Insulin resistance in the brain: A new therapeutic target for Alzheimer's disease

Alzheimer's disease (AD) is the most common form of dementia, accounting for more than 50% of cases at autopsy and in clinical series. The incidence of the disease doubles every 5 years after 65 years-of-age. With the aging of the population, the number of AD patients continues to increase. AD affects memory and other cognitive domains, leading to the subsequent deprivation of independence in daily life. The disease places a substantial burden not only on the sufferers themselves, but also on family members, and is responsible for a substantial economic cost to society. Existing treatments, however, only slow the progression of the symptoms of the disease. Furthermore, their efficacy does not extend to all people with AD, and benefits are not conveyed beyond an average of 6 months. Therefore, more disease-modifying therapeutics are definitely required.

Cerebral plaques laden with β-amyloid peptide (Aβ) and dystrophic neurites in neocortical terminal fields are important pathological features of AD. Neurofibrillary tangles (NFTs), another pathological feature of AD, are filamentous inclusions in pyramidal neurons that occur in AD and other neurodegenerative disorders termed tauopathies. The number of NFTs is known to be paralleled with the severity of AD. The primary component of such tangles is an abnormally hyper-phosphorylated and aggregated form of tau. These amyloid plaques and NFTs have been unambiguously considered hallmarks of AD, accompanied by devastating brain atrophy and cell loss. An Aβ that consists of 40–42 amino acid peptides was identified as a main component of amyloid plaques, and several genetic cases of AD have been linked to the Aβ metabolism. It was initially thought that aggregates of Aβ might be capable of interfering with brain function and causes the generation of NFTs, which ultimately leads to the death of neurons. The hypothesis of 'amyloid cascade theory' has attributed dementia to nerve cell death caused by the toxicity of large insoluble aggregates of amyloid fibrils. However, recent research advances during the past decade showed that soluble rather than deposited Aβ is associated with dementia. Many studies have suggested that prefibrilar Aβ oligomers were potent neurotoxins. It has been found that Aβ oligomers inhibit functional synaptic plasticity, although they do not induce neuronal cell death in general. Long-term neurophysiological impairment ultimately causes the degeneration of synapses, which becomes most apparent on the morphological level by the retraction of dendritic spines. The loss of meaningful synaptic connections in the brain of AD patients impairs their memory function. The precise mechanism of the inhibition of synaptic function by Aβ oligomers remains to be elucidated.

Insulin resistance (IR) and/or hyperinsulinemia is one of the main disease characteristics of type 2 diabetes mellitus, especially in conjunction with obesity. Numerous clinical, basic and epidemiological studies have established that IR contributes to AD pathogenesis. For example, the Hisayama Study showed that systemic IR is related to AD pathology[1], and ample evidence shows that IR is associated with cognitive dysfunction. Obesity, the pathological state that is often accompanied by IR, in middle age is also known to be a risk factor for AD in later life. However, the mechanism of how IR is associated with AD remains largely unknown.

It is generally agreed that insulin located within the brain is mostly of pancreatic origin, having passed through the blood–brain barrier, although there is some debate about the amount of insulin that is produced de novo within the central nervous system (CNS). The receptor of insulin distributes throughout wide regions in the brain, and the hippocampus that has close association with memory function has dense distribution of the insulin receptor. The major known actions of insulin in the brain include control of food intake (through insulin receptors located in the olfactory bulb and thalamus) and effects on cognitive functions, including memory. Insulin also regulates the expression of acetylcholine transferase, which is an enzyme responsible for acetylcholine (ACh) synthesis. ACh is a critical neurotransmitter in cognitive function, and it might be relevant to neurocognitive disorders in diabetics. Recent basic research has shown that insulin signaling in the CNS prevents the pathological binding of Aβ oligomers[2].

Some basic research suggests that insulin signaling is involved in AD-related pathology through its effects on the Aβ metabolism and tau phosphorylation[3]. Insulin signaling activates the phosphatidylinositol-3 kinase (PI3K)/Akt pathway, which leads to the inactivation of glycogen synthase kinase-3β (GSK-3β). GSK-3β regulates tau phosphorylation, one of the main pathological components of AD. Less insulin signaling might also induce increased activity of GSK-3β, which leads to the enhanced phosphorylation of tau protein and the formation of NFTs. Decreased insulin signaling reduces the synthesis of several proteins, including insulin-degrading enzyme (IDE), which degrades Aβ as well as insulin, and reduced amounts of IDE might result in greater amyloid deposition.

*Corresponding author. Hiroyuki Umegaki
Tel.: +81-52-744-2364 Fax: +81-52-744-2371
E-mail address: Umegaki@med.nagoya-u.ac.jp

A recent study by Talbot et al. reported in the *Journal of Clinical Investigation* showed that insulin signaling is impaired in the AD brain[4]. The study showed that through *ex vivo* insulin receptor stimulation, insulin signaling is greatly reduced where there is phosphorylation of insulin receptor substrate 1 (IRS-1) at several serine residues, which was previously confirmed as a feature of IR in the brain of AD patients without diabetes. Brain insulin resistance in AD is not dependent on diabetes, or on the apolipoprotein E4 (Apo E4) genotype, which is a major determinant of risk for sporadic AD. Furthermore, the levels of IRS-1 phosphorylation in hippocampal neurons were found to be negatively correlated with episodic and working memory. Although the underlying mechanism of the induction of IR in the brain remains to be elucidated, neurotoxicity mediated by Aβ oligomers can be suggested. Furthermore, systemic IR may induce brain IR. (Figure 1).

In the same issue of the *Journal of Clinical Investigation*, Bomfim et al. showed a critical role of the soluble Aβ oligomer in producing brain IR in AD, and successfully showed the pharmacological manipulation of this pathway by a glucagon-like peptide 1 (GLP-1) agonist[5]. Using multiple model systems, the authors show that soluble Aβ oligomers increase the production of the inflammatory cytokine tumor necrosis factor-α (TNF-α), leading to the phosphorylation of IRS-1 by c-Jun N-terminal kinase (JNK). Furthermore, a small-molecule activator of the GLP-1 receptor, developed to treat type 2 diabetes, reduced the phosphorylation of IRS-1 in the brain and improved cognition in a mouse model of AD.

These findings suggest that IR in the brain might play a pathogenic role in the early stages of AD and might be a new therapeutic target for disease process modification, and possibly prevention. Brain IR can be modified by insulin-sensitizing drugs, such as metfor-
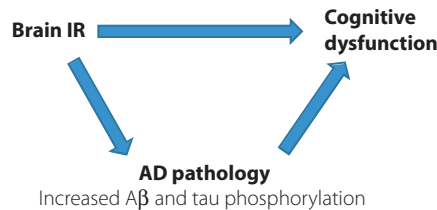

Figure 1 | Brain insulin resistance (IR) might induce cognitive dysfunction directly through synaptic dysfunction and/or through increase of β-amyloid peptide (Aβ) and tau phosphorylation. AD, Alzheimer's disease.
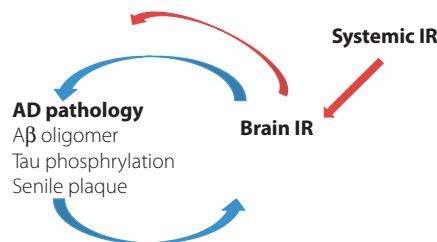

Figure 2 | Brain insulin resistance (IR) might exacerbate Alzheimer's disease (AD) pathology. The systemic IR might be associated with increased brain IR. Aβ, β-amyloid peptide.

min, the GLP-1 mimetics exenatide and liraglutide, and peroxisome proliferator-activated receptor γ (PPARγ) agonists. One clinical study reports that the administration of pioglytazone, a PPARγ agonist, to patients with mild AD has beneficial effects on cognition[6]; and, as shown in the study by Bomfim et al., the effects of GLP-1 agonist can be promising[5]. This class of drug has been shown to be effective in terms of decreasing blood glucose, insulin and lipid levels, and improving hypertension; these actions might contribute to preventing the development of AD.

Systemic IR states, such as obesity, can induce IR in the brain. The new hypothesis of the development of AD suggests that Aβ oligomer induces IR in the neurons in the brain to enhance synaptic dysfunction and neuronal damage directly or through reduced expression of IDE, Aβ breakdown enzyme and

enhanced tau phosphorylation through the disinhibition of GSK-3β (Figure 1). Systemic IR also exacerbates brain IR to expedite this disease process (Figure 2), showing that IR in the AD brain has therapeutic implications.

In conclusion, the demonstration of IR in the AD brain by Talbot et al.[4] has a great impact on our understanding of the disease mechanism and suggests promising new therapeutic targets for the treatment of AD patients.

Hiroyuki Umegaki*
Department of Geriatrics, Nagoya University Graduate School of Medicine, Nagoya, Aichi, Japan

REFERENCES

1. Matsuzaki T, Sasaki K, Tanizaki Y, et al. Insulin resistance is associated with the pathology of Alzheimer disease: the Hisayama Study. *Neurology* 2010; 75: 764–770.
2. De Felice FG, Vieira MN, Bomfim TR, et al. Protection of synapses against Alzheimer's-linked toxins: insulin signaling prevents the pathogenic binding of Abeta oligomers. *Proc Natl Acad Sci USA* 2009; 106: 1971–1976.
3. Li L, Hölscher C. Common pathological processes in Alzheimer disease and type 2 diabetes: a review. *Brain Res Rev* 2007; 56: 384–402.
4. Talbot K, Wang HY, Kazi H, et al. Demonstrated brain insulin resistance in Alzheimer's disease patients is associated with IGF-1 resistance, IRS-1 dysregulation, and cognitive decline. *J Clin Invest* 2012; 122: 1316–1338.
5. Bomfim TR, Forny-Germano L, Sathler LB, et al. An anti-diabetes agent protects the mouse brain from defective insulin signaling caused by Alzheimer's disease-associated Aβ oligomers. *J Clin Invest* 2012; 122: 1339–1353.
6. Sato T, Hanyu H, Hirao K, et al. Efficacy of PPAR-γ agonist pioglitazone in mild Alzheimer disease. *Neurobiol Aging* 2011; 32: 1626–1633.