observed 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 peptide accumulation → PAK activity loss → drebrin loss/cofilin pathology → synaptic dysfunction → cognitive decline (Fig. 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 the total fatty acids in the brain. Epidemiological studies suggest that the consumption of large amounts of DHA protects the brain from its 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, the dietary depletion of $n-3$ PFA leads to the degradation of actin (increase in fractin level) and a decrease in the level of 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 inhibits 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 (Fig. 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 (2× KI) mouse, which harbors both mutant APP and mutant presenilin-1 (PS-1) genes (Flood et al., 2002). The brains of these mice accumulate Aβ peptide with aging without inducing APP overexpression. Electrophysiological analysis revealed that these mice show a decreased AMPA receptor activity in the CA1 region of the hippocampus and an impaired 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 analysis showing a decrease in synaptic AMPA receptor number in CA1 pyramidal cells. Thus, these data suggest that the regulation of AMPA receptor trafficking on the postsynaptic membrane is impaired in 2× KI mice.

Quantitative immunoelectron microscopy also revealed that, by the age of 6 months, 2× KI mice have proportionately fewer drebrin-immunopositive spines than 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 (Fig. 2). Recently, Hsieh et al. (2006) have shown that an increased Aβ peptide level leads to endocytosis of surface and synaptic AMPA receptors, which then causes loss of spines and NMDA receptors. Drebrin may serve as a link between the reduced AMPA receptor activity and the loss of spines.

Because 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 the abnormal regulation of NMDA receptor trafficking (Fig. 2). Moreover, the dietary depletion of $n-3$ PFA causes a decrease in NMDA

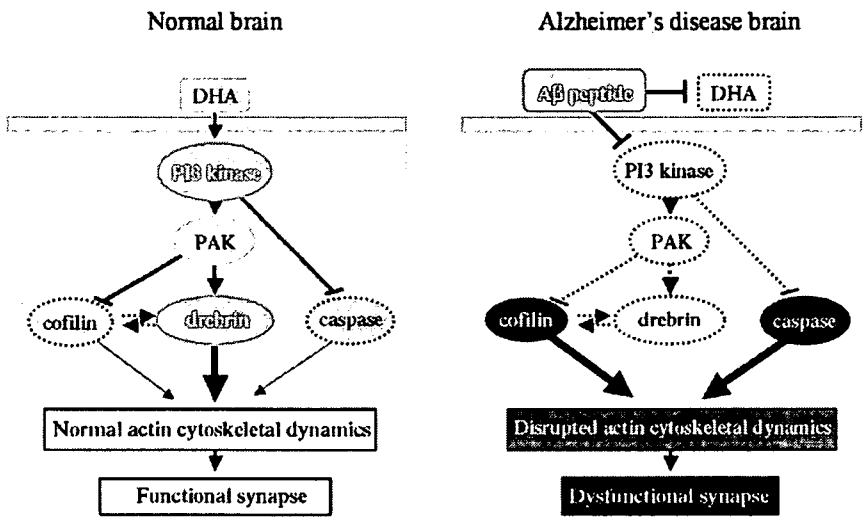

Fig. 1. Proposed mechanistic pathway for regulation of actin cytoskeletal dynamics in dendritic spines and how this mechanism is related to synaptic dysfunction in AD. PAK activity correlates with the drebrin level in dendritic spines, and PAK negatively regulates cofilin activity. These actin-binding proteins support synaptic function by regulating actin cytoskeletal dynamics in dendritic spines. The accumulation of Aβ peptide inhibits PI3 kinase and reduces PAK activity in AD brain. The reduction in PAK activity causes drebrin loss in spines and simultaneously activates cofilin, whereas 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 peptide accumulation. Arrows do not necessarily indicate direct interactions between molecules.

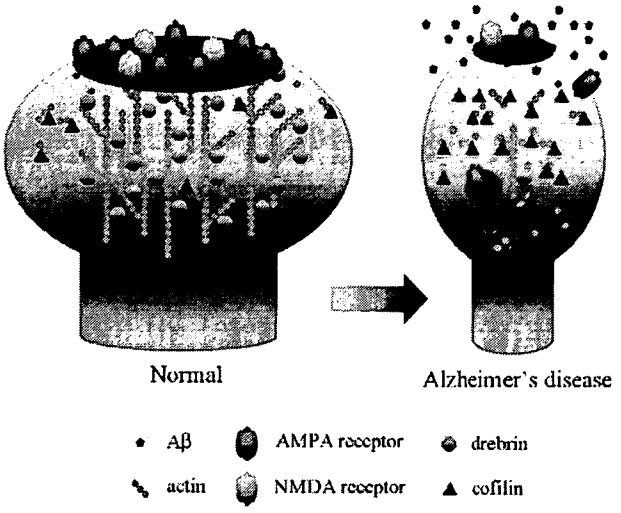

Fig. 2. Altered actin organization and trafficking of AMPA and NMDA receptors in the dendritic spines of AD brain. In a normal brain, increased AMPA receptor activity causes drebrin to accumulate in spines. Drebrin regulates not only spine size but also activity-dependent NMDA receptor targeting on postsynaptic sites via the regulation of actin cytoskeletal dynamics. In AD brain, reduced 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 a decreased spine size and the abnormal regulation of NMDA receptor trafficking.

receptor expression level in the brains of Tg2576 mice (Calon et al., 2005).

Although the precise molecular mechanism of NMDA receptor trafficking is largely unknown, the targeting of the NMDA receptor in the postsynaptic membrane has recently been reported to be regulated by the tyrosine phosphorylation of the NMDA receptor subunit 2B (NR2B) by Fyn tyrosine kinase (Prybylowski et al., 2005). Synaptotoxicity due to the overexpression of APP depends on Fyn kinase activity. Moreover, the deletion of Fyn protects hippocampal neurons from synaptotoxicity resulting from the accumulation of Aβ peptide and the overexpression of Fyn, and reduces synapse loss in APP transgenic mice (Chin et al., 2004). These findings support the idea that the tyrosine phosphorylation of Fyn substrates, including NR2B, represents a downstream component of synaptotoxicity resulting from the accumulation of Aβ peptide. 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 the changes in synaptic NMDA receptors and cognitive function in genetically manipulated mice lacking drebrin.

6. Conclusion

Here, we discuss how defects in the postsynaptic components of synapses may contribute to the development of neurological disorders that are accompanied by cognitive deficits such as AD. The disruption of the actin-regulatory machinery that includes the degradation of actin, the accumulation of cofilin, and the loss of drebrin, is a prominent pathological feature in AD brain. Drebrin level correlates well with the severity of cognitive impairment, suggesting that drebrin is involved at the molecular level in the development of cognitive impairment that accompanies neurological disorders and normal aging.

Thus far, research on neurological disorders, including AD, has been focused on neuropathological aspects, such as the 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 given to the physiological mechanisms underlying these disorders, such as the functional vulnerability of synapses and the resulting synaptic dysfunction.

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