessary for the homeostatic synaptic accumulation of NMDA receptors (Takahashi *et al*., 2006).

The proportion of drebrin-immunopositive spines *in vivo* is fairly constant; about 75% of spines in the adult rat cerebral cortex are immunoreactive for drebrin A (Aoki et al., 2005). However, the proportion of drebrin-immunopositive spines is regulated in an

activity-dependent manner: Blockade of NMDA receptor activity for two hours increases the proportion of drebrin-immunopositive spines (Fujisawa et al., 2006). Thus, drebrin may act as a key regulator not only of spine morphology but also of spine function, such as synaptic plasticity.

3. Pathological changes in drebrin in neurological disorders accompanied by the cognitive deficits

Harigaya and colleagues (1996) were the first to observe that drebrin disappears from the hippocampus of AD patients. Further study demonstrated that the disappearance of drebrin is not restricted to the hippocampus but also occurs throughout the cerebral cortex (Hatanpaa *et al*., 1999). In contrast to the drastic postsynaptic changes in drebrin occurring in AD, presynaptic changes in the content and distribution of synaptophysin are not so obviously changed. This asymmetric change in presynaptic and postsynaptic proteins indicates that synaptic dysfunction may result in cognitive impairment in certain neurological disorders, even when neuronal cell death and synapse loss have not yet occurred.

As in AD, a decrease in drebrin content is also observed in Down syndrome (Shim and Lubec, 2002). Recently, drebrin gene expression was reported to be activated by a basic helix-loop-helix (bHLH)–Per-Arnt-Sim (PAS) transcriptional factor, NXF, that competes with another bHLH-PAS transcriptional factor, Sim2, for regulatory DNA elements on the drebrin gene (Ooe *et al*., 2004). Since Sim2 is thought to be involved in the pathogenesis of some of the morphological features and brain anomalies observed in Down syndrome (Dahmane *et al.*, 1995), drebrin may be directly related to the pathogenesis of Down syndrome.

In mild cognitive impairment (MCI), drebrin content is decreased in the superior temporal cortex although it is unchanged in most cortical regions. Stepdown effect in drebrin content is exhibited in the superior temporal cortex from no cognitive impairment to MCI to AD. Further, drebrin levels likely correlate with the severity of cognitive impairment, which is assessed antemortem with the Mini-Mental State Examination (Counts et al. 2006). On the other hand, drebrin content is increased in the superior frontal cortex of MCI. This might be explained as the compensatory response to reduced synaptic function in MCI, although the molecular mechanism is not

known. Together, the disparity of drebrin levels between cortical regions may account for the preservation of certain cognitive functions in MCI patients. Interestingly, a significant decrease in drebrin occurs during normal aging (Hatanpaa *et al.* 1999). Taken together, these findings indicate that drebrin is involved at the molecular level in the cognitive decline observed in neurological disorders as well as in normal aging.

4. Accumulation of amyloid β (Aβ) induces changes in actin-binding proteins, cofilin and drebrin, in Tg2576 transgenic mice

Since detailed analyses of molecular mechanisms underlying synaptic dysfunction in various neurological disorders is difficult to perform using postmortem human tissue, many laboratories have endeavored to generate genetically modified mice that mimic some symptoms of the disorder. A useful mouse model of AD is the transgenic mouse Tg2576, which harbors the amyloid precursor protein (APP) transgene with a Swedish mutation (βAPP695.K595N/M596L) (Hsiao *et al*., 1996). The brains of aged Tg2576 mice accumulate Aβ peptide in the absence of cell loss and neurofibrillary tangles. Paralleling the accumulation of Aβ is a drastic decline in drebrin content with no

significant change in synaptophysin (Calon *et al*., 2004). Cofilin content, however, is increased, and intense immunostaining of cofilin and fractin is observed in the dendrites of aged Tg2576 mouse brain. A reciprocal relationship between drebrin and cofilin may be a consequence of competitive binding of their N-terminal ADF-H domains with F-actin.

The actin depolymerizing activity of cofilin is downregulated by phosphorylation through the signaling cascade of the P21-activated kinase (PAK)/LIM-kinase (LIM-K) pathway (Arber *et al*., 1998; Yang *et al*., 1998). Since PAK and LIM-K activities are reduced in the brains of aged Tg2576 mice and AD patients (Zhao *et al*., 2006), the actin depolymerizing activity of cofilin may be upregulated in these brains. Interestingly in cultured hippocampal cells, overexpression of active PAK prevents drebrin loss resulting from treatment with soluble Aβ1-42 oligomer, whereas intracerebroventricular infusion of a PAK inhibitor causes drebrin loss and significant memory deficits in normal mice (Zhao *et al*., 2006). Thus, downregulation of PAK is sufficient to cause the defects seen in AD, including drebrin loss and cognitive deficits. Overall these data suggest that the following sequential events may occur in the brains of individuals with

AD: Aβ accumulation → PAK activity loss → drebrin loss/cofilin pathology → synaptic dysfunction → cognitive decline (Figure 1).

In addition to genetic vulnerability, a number of environmental risk factors are involved in the pathogenesis and progression of AD. One candidate risk factor is docosahexaenoic acid (DHA), an essential dietary n-3 polyunsaturated fatty acid (PFA) that represents approximately 15% of total fatty acids in the brain. Epidemiological studies suggest that consumption of higher levels of DHA protects the brain from susceptibility to AD (Conquer *et al*., 2000; Tully *et al*., 2003). Lipid peroxidation, which is enhanced in AD brain, accelerates the degradation of PFAs, including DHA (Montine and Morrow, 2005).

In aged Tg2576 mice, dietary depletion of n-3 PFA leads to the degradation of actin (increase in fractin) and a decrease in postsynaptic proteins including drebrin (Calon *et al.*, 2004). These changes are partially restored by supplementing the mice's diet with DHA. DHA directly activates the PI3 kinase/Akt pathway and prevents caspase activation in neuroblastoma cells (Akbar *et al*., 2005). DHA deprivation may activate

caspase, which in turn promotes actin degradation by reducing PI3 kinase activity in the brains of Tg2576 mice (Figure 1).

5. Altered AMPA receptor and drebrin levels in mutant APP and presenilin-1 double knockin mice

Another useful animal model of AD is the $APP^{NLh/NLh}$/$PS\text{-}1^{P264L/P264L}$ double knockin (2xKI) mouse, which harbors both mutant APP and mutant presenilin-1 (PS-1) genes (Flood *et al*., 2002). The brains of these mice accumulate Aβ with aging in the absence of APP overexpression. Electrophysiological analysis revealed that these mice show decreased AMPA receptor activity in the CA1 region of the hippocampus and impairment of long-lasting synaptic plasticity, such as long-term potentiation and depression (Chang *et al*., 2006). These findings are supported by anatomical data obtained from quantitative immunoelectron microscopy analyses showing a decrease in synaptic AMPA receptors in CA1 pyramidal cells. Thus, these data suggest that regulation of AMPA receptor trafficking on the postsynaptic membrane is impaired in 2xKI mice.

Quantitative immunoelectron microscopy also revealed that, by the age of 6 months, 2xKI mice had proportionately fewer drebrin-immunopositive spines than did wild-type mice (Mahadomrongkul *et al*., 2005). In cultured hippocampal neurons, drebrin accumulation within spines depends on AMPA receptor activity (Takahashi *et al*., 2004). Thus, in AD brain, reduced AMPA receptor activity may lead to drebrin loss in postsynaptic sites (Figure 2). Recently, Hsieh *et al.* (2006) showed that increased Aβ level leads to endocytosis of surface and synaptic AMPA receptors, which then causes loss of spines and NMDA receptors. Drebrin may mediate the link between the reduced AMPA receptor and loss of spines.

Since drebrin is involved in the homeostatic synaptic scaling of NMDA receptors (Takahashi *et al*., 2006), a disruption of drebrin-actin cytoskeletal networks in the dendritic spines of AD brains may lead to abnormal regulation of NMDA receptor trafficking (Figure 2). In fact, dietary depletion of n-3 PFA causes a decrease in NMDA receptor expression in the brains of Tg2576 mice (Calon *et al*., 2005).

Although the precise molecular mechanism for NMDA receptor trafficking is largely unknown, the targeting of the NMDA receptor in the postsynaptic membrane

has been recently reported to be regulated by tyrosine phosphorylation of the NMDA receptor subunit 2B (NR2B) by Fyn tyrosine kinase (Prybylowski *et al*., 2005). Synaptotoxicity due to overexpression of APP depends on Fyn kinase activity. Moreover, deletion of Fyn protects hippocampal neurons from synaptotoxicity resulting from the accumulation of Aβ and the overexpression of Fyn and reduces synapse loss in APP-transgenic mice (Chin *et al*., 2004). These findings support the idea that tyrosine phosphorylation of Fyn substrates, including NR2B, represents a downstream component of synaptotoxicity resulting from the accumulation of Aβ. The drebrin-actin complex may contribute to the trafficking of the tyrosine-phosphorylated NR2B-containing NMDA receptor to the postsynaptic site. It would be interesting to determine what happens to synaptic NMDA receptors and cognitive function in genetically manipulated mice lacking drebrin.

6. Conclusion

In this article, we discuss how defects in the postsynaptic components of synapses may contribute to neurological disorders associated with cognitive deficits such as AD. Disruption of actin-regulatory machinery that includes the degradation of actin, accumulation of cofilin, and loss of drebrin, is prominent in AD brain. Drebrin content correlates well with the severity of cognitive impairment, suggesting that drebrin is involved at the molecular level in cognitive impairment associated with neurological disorders and normal aging.

Research on neurological disorders, including AD, has thus far focused on neuropathological aspects, such as formation of senile plaques, neurofibrillary tangles, and Hirano bodies; neuronal cell death; and synapse loss. However, to better understand the nature of the neurological symptoms observed in these disorders, attention must be paid to the physiological mechanisms underlying these disorders, such as functional vulnerability of synapses and resulting synaptic dysfunction.

Figure legends

Figure 1. Proposed mechanistic pathway for the regulation of actin cytoskeletal dynamics in dendritic spines and how it relates to synaptic dysfunction in AD.

The level of PAK activity correlates with the level of drebrin protein in dendritic spines, and PAK negatively regulates cofilin activity. These actin-binding proteins support synaptic function by regulating actin cytoskeletal dynamics in dendritic spines. The accumulation of Aβ inhibits PI3 kinase and reduces PAK activity in AD brain. The reduction in PAK activity causes drebrin loss in spines and simultaneously activates cofilin, while caspase is activated in response to the reduced PI3 kinase activity. Caspase degrades actin, thereby disrupting the actin cytoskeletal network. DHA intake ameliorates the effects of Aβ. Arrows do not necessarily indicate direct interactions between molecules.

Figure 2. Altered actin organization and trafficking of AMPA and NMDA receptors in the dendritic spines of AD brain.

In normal brain, AMPA receptor activity causes drebrin to accumulate in spines. Drebrin regulates not only spine size but also activity-dependent NMDA receptor targeting on postsynaptic sites via the regulation of actin cytoskeletal dynamics. In AD brain, decreased AMPA receptor activity leads to drebrin loss from spines, causing the actin-binding partner to be replaced by cofilin. The actin depolymerizing activity of cofilin severs actin filaments, resulting in decreased spine size and abnormal regulation of NMDA receptor trafficking.

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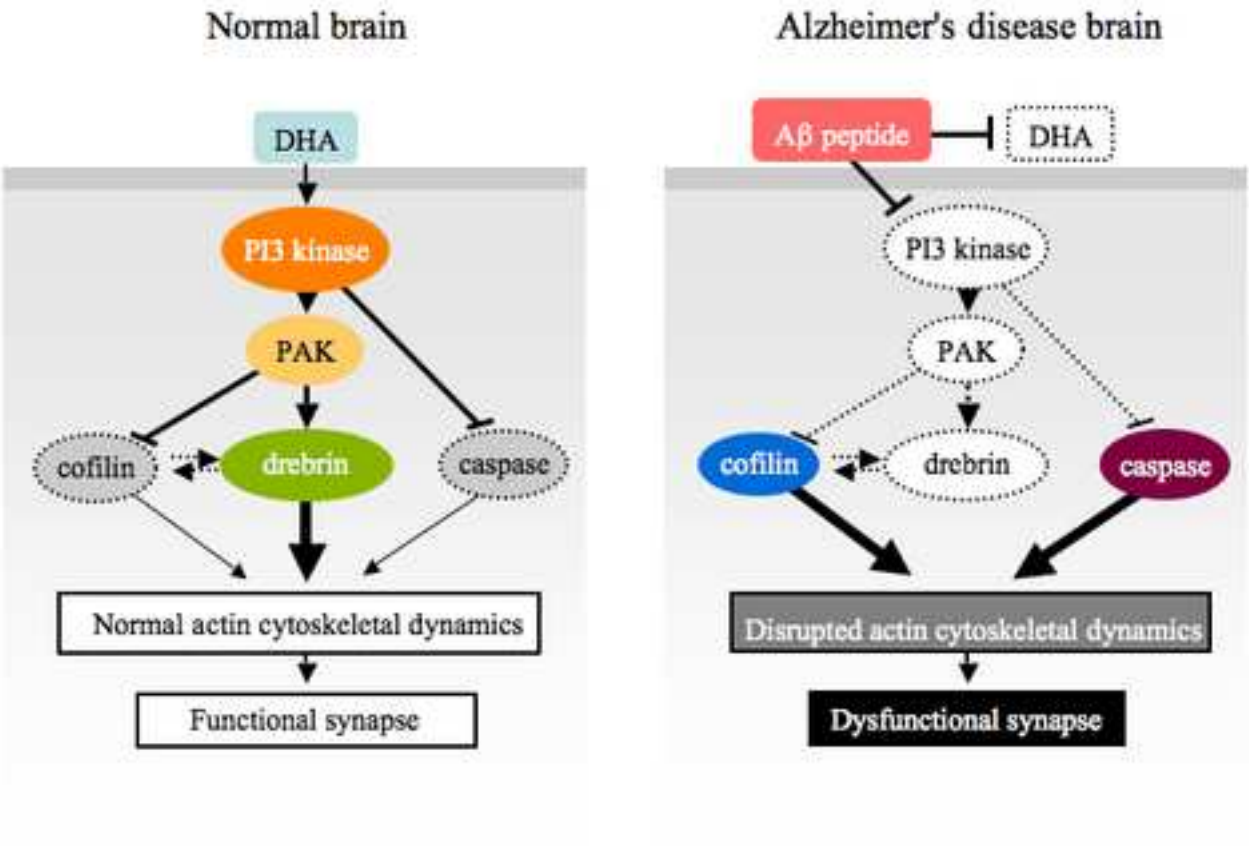

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