Chapter 8
Diabetes and Alzheimer's Disease

Shuko Takeda and Ryuichi Morishita

Abstract It is well documented that diabetes mellitus increases patients' risk of developing cerebrovascular diseases and subsequent vascular dementia. Recent epidemiological studies have provided intriguing evidence that diabetes increases patients' risk of developing Alzheimer's disease, the most common cause of dementia in the elderly population. This might be partly explained by vascular complications in patients with diabetes, which lead to neurodegeneration. The results of the Nun Study, a longitudinal study of aging Catholic sisters that examined the onset of Alzheimer's disease, demonstrated the impact of cerebrovascular alterations on the progression of dementia. However, a growing body of research indicates that diabetes directly affects the pathogenesis of Alzheimer's disease via multiple mechanisms. This chapter will discuss the current knowledge of (1) epidemiological studies supporting the interplay between diabetes and Alzheimer's disease, (2) the role of insulin signaling in the central nervous system, (3) the pathophysiology of Alzheimer's disease, and (4) the molecular mechanisms that link diabetes to Alzheimer's disease in order to provide new therapeutic targets for Alzheimer's disease.

Keywords Alzheimer's disease • Aβ • Tau • Dementia • Brain insulin signaling

8.1 Epidemiology: Diabetes Is Associated with a High Risk of Alzheimer's Disease

The incidence of dementia is increasing at an alarming rate, not only in the developed countries but also in countries with low and middle incomes [1]. More than 35 million people worldwide are affected by dementia, with numbers expected to almost double every 20 years to 115.4 million in 2050 [1]. AD is the most common form of dementia, and it is estimated that currently more than 12 million individuals

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around the world suffer from the devastating disease [2]. The global prevalence of DM also continues to be rising worldwide [3].

Interestingly, epidemiological studies have demonstrated that diabetic individuals have a higher risk of developing AD, independent of the risk for vascular dementia [4, 5]. Ott et al., in a prospective population-based Rotterdam study, found that DM almost double the risk of AD. They reported that patients with DM treated with insulin were at highest risk. Another population-based study reported that hyperinsulinemia was highly associated with a risk of AD and decline in memory-related cognitive scores [6]. A clinicopathological study from Japan, Hisayama study, found a strong association between insulin resistance and a development of AD pathology (senile plaque), giving a direct evidence demonstrating that DM conditions could affect fundamental mechanisms of AD [7]. These imply common cellular and molecular mechanisms underlying AD and DM.

8.2 Pathophysiology of Alzheimer's Disease

AD is the most common form of neurodegenerative dementia and is characterized by progressive cognitive and behavioral deficits. AD is characterized by a typical symmetric pattern of brain atrophy predominantly affecting the medial temporal lobes, including hippocampus, which is associated with typical memory deficit observed in AD.

Microscopically, AD is characterized by two main neuropathological features: senile plaques and neurofibrillary tangles. Amyloid plaque is the abnormal extracellular accumulation and deposition of beta-amyloid (Aβ) in the brain. Aβ is a 38- to 43-amino acid peptide produced by sequential cleavage of amyloid precursor protein (APP) by β- and γ-secretase in neurons [8]. Three genes with a missense mutation that cause familial AD have been identified: APP, presenilin 1, and presenilin 2. All these mutations lead to abnormal accumulation of Aβ, suggesting the significant role of Aβ in AD pathogenesis. The so-called amyloid hypothesis, in which accumulation of neurotoxic Aβ is the initial trigger of a cascade leading to neurodegeneration, has been widely accepted by researchers and the main therapeutic target in drug development against AD [8].

Cerebral accumulation and aggregation of tau protein, as intracellular inclusions known as neurofibrillary tangles (NFTs), is another neuropathological hallmark of AD [9]. Tau is a member of microtubule-associated protein family, enriched in axons of neurons, that contributes to the assembly and stabilization of microtubules. Importantly, cognitive decline in patients of AD are most tightly linked with progression of NFTs in a hierarchical pattern, starting in the medial temporal lobes and marching throughout the brain during disease progression [10]. Pathological accumulation of tau is believed to be more directly linked with a neuronal malfunction and cell death.

Considerable research efforts have been directed toward the development of therapeutic strategies to slow, or even stop, the progression of AD, focusing on Aβ

or tau pathology. However, promising therapies targeting Aβ such as γ-secretase inhibitors or immunotherapy tested in clinical trials have been disappointing so far. On the other hand, the therapeutic strategy is shifting to the prevention of AD by management of the risk factors, such as DM and hypertension. It is estimated that delaying the onset of AD by just a few years could substantially decrease the number of patients with AD over the next 50 years [2].

8.3 Insulin Signaling, Cognitive Function, and AD Pathogenesis

8.3.1 Brain Is Insulin-Insensitive?

The brain has been generally considered a so-called "insulin-insensitive" organ; however, it is becoming accepted that insulin plays physiological and pathophysiological roles in the brain, including neuronal development, synapse formation, learning and memory, glucoregulatory function, and feeding behavior [11]. Although the origin of brain insulin remains largely unknown, the presence of high concentration of insulin in the brain has been reported in human and animal models [12], suggesting that insulin is produced locally in the brain or actively transported from peripheral source. Detection of insulin C-peptide and mRNA in the brain strongly suggest that brain has its own insulin-producing machinery. Furthermore, experiments using primary neuron culture demonstrated neurons produce and release insulin in vitro [13]. Insulin has been shown to be able to cross the blood-brain barrier (BBB) in animal models (Fig. 8.1). It is assumed that insulin crosses the BBB via specific transporter, which can be regulated by multiple conditions including AD and DM.

Insulin receptors (IRs) are known to be expressed in various regions of the central nervous system. IR is a transmembrane receptor that mediates a cascade of signaling pathways regulating a variety of cellular events, including cell proliferation, protein synthesis, and glucose transport [14]. Notably, IRs are demonstrated in the hippocampus and cerebral cortex, which play a critical role in learning and memory formation [14]. Learning and memory are cognitive domains often impaired in patients with AD in the early stage.

Although the role and significance of IRs in the central nervous system remain largely unknown, IRs are reported to be involved in a variety of neuronal functions (Fig. 8.1). Phosphatidylinositol 3-kinase (PI3K) and extracellular signal-regulated kinase (ERK) are major downstream targets of IR signaling. Binding of insulin to IR initiates activation of Ras-ERK cascade, which is thought to play a role in synaptic plasticity [15]. Activation of cAMP response element binding protein (CREB), a downstream target of ERK, induces structural changes associated with long-term memory formation [16]. Activated PI3K is known to promote GABAergic transmission that plays a vital role in learning and memory [17]. Significance of IR signaling

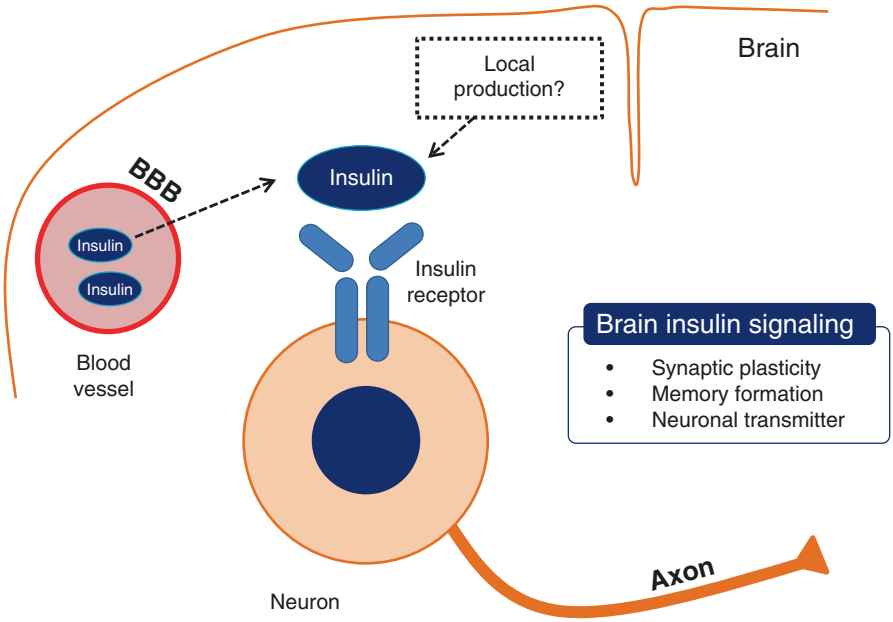

Fig. 8.1 Insulin signaling and neuronal functions. Insulin and insulin receptors exist in the central nervous system. Insulin receptors are involved in a variety of neuronal functions, including synaptic plasticity, memory formation, and the regulation of neuronal transmitters. *BBB* blood-brain barrier

pathway in cognitive function has been demonstrated in animal models as well. Kleinridders et al. reported age-related behavioral impairment in brain-specific knockout of IR mice [18], which was associated with altered dopamine turnover.

8.3.2 Insulin Signaling in Alzheimer's Brain

Aβ itself has been shown to affect the insulin signaling pathway. Xie and coworkers reported that synthetic Aβ peptide could attenuate insulin binding and receptor autophosphorylation, suggesting that Aβ is a direct competitive inhibitor of insulin binding and action [19]. Another report demonstrated that Aβ could induce insulin resistance in cultured cells via downregulation of IRs [20].

Postmortem analyses of brain tissues from patients with AD revealed a downregulated expression of insulin and insulin signaling pathway molecules, including IR, insulin-like growth factor (IGF)-1 receptor, IRS-1, and IRS-2 [21], indicating an attenuation of insulin signaling in the AD brain. Mammalian target of rapamycin (mTOR), which is downstream target of IR signaling, has been also implicated in the pathogenesis of AD [22].

8.4 Diabetes Affects Alzheimer's Amyloid Pathology Via Multiple Mechanisms

Pathological accumulation and aggregation of Aβ, a major component of senile plaque, contribute to the AD pathogenesis. Aβ is a normal product of APP and present in healthy brain. At physiological concentrations, Aβ exists as a soluble, non-toxic form, mainly in the extracellular space of the brain. A physiological role of Aβ (and other APP-related products) is not yet well understood. In the AD brain, rise in Aβ levels leads to pathological aggregation and formation of senile plaques. The steady-state level of Aβ in the brain is determined by the balance between its production and clearance [23]; increased production, decreased clearance, or both can lead to rise in Aβ concentration. Senile plaque, fibrillar form of Aβ, has been believed to cause neuronal dysfunction and cell death; however, recent studies highlight the critical role of soluble, intermediate oligomers in AD pathogenesis [24]. Diabetic conditions have been reported to affect Aβ turnover and aggregation mechanisms (Fig. 8.2).

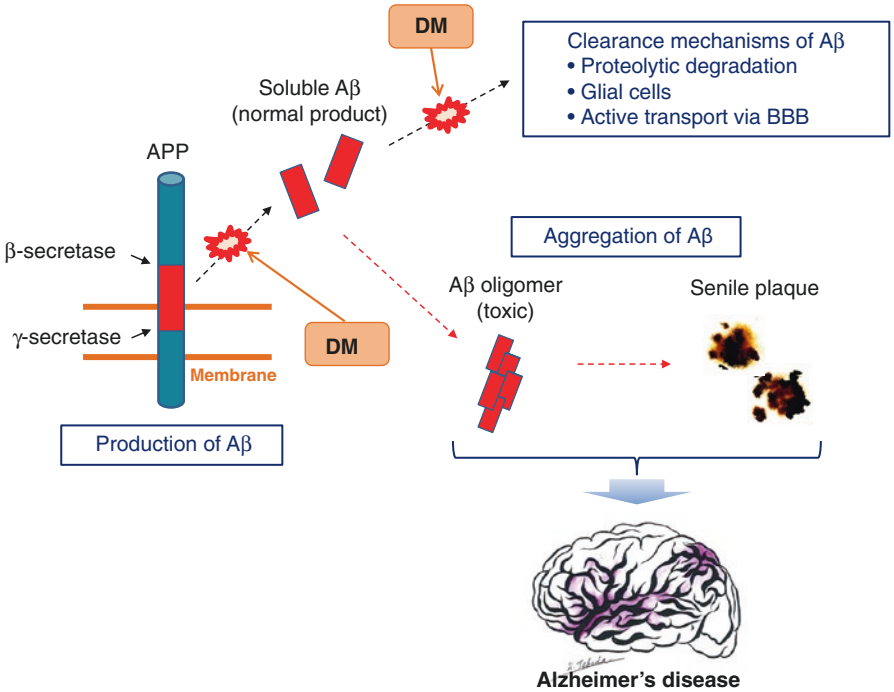

Fig. 8.2 Effect of diabetes on Alzheimer's amyloid pathology via multiple mechanisms. DM increases the brain's Aβ load via multiple mechanisms, which leads to toxic Aβ oligomer and senile plaque formation. *APP* amyloid precursor protein, *BBB* blood-brain barrier, *DM* diabetes mellitus

8.4.1 Effect of DM of Aβ Synthesis

Cellular resistance for insulin/insulin-like growth factor-1 (IGF-1) represents one of the key molecular bases of DM. The role of insulin signaling in the APP processing and Aβ accumulation has been reported by independent research groups using animal models [21, 25]. Stohr et al. generated a unique mouse model by crossing neuron-specific insulin receptor (IR) knockout mice with Alzheimer's APP transgenic mice [25]. The crossed mice had significantly lower levels of Aβ in the brain, suggesting that neuronal IR signaling mediates APP processing and contribute to AD pathogenesis. Along the same line, Ho et al. demonstrated that diet-induced insulin resistance in Alzheimer's APP transgenic mice promoted Aβ synthesis in the brain with increased γ-secretase activities [26]. They also reported a functional decline in IR-mediated signal transduction in the brains. Another group reported that insulin resistance, induced by excessive sucrose intake, increased cerebral Aβ peptide levels and exacerbated learning impairment in Alzheimer's APP transgenic mice [27].

8.4.2 Effect of DM on Aβ Clearance from Brain

The clearance of Aβ from the brain is accomplished by multiple mechanisms, including proteolytic degradation, uptake by glial cells, and active transport via the blood-brain barrier (BBB). Dysregulation of these mechanisms can lead to increase in brain Aβ load.

Proteolytic degradation is a potent determinant of brain Aβ load. Neprilysin (NEP), angiotensin-converting enzyme (ACE), insulin-degrading enzyme (IDE), matrix metalloproteinases (MMPs), and endothelin-converting enzyme (ECE) have been implicated in the degradation of Aβ in the brain [28]. Hyperinsulinemia in DM condition is postulated to increase Aβ levels via insulin's competition with Aβ for IDE [29]. This hypothesis is partly supported by genetic studies reporting that IDE gene variation is associated with a high risk of AD, as well as DM [29].

Enhancing Aβ clearance from the brain, via the BBB, into peripheral circulation is considered to be one of the therapeutic targets for AD. Exchange of Aβ through BBB is tightly regulated and free exchange is not allowed because of the presence of tight junctions between endothelial cells on the cerebrovascular wall. Active transport of Aβ through BBB is believed to be predominantly mediated by two molecules: low-density lipoprotein receptor related protein 1 (LRP) and the receptor for advanced end glycation products (RAGE) [30].

RAGE, implicated in the pathogenesis DM, is postulated to bind Aβ and mediate influx of Aβ into brain from the peripheral circulation. Increased expression of RAGE on the BBB could enhance Aβ influx, leading to the accumulation and aggregation of Aβ in the brain. Takeda et al. generated a unique mouse model by crossing Alzheimer's APP transgenic mice with ob/ob diabetic mice [31]. The diabetic-Alzheimer mice showed increased expression of RAGE on the cerebrovasculature at an early age and severe cerebral amyloid angiopathy (CAA, deposition

of Aβ on cerebral blood vessels) at older age. This implies the role of cerebrovascular RAGE and Aβ in the AD pathogenesis. Dysregulated expression/function of RAGE at the BBB might represent a molecular link between DM and AD.

8.5 Diabetes Affects Alzheimer's Tau Pathology

Abnormal accumulation and aggregation of tau protein in the neurons represent one of the fundamental aspects of AD pathogenesis. Tau plays an important role in stabilizing neuronal microtubules under normal physiological conditions. In pathological condition, such as in the AD brain, tau undergoes a change toward a pathological conformation which leads to aggregation and fibrillization. Phosphorylation of tau is known to play a critical role in aggregation process and neuronal toxicity [32].

8.5.1 Insulin Resistance, GSK-3, and Tau Phosphorylation

Glycogen synthase kinase-3 (GSK-3) is a serine/threonine kinase with multiple physiological roles in the regulation of glycogen synthesis, cellular differentiation and proliferation, and apoptosis. Impaired insulin signaling with inactivation of Akt in diabetic condition leads to an activation of GSK-3, a key target for the development of novel treatment for type 2 diabetes.

GSK-3β is known to be one of key regulators of tau phosphorylation. In diabetic condition, activated GSK-3β induces hyper-phosphorylation of tau, which could enhance NFT formation. Experimental study using rat model of obesity and diabetes reported that obesity-induced peripheral insulin resistance was associated with central insulin resistance and tau hyper-phosphorylation [33] (Fig. 8.3). GSK-3 has been also shown to mediate APP processing, leading to increased Aβ synthesis [34]. Activation of GSK-3, in theory, induces abnormal accumulation of Aβ and development of AD pathology. This is also one potential mechanism through which diabetes accelerates progression of AD.

Importantly, GSK-3 expression is reported to be upregulated in the hippocampus of the brain and peripheral lymphocytes of patients with AD [34]. Dysregulation of GSK-3 activity may represent a common molecular mechanism between DM and AD.

8.5.2 Other Effects of Diabetes on Tau Pathology

Protein glycation plays a role in the pathogenesis of diabetic complications. Glycation happens even in the normal physiological conditions; however, excessive glycation due to prolonged hyperglycemia interferes with the protein's normal

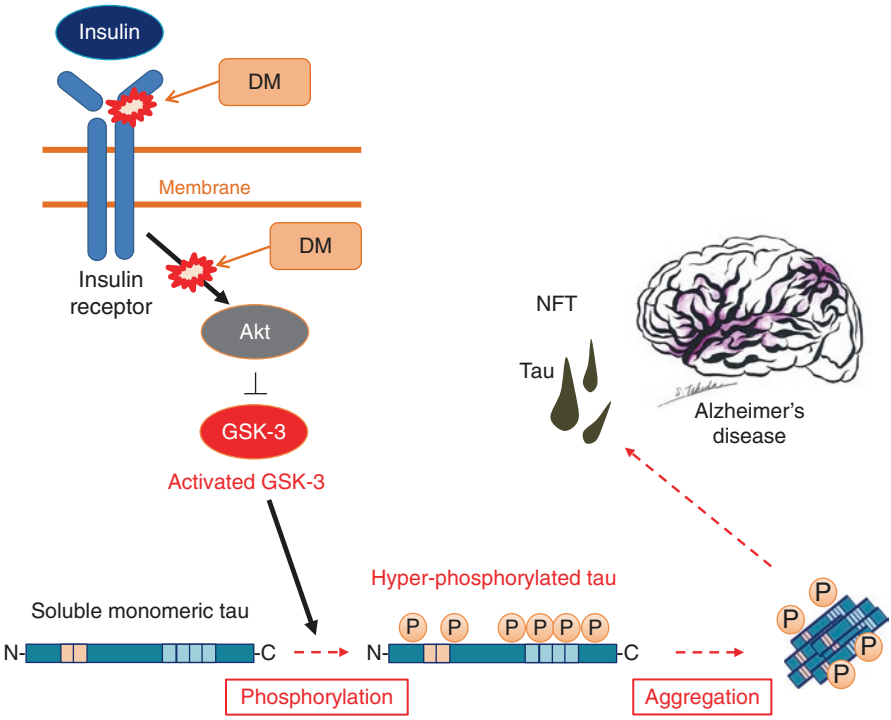

Fig. 8.3 Effect of diabetes on Alzheimer's tau pathology. Insulin resistance caused by DM induces the activation of GSK-3, which enhances the phosphorylation of the tau protein. Phosphorylation plays an important role in the aggregation of tau, leading to Alzheimer's NFT formation. *GSK-3* glycogen synthase kinase-3, *NFT* neurofibrillary tangle, *DM* diabetes mellitus, *P* phosphorylation

function by disrupting molecular conformation. In line with Alzheimer's tau pathology, glycation of tau is reported to mediate NFT formation in AD brain [35].

Tau pathology is known to "spread" in a stereotypical pattern in AD brain during disease progression, likely by transsynaptic mechanism between neurons [10]. So-called "tau propagation" phenomenon has been getting attention among researchers lately since it may provide new therapeutic opportunities for AD. Effects of diabetic conditions on tau propagation remain largely unknown and need to be investigated in future studies.

8.6 Therapeutic Aspects of Diabetes-Alzheimer Interaction

An important question that remains to be answered is whether altered insulin signaling in the brain is a cause or a consequence of neurodegeneration in AD. Lester et al. clearly demonstrated that multiple aspects of AD neuropathology, such as Aβ

accumulation and tau hyper-phosphorylation, can be reproduced by selectively impairing insulin/IGF signaling using an intracerebral streptozotocin injection model in rodent [36]. This means that altered brain insulin signaling might be a causative event in the AD pathogenesis. Other reports, however, indicate that reduction in brain insulin signaling could be a compensatory response against AD pathology [21, 37]. The causal relationship issue between altered insulin signaling and AD pathogenesis is critical when considering the therapeutic implications of modulating brain insulin signaling. Although further research is needed to reveal the role and significance of brain insulin signaling in AD pathogenesis, modulating the signaling pathway could be a potentially promising strategy for AD treatment. In line with therapeutic potential, nasal insulin delivery has been widely investigated by researchers, and recent pilot studies have reported promising results in mild AD patients [38].

Takeda et al. reported the possibility that Alzheimer's pathogenesis might exacerbate glucose intolerance in peripheral organs [31]. It has been becoming apparent that the central nervous system plays a role in the regulation of energy metabolism in peripheral organs. There may be a mutual interaction between DM and AD, which establish a vicious cycle (Fig. 8.4). Management of DM in patients with AD may halt the vicious cycle and prevent the progression of both diseases.

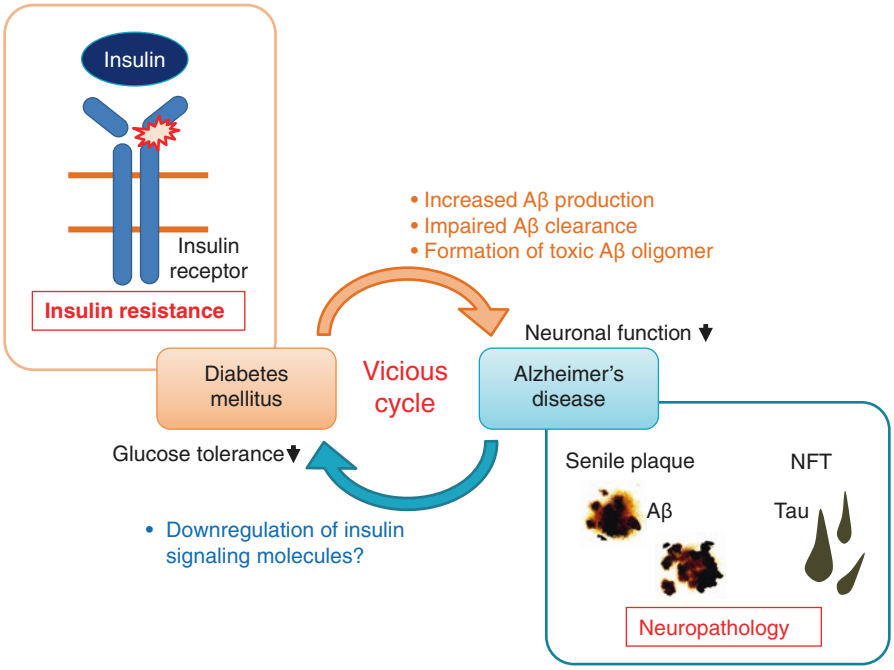

Fig. 8.4 Interaction between diabetes and Alzheimer's disease. Results from animal models suggest an interaction between DM and AD, which establishes a vicious cycle. *NFT* neurofibrillary tangle

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