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Toshiharu Ninomiya *Editors*

Diabetes Mellitus

A risk factor for Alzheimer's Disease

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Chapter 1
Origins of Brain Insulin and Its Function

Yusaku Nakabeppu

Abstract The brain or central nervous system (CNS) utilizes a vast amount of energy to sustain its basic functions, and most of the energy in the brain is derived from glucose. Whole-body energy and glucose homeostasis in the periphery of the human body are regulated by insulin, while the brain had been considered as an "insulin-insensitive" organ, because bulk brain glucose uptake is not affected by insulin in either rodents and humans. However, recently it has become clear that the actions of insulin are more widespread in the CNS and are a critical part of normal development, food intake, and energy balance, as well as plasticity throughout adulthood. Moreover, there are substantial evidence demonstrating that brain insulin is derived from pancreas, neurons, and astrocytes. In this chapter, I reviewed recent progress in roles of insulin in the brain, expression of insulin genes, and multiple origins of the brain insulin.

1.1 Introduction

The brain or central nervous system (CNS) utilizes a vast amount of energy to sustain its basic functions, such as maintaining or re-establishing of membrane potentials, signaling, and other essential cellular activities. While an adult human brain typically weighs only about 2% of the body weight, a resting brain consumes more than 20% of all the oxygen consumed in the whole body, thus indicating a tenfold greater energy requirement than other tissues. This high demand for energy in the brain is mainly achieved by ATP production during oxidation of glucose or oxidative phosphorylation in the mitochondria (Chen and Zhong 2013; MacKenna et al. 2012).

Whole-body energy and glucose homeostasis in the periphery of the human body are regulated by insulin; however, the brain had been considered as an "insulin-

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insensitive" organ, because bulk brain glucose uptake is not affected by insulin in either rodents (Cooney et al. 1985; Hom et al. 1984) and humans (Hasselbalch et al. 1999; Seaquist et al. 2001). The initial acceptance that insulin mediates activities in the brain came from studies demonstrating that insulin plays important roles in homeostatic regulation mediated by the hypothalamus (Bruning et al. 2000; Schwartz et al. 1992, 2000). However, more recently it has become clear that the actions of insulin are more widespread in the CNS and are a critical part of normal development (Chiu and Cline 2010), food intake, and energy balance (Kullmann et al. 2015; Loh et al. 2017), as well as plasticity throughout adulthood (Feld et al. 2016; Ferrario and Reagan 2018; Park 2001).

In this chapter, I reviewed recent progress in roles of insulin in the brain, expression of insulin genes, and multiple origin of the brain insulin.

1.2 Roles of Insulin in Brain

In the brain, astrocytes are the main energy reservoirs, accumulate glycogen, and help to sustain high-energy demands associated with neuronal activity. Recently, it has been revealed that astrocytes play an essential role in long-term memory formation by converting glycogen into lactate and transporting it to the neurons (Newman et al. 2011; Suzuki et al. 2011). Astrocytes express an insulin-independent glucose transporter, GLUT1; thus it has been believed that astrocytes take up glucose through the blood-brain barrier (BBB) in an insulin-independent manner and convert the intracellular glucose to glucose-6-phosphate and then store as glycogen (Jurcovicova 2014). Upon greater energy demand during synaptic transmission, glycogenolysis is triggered to produce lactate. Lactate is then transported to the extracellular space by monocarboxylate transporters (MCT1, MCT4), and is taken up by neurons via MCT2, and contributes to memory consolidation processes (Belanger et al. 2011; Bezzi and Volterra 2011; Stobart and Anderson 2013). While these steps are likely to be insulin independent, it has been reported that astrocytes express insulin receptor (INSR) and respond to insulin or insulin-like growth factor (IGF)-1 (Garwood et al. 2015), suggesting that there may be an insulin-dependent glucose metabolism in astrocytes.

Recently, it has been shown that the combined action of IGF-I and insulin synergistically stimulates a mitogen-activated protein kinase/protein kinase D pathway resulting in translocation of GLUT1, which had been known as an insulin-independent glucose transporter, to the cell membrane, thus enhancing glucose uptake on demand without changes in circulating insulin levels (Fernandez et al. 2017). Moreover, insulin or IGF-1 itself promotes glycogen storage and cell proliferation in astrocytes (Heni et al. 2011; Muhic et al. 2015); the increase in glycogen storage in the astrocytes has a contributory effect of an insulin-dependent increase in glucose utilization during increases in neuronal activity associated with hippocampal-dependent learning.

The brain expresses mainly insulin-independent glucose transporters GLUT1 (endothelial cells of BBB, astrocytes), GLUT2 (hypothalamic and hippocampal neurons, astrocytes), GLUT3 (endothelial cells of BBB, astrocytes), GLUT5 (microglia), and GLUT6 (neurons); however, there are also some expression of insulin-dependent transporters GLUT4 and GLUT8 (Duelli and Kuschinsky 2001; Grillo et al. 2009; Wood and Trayhurn 2003). GLUT4 and GLUT8 are localized in neuronal cell bodies in the cortex and cerebellum, but mainly in the hippocampus and amygdala, where they maintain hippocampus-dependent cognitive functions. Insulin translocates GLUT4 from cytosol to plasma membrane to transport glucose into cells and GLUT8 from cytosol to rough endoplasmic reticulum to recover redundant glucose to cytosol after protein glycosylation (Jurcovicova 2014).

It has been shown that insulin controls not only whole-body energy and glucose homeostasis in the periphery of the human body but also exerts specific effects in the brain through INSR and the closely related IGF-1 receptor (IGF-1R) (Ghasemi et al. 2013; Gray et al. 2014; Kleinridders et al. 2014). INSR and IGF-1R, as well as their downstream targets such as INSR substrate-1 (IRS-1) and IRS-2, are distributed throughout the brain including the olfactory bulb, cortex, hippocampus, hypothalamus, and cerebellum (Kleinridders et al. 2014). Through these receptors and signaling pathways in the brain, insulin affects feeding behavior and how the body stores energy, the metabolism of glucose and fats in the liver and adipose, as well as various aspects of memory and cognition (Gray et al. 2014). Furthermore, insulin signaling also modulates neurotransmitter channel activity, brain cholesterol synthesis, and mitochondrial function (Kleinridders et al. 2014).

The brain is known to contain a high concentration of insulin, which appears to be 10–100 times higher than in plasma, subject to change during brain development (Havrankova et al. 1979; Schechter et al. 1992). There are many literatures reporting that brain insulin is partly the result of an uptake from the peripheral blood through the BBB, via a specific transporter system coupled to INSR present in the brain microvessels or blood-cerebrospinal fluid (CSF) barrier at the choroid plexus in the ventricles (Csajbok and Tamas 2016; Gray et al. 2014; Meijer et al. 2016); however, the level of brain insulin appears to be regulated independently from insulin in the periphery (Stanley et al. 2016). This suggests that brain insulin is synthesized by the neural elements and plays a role in the central nervous system which is unrelated to peripheral glucose metabolism (Havrankova et al. 1979), as discussed Sect. 1.4.

In conclusion, insulin plays important roles to regulate glucose metabolism and neuronal functions in the brain.

1.3 Structure and Expression of the Insulin Genes

Insulin, the major secreted product of the β-cells of the pancreatic islets of Langerhans, is initially synthesized as a precursor (preproinsulin), from which the mature hormone is excised by a series of proteolytic cleavages (Davidson 2004; Steiner 2011). Signal peptide in the preproinsulin is cleaved by signal peptidase

(SPase), and generated proinsulin is further cleaved by two proprotein convertase subtilisin/kexin type 1 (PCSK1) and type 2 (PCSK2), followed by carboxypeptidase E (CPE), thus converting proinsulin to mature insulin consisting of A and B chains and C-peptide (Fig. 1.1).

Most of mammals including human carry a single insulin (*INS*) gene encoding preproinsulin, which is a precursor of insulin synthesized as a primary translational product. Human *INS* gene is located on chromosome 11p15.5 and consists of three exons; exon 2 encodes the signal peptide, the B chain, and part of the C-peptide, and exon 3 encodes the remainder of the C-peptide and the A chain. The 5′ flanking sequences immediately upstream (~400 base pairs) of the transcription start site are defined as the insulin promoter, which has been reported to be exclusively active in the β-cell (Bell et al. 1980; Fu et al. 2012; German et al. 1995; Hay and Docherty 2006; Walker et al. 1983). During fetal development and childhood, *INS* gene is imprinted and expressed at low levels in the human thymus and yolk sac (Moore et al. 2001; Pugliese et al. 1997; Vafiadis et al. 1997).

Exceptionally in mammals, insulin genes in mouse and rat compose a two-gene system, namely, *Ins1* and *Ins2*, in which *Ins1* lacking intron 2 sequence was retroposed from the partially processed mRNA of *Ins2*. *Ins2* gene is the ortholog of human *INS* gene with three exons (Shiao et al. 2008). In mouse, *Ins1* gene mapped to the telomeric region of the chromosome 19 is expressed exclusively in the β-cells in the islets of Langerhans of the pancreas, while *Ins2* gene mapped to the chromosome 7 is expressed in both the β-cells and extra-pancreatic tissues including the thymus, brain, and yolk sac (Chentoufi et al. 2004; Chentoufi and Polychronakos 2002; Deltour et al. 1993, 2004). In mouse yolk sac, *Ins2* gene is also imprinted as is the human ortholog *INS* gene (Deltour et al. 1995).

In thymus, the mouse *Ins2* gene is expressed exclusively in medullary thymic epithelial cells (mTECs). Specific deletion of insulin expression in mouse mTECs results in spontaneous diabetes around 3 weeks after birth with β-cell-specific autoimmune destruction, indicating that that depletion of *Ins2* expression in mTECs was sufficient to break central tolerance and induce anti-insulin autoimmunity (Fan et al. 2009).

1.4 Origins of Brain Insulin

There are two sources of intracerebral insulin: pancreatic insulin and insulin synthesized in the brain (Csajbok and Tamas 2016). It has been considered that insulin is produced mainly from the endocrine β-cells in the islets of Langerhans of the pancreas, even though insulin had been detected in both human and rodent brains (Baskin et al. 1983; Dorn et al. 1982a, b, 1983a, b, 1984; Havrankova et al. 1978, 1979, 1980, 1981). Insulin secreted from the β-cells can cross the blood-brain barrier (BBB) through a saturable, receptor-mediated process, or cross the blood-cerebrospinal fluid (CSF) barrier at the choroid plexus in the ventricles (Gray et al. 2014; Meijer et al. 2016), thus acting in the brain.

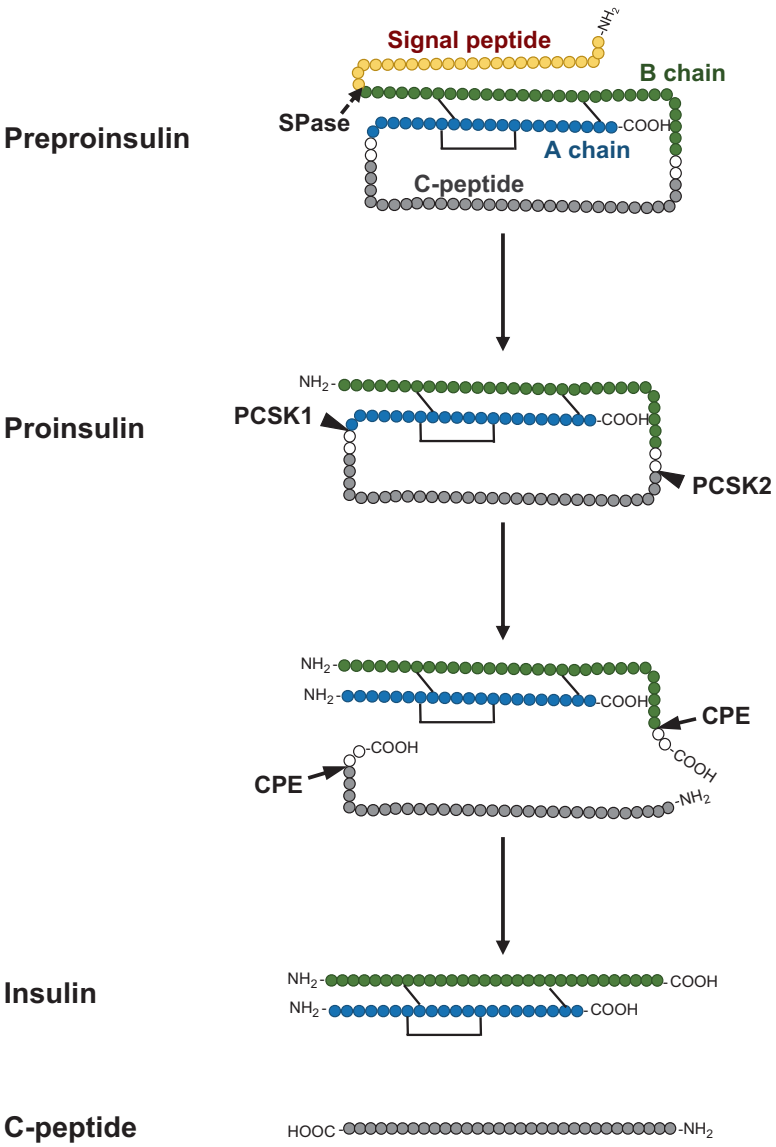

Fig. 1.1 Processing preproinsuin to mature insulin. Signal peptide in the peproinsulin is cleaved by signal peptidase (SPase), and generated proinsulin is further cleaved by two proprotein convertase subtilisin/kexin type 1 (PCSK1) and type 2 (PCSK2), followed by carboxypeptidase E (CPE), thus converting proinsulin to mature insulin consisting of A and B chains and C-peptide

Recently, however, it has been reported that hyperinsulinemic-euglycemic clamps resulting in physiological hyperinsulinemia in young, awake, behaving $APP_{swe}/PS1_{dE9}$ transgenic mice do not increase insulin level in either CSF or interstitial fluid (ISF), or insulin signaling in hippocampus and hypothalamus, without altering glucose and lactate levels in ISF, yet modestly increases extracellular amyloid β (Aβ) in ISF (Stanley et al. 2016). Moreover, it has been shown that subcutaneous administration of insulin increases brain insulin level less than 1/200 level of plasma insulin, indicating that the peripheral insulin contributes to the brain insulin in a limited level. Since the speed of change in peripheral insulin concentration is controlled by blood glucose level and rather slow, it seems that peripheral insulin contributes to maintenance of steady-state level of insulin in the brain (Csajbok and Tamas 2016).

It has been long time under debate as to whether insulin is synthesized in the brain (Akintola and van Heemst 2015; Banks et al. 2012; Csajbok and Tamas 2016; Ghasemi et al. 2013; Gray et al. 2014; Kleinridders et al. 2014), since insulin had been detected in both human and rodent brains in late 1970s to early 1980s (Baskin et al. 1983; Dorn et al. 1982a, b, 1983a, b, 1984; Havrankova et al. 1978, 1979, 1981, Rosenzweig et al. 1980). Recent studies, however, with PCR-based detection of insulin mRNA in a single-cell or high-resolution imaging with genetically modified animals established that functional insulin is produced in certain neurons in the brain (Lee et al. 2016; Mehran et al. 2012; Molnar et al. 2014; Nemoto et al. 2014).

Molnar et al. (2014) have shown that *Ins2* mRNA is strongly expressed in GABAergic neurogliaform cells in the cerebral cortex of the rat detected by single-cell digital PCR. Focal application of glucose or glibenclamide to neurogliaform cells mimics the excitation-suppressing effect of external insulin on local microcircuits via insulin receptors. Thus, neurogliaform cells might link GABAergic and insulinergic action in cortical microcircuits. Mehran et al. (2012), on the other hand, clearly demonstrated that *Ins2* is broadly expressed (most prominently in the hippocampus) in both developing and adult mouse brain, while *Ins1* is virtually absent in the brain. Nemoto et al. (2014) demonstrated that primary cultured hippocampal neurons have the ability of rapid and transient secretion of insulin from dense-core vesicles upon stimulation. These findings indicate that neurons in specific regions of the brain are thought to produce and secrete insulin in response to neural excitement, thus supplying insulin rapidly corresponding to the speed of neural response, in contrast to peripheral insulin (Csajbok and Tamas 2016).

Recently, it has been reported that astrocytes isolated from brain cortices from rat embryos express *Ins2* mRNA, and to a lesser extent *Ins1* mRNA, and secrete insulin, which is neuroprotective for co-cultured neurons (Pitt et al. 2017; Takano et al. 2018).

1.5 Conclusions

There are substantial evidence demonstrating that brain insulin is derived from the pancreas, neurons, and astrocytes. When the glucose concentration in the blood rises after a meal, the insulin level in the blood derived from the pancreas rises, and

the blood glucose level is maintained low, but when the blood glucose level decreases, the peripheral insulin level returns to the basal low level. Insulin in the blood is known to reach the brain beyond the blood-brain barrier. When the blood glucose level is low, the peripheral insulin level is also low. In such condition, the latter may not be sufficient to secure the glucose level required for the brain. Insulin secreted by the neurons or astrocytes thus plays essential roles to sustain high-energy demands associated with brain functions (Fig. 1.2).

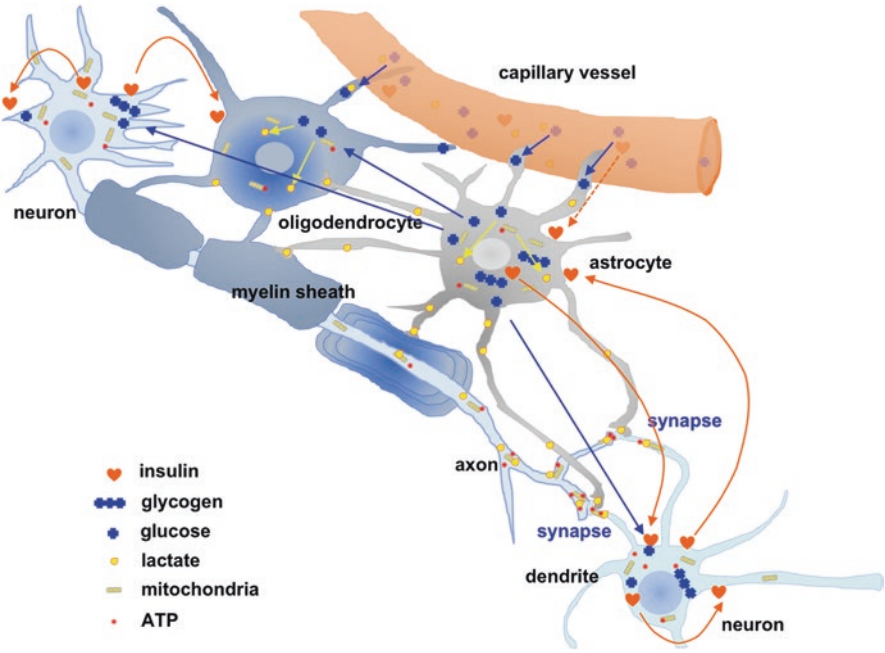

Fig. 1.2 Origins of brain insulin and its function. Brain insulin is derived from pancreas, neurons and astrocytes (See text). Recently, it has been revealed that astrocytes play an essential role in long-term memory formation by converting glycogen into lactate and transporting it to the neurons (Newman et al. 2011; Suzuki et al. 2011). Astrocytes express GLUT1, thus take up glucose through BBB, and convert the intracellular glucose to glucose-6-phosphate and then store as glycogen (Jurcovicova 2014). Upon greater energy demand during synaptic transmission, glycogenolysis is triggered to produce lactate. Lactate is then transported to the extracellular space by monocarboxylate transporters (MCT1, MCT4), and is taken up by neurons via MCT2, and contributes to memory consolidation processes (Belanger et al. 2011; Bezzi and Volterra 2011; Stobart and Anderson 2013). While these steps are likely to be insulin independent, it has been reported that astrocytes express INSR and respond to insulin or IGF-1 (Garwood et al. 2015). Since insulin and/or IGF-1 promotes glucose uptake, glycogen storage and cell proliferation in astrocytes (Fernandez et al. 2017; Heni et al. 2011; Muhic et al. 2015), these events in the astrocytes have a contributory effect of an insulin-dependent increase in glucose utilization during increases in neural activity associated with hippocampal-dependent learning, as well as GLUT4-dependent glucose uptake by neurons. Insulin secreted by the neurons or astrocytes, thus plays essential roles to sustain high-energy demands associated with brain functions, while peripheral insulin contributes to maintenance of steady state level of brain function

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Chapter 2
Epidemiological Evidence of the Relationship Between Diabetes and Dementia

Toshiharu Ninomiya

Abstract Growing epidemiological evidence has suggested that subjects with diabetes mellitus are at an increased risk for the development of dementia. However, the results for the subtypes of dementia are inconsistent. This review examined the risk of dementia in subjects with diabetes mellitus and discusses the possible mechanism underlying this association. Diabetes mellitus is associated with a 1.5- to 2.5-fold greater risk of dementia among community-dwelling elderly people. Notably, diabetes mellitus is a significant risk factor for not only vascular dementia but also Alzheimer's disease. The mechanisms underlying the association are unclear, but it may be multifactorial in nature, involving factors such as cardiovascular risk factors, glucose toxicity, changes in insulin metabolism, and inflammation. The optimal management of these risk factors in early life may be important to prevent future dementia. Furthermore, novel therapeutic strategies will be needed to prevent or reduce the development of dementia in subjects with diabetes mellitus.

Keywords Diabetes mellitus · Dementia · Alzheimer's disease · Vascular dementia · Epidemiology · Prospective study

2.1 Introduction

Dementia is a syndrome that affects memory, thinking, behavior, and the ability to perform everyday activities. The number of people with dementia worldwide is currently estimated at 46.8 million and will double to 74.7 million by 2030 and more than triple to 131.5 million by 2050 (The World Alzheimer Report 2015). Additionally, the global costs of dementia are enormous and still inequitably distributed; it has been estimated to be United States (US) $818 billion in 2015, which will become US$ 1 trillion by 2018, rising US$ 2 trillion by 2030 (Wimo 2017; The

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World Alzheimer Report 2015). This increase in costs arises from the increase in the numbers of people with dementia and the per person costs, especially in high-income countries (Wimo 2017). Therefore, dementia is widely acknowledged as a public health and social care priority worldwide.

The rising prevalence of diabetes mellitus is also a great public health concern, because diabetes mellitus can lead to complications in several organ systems (The IDF diabetes atlas 2012). Advances in prevention and treatment strategies for the macro- and microvascular complications of diabetes mellitus have improved life expectancy in individuals with diabetes mellitus, and this improved longevity is likely to increase the population at risk of geriatric health complications, including cognitive impairment and dementia (Lu et al. 2009). Several epidemiologic studies have suggested that subjects with diabetes mellitus are at an increased risk of developing cognitive impairment and dementia (Biessels et al. 2006). However, the results for the subtypes of dementia are inconsistent across studies. Alzheimer's disease is the most common and has traditionally been considered a primarily neurodegenerative disorder characterized by neuritic plaques and the neurofibrillary tangles, which are the accumulation of amyloid beta protein and abnormally phosphorylated tau protein in neurons, respectively (Schneider et al. 2009). On the other hand, vascular dementia is the second most common type of dementia and develops as a consequence of strokes or chronic brain ischemia generated by small vessel disease. Therefore, these dementia subtypes are thought to have different etiologies. Herein, we review the findings of population-based prospective studies addressing the association between diabetes mellitus and dementia, and discuss the possible mechanisms underpinning this association, which may be useful from a clinical and public health perspective.

2.2 Epidemiological Evidence of an Increased Risk of Dementia in Patients with Diabetes Mellitus

A number of population-based prospective studies have reported an association between diabetes mellitus and the development of dementia (Ninomiya 2014; Chatterjee et al. 2016). Previously, we performed a systematic review and meta-analysis regarding the association between diabetes and the risk of dementia (Ninomiya 2014). In this meta-analysis, diabetes mellitus was associated with a 1.7-fold (95% confidence interval [CI] 1.5–1.8) greater risk of all dementia, without any heterogeneity in the magnitude of the association (I^2 = 0.0%, p = 0.51). Substantially similar findings were observed in the subtypes of dementia, such as Alzheimer's disease and vascular dementia (Fig. 2.1). The pooled hazard ratio (HR) for Alzheimer's disease in individuals with diabetes mellitus was 1.6 (95% CI 1.4–1.8). Similarly, a significant increase in the risk of vascular dementia was found with a pooled HR of 2.2 (95% CI 1.7–2.8). There were no evidences of heterogeneity in the association for either subtype of dementia across the studies (both

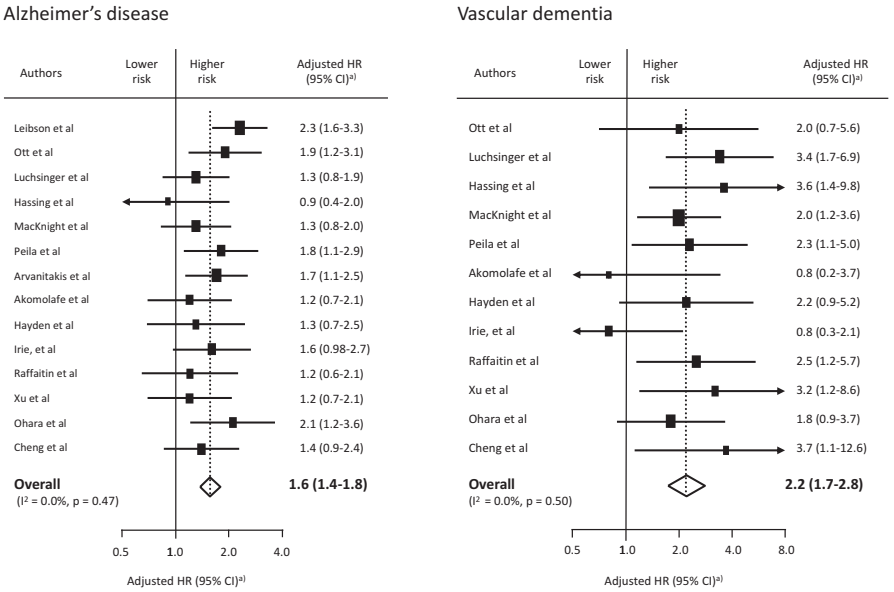

Fig. 2.1 Pooled risk estimates of diabetes mellitus on the development of Alzheimer's disease and vascular dementia; meta-analysis of population-based cohort studies. *HR* hazard ratio, *CI* confidence interval. (Cited by reference of Ninomiya 2014 [modified])

$I^2 = 0.0\%$, $p > 0.4$). Another meta-analysis of addressing the sex-specific relationship between diabetes and the incident risk of dementia also showed diabetes was associated with a 60% greater risk of all dementia in either sex: pooled HR 1.6 (95% CI 1.5–1.8) for women and 1.6 (95% CI 1.4–1.8) for men (Chatterjee et al. 2016). Diabetic subjects had 2.3-fold (95% CI 1.9–2.9) and 1.7-fold (95% CI 1.6–1.9) greater risk of vascular dementia than nondiabetic subjects for women and men, respectively. Diabetes-associated HRs on nonvascular dementia were 1.5 (95% CI 1.4–1.7) in women and 1.5 (95% CI 1.3–1.7) in men. This meta-analysis concluded that women with diabetes had a 19% greater risk for vascular dementia than men, but not for nonvascular dementia. These findings provide convincing evidence that subjects with diabetes mellitus have a 1.5- to 2.5-fold greater risk of dementia than those without it among community-dwelling elderly people. Importantly, diabetes mellitus is a significant risk factor for not only vascular dementia but also Alzheimer's disease.

The Hisayama Study is a population-based cohort study conducted to explore the risk factors for cardiovascular disease and dementia in a general Japanese population (Hata et al. 2013; Ohara et al. 2017). The most important feature of the study is that diabetes status was determined by oral glucose tolerance test and dementia subtypes were diagnosed by detailed neurologic and morphologic examination, including neuroimaging and autopsy. Intriguingly, this study revealed that greater 2-h post-load plasma glucose (2-h PG) levels, but not greater fasting plasma glucose (FPG) levels, were linked to an increased risk of both Alzheimer's disease and

vascular dementia in an elderly Japanese population (Ohara et al. 2011). It is reasonable to suppose a close association between 2-h PG levels and vascular dementia, because the risk of cerebrovascular disease increased with a higher 2-h PG levels (Thacker et al. 2011; Doi et al. 2010). Meanwhile, the risk of Alzheimer's disease almost doubled in those with 2-h PG of 7.8–11.0 mmol/L and tripled in those with 2-h PG above 11.0 mmol/L as compared with those with 2-h PG below 6.7 mmol/L (Fig. 2.2). These findings may suggest that hyperglycemia after glucose load is involved in the development of Alzheimer's disease, as well as vascular dementia.

2.3 Morphological Changes of the Brain in Elderly Subjects with Diabetes Mellitus

The morphological changes of Alzheimer's disease occur in the hippocampus, amygdala, and medial temporal lobe in the early stages of the disease (Braak and Braak 1991). The assessment of hippocampal and amygdalar volume on magnetic resonance imaging (MRI) of the brain provides a good estimate of the degree of Alzheimer neuropathology (Gosche et al. 2002), which shows that patients in the early stage of Alzheimer's disease have smaller volumes of the hippocampus and amygdala on MRI compared to healthy control subjects (Convit et al. 1997; Schott et al. 2003; Krasuski et al. 1998). The Hisayama Study investigated the association between diabetes and hippocampal atrophy in 1238 community-dwelling Japanese subjects aged 65 years or older, who underwent brain MRI scans (Hirabayashi et al. 2016). As a consequence, diabetic subjects, especially subjects with

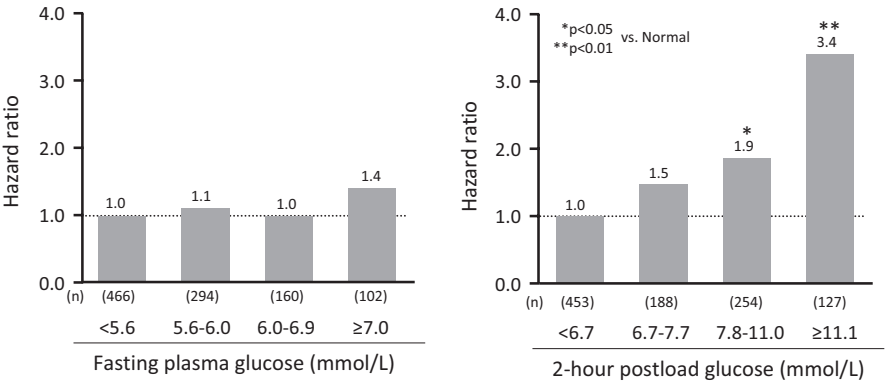

Fig. 2.2 Risk of dementia subtype according to the fasting and 2-h post-load plasma glucose levels. The hazard ratios were adjusted for age, sex, education level, hypertension, serum total cholesterol, body mass index, waist-to-hip ratio, electrocardiogram abnormalities, history of stroke, smoking habits, alcohol intakes, and regular exercise. (Cited by reference of Ohara et al. 2011 [modified])

post-glucose-loaded hyperglycemia, had a significantly lower hippocampal volume than nondiabetic subjects. Furthermore longer duration of diabetes was significantly associated with lower hippocampal volume (Fig. 2.3). In the Rotterdam Scan Study, likewise, subjects with diabetes mellitus had significantly lower volumes of the hippocampus and amygdala on MRI than subjects without diabetes mellitus (den Heijer et al. 2003).

The pathological studies also showed the significant association between the diabetes-related factors and the neuropathology of Alzheimer's disease (Matsuzaki et al. 2010; Peila et al. 2002). The Hisayama Study revealed that the risk of the presence of neuritic plaque increased significantly with elevating 2-h PG levels, fasting insulin, and homeostasis model assessment of insulin resistance, but not FPG level after adjusting for confounding factors (Fig. 2.4) (Matsuzaki et al. 2010). The magnitudes of these associations were significantly greater in subjects with the *APOEe4* allele than in those without. This suggests that hyperinsulinemia and insulin resistance may be involved in the etiology of Alzheimer's disease. The Honolulu Heart Program also showed that subjects with diabetes mellitus and *APOEe4* allele had a higher number of hippocampal neuritic plaques (odds ratio [OR] 3.0 [95% CI, 1.2–7.3]) and higher numbers of neurofibrillary tangles in the cortex (OR 3.5 [95% CI, 1.2–7.3]) and hippocampus (OR 2.5 [95% CI, 1.5–3.7]) than those with neither of these risk factors (Peila et al. 2002). There were no clear associations between diabetes mellitus and these neuropathologies of Alzheimer's disease in *APOEe4* noncarriers. This finding implies that the pathological link between diabetes mellitus,

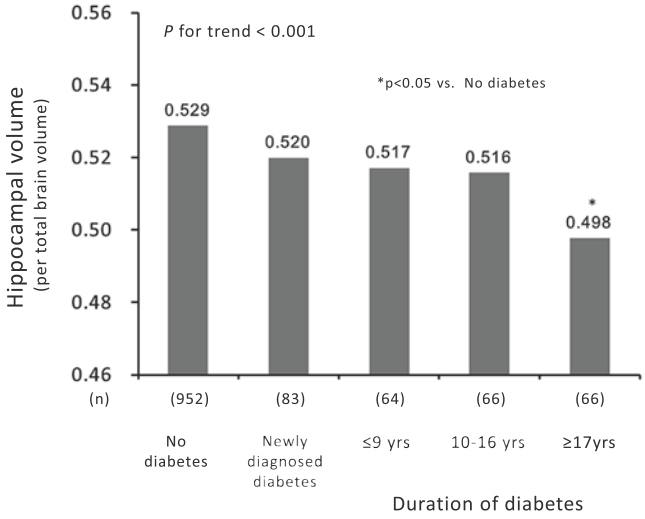

Fig. 2.3 Relationship between diabetes and hippocampal atrophy. The values were adjusted for age, sex, education level, hypertension, serum total cholesterol, body mass index, smoking habits, alcohol intakes, regular exercise, and cerebrovascular disease. (Cited by reference of Hirabayashi et al. 2016 [modified])

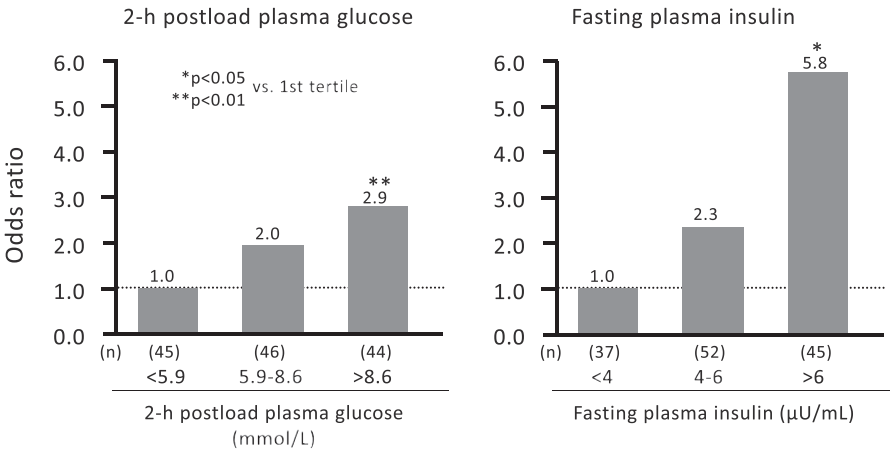

Fig. 2.4 Glucose intolerance and presence of senile plaques. The presence of senile plaques was defined as the Consortium to Establish a Registry for Alzheimer's disease (CERAD) score ≥1. Odd ratios were adjusted for age, sex, systolic blood pressure, serum total cholesterol, body mass index, history of stroke, smoking habits, and regular exercise. (Cited by reference of Matsuzaki et al. 2010 [modified])

APOEe4, and Alzheimer's disease may be partially due to an increased risk of the formation of cerebral amyloid angiopathy.

2.4 Possible Biological Mechanisms Underlying the Association Between Diabetes Mellitus and Dementia

The exact mechanisms underlying the association between diabetes mellitus and dementia are unclear. However, the association is likely to be multifactorial in nature, reflecting the metabolic complexity of diabetes mellitus. It is increasingly recognized that the brains of subjects with dementia are likely to show mixed pathologies of subtypes of dementia. Several factors related to diabetes mellitus—namely, cardiovascular risk factors, glucose toxicity, oxidative stress, hyperinsulinemia, and inflammation—can lead to different pathologies (Fig. 2.5) (Craft and Watson 2004). In addition, demographic and socioeconomic factors (e.g., aging and education), other comorbidities (e.g., depression, hypoglycemic episodes), and genetic factors (e.g., *APOEe4* genotype) could also be important determinants of increased risk of dementia in subjects with diabetes mellitus. These combined mechanisms could cause a mixture of pathologies, which would complicate the clarification of the biological mechanism.

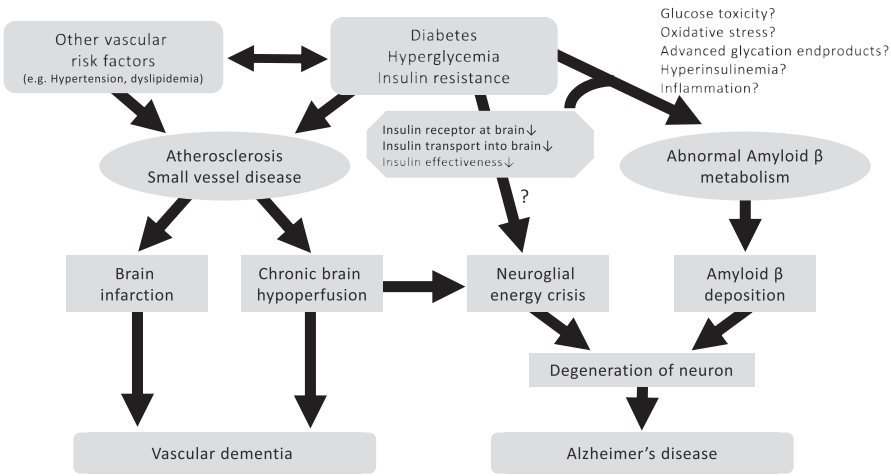

Fig. 2.5 Possible underlying mechanisms linking diabetes to dementia

2.4.1 Cardiovascular Risk Factors

Diabetes mellitus is known to be a risk factor for ischemic stroke and small vessel disease (Mankovsky and Ziegler 2004). Type 2 diabetes mellitus can be associated with multiple cardiovascular risk factors, including obesity, insulin resistance, atherogenic dyslipidemia, hypertension, and proinflammatory states. The accumulation of these risk factors accelerates stroke, small vessel disease, and subsequent vascular dementia (Kalmijn et al. 2000; Whitmer 2005). Chronic exposure to hyperglycemia in diabetes mellitus also induces abnormalities in the cerebral capillaries (Serlin et al. 2011). Stroke and small vessel disease disrupt oxygenated blood supply in the brain, leading to the brain damage and cognitive dysfunction. Therefore, good control of cardiovascular risk factors could be expected to reduce the risk of dementia. Nevertheless, current evidences from randomized control trials failed to reveal the favorable effect of standard strategies of cardiovascular risk reduction (e.g., antihypertensive agents, antiplatelet therapy, and statin) on the development of dementia among older people aged 70 years or older (McGuinness et al. 2009a, b; Tzourio et al. 2003). However, a long exposure to poorly controlled cardiovascular risk factors presumably worsens arteriolosclerotic changes and lipohyalinosis in the deep subcortical white matter circuits, which may be less reversible by treatment once these changes are established (Qiu et al. 2005; Ninomiya et al. 2011). Furthermore, cardiovascular risk reduction strategies are unlikely to affect the risk of Alzheimer's disease, as compared to vascular dementia, although these strategies might have a modest effect in reducing the rate of cognitive decline in subjects with Alzheimer's disease mixed with vascular abnormalities. Optimal management of the risk factors in earlier life and more prolonged therapy could provide cognitive benefits in later life in subjects with diabetes mellitus.

2.4.2 Glucose Toxicity and Oxidative Stress

Hyperglycemia could cause decrements in working memory and attention (Sommerfield et al. 2004). In the Diabetes Control and Complications Trials/Epidemiology of Diabetes Interventions and Complications Study, higher glycated hemoglobin values were associated with moderate declines in motor speed and psychomotor efficiency among patients with type 1 diabetes during 18-year follow-up (Jacobson et al. 2007). Chronic hyperglycemia may induce an increased flux of glucose via the polyol and hexosamine pathway, an increase in oxidative stress, and an accumulation of advanced glycation end products, subsequently causing cognitive impairments and abnormalities in synaptic plasticity (Biessels et al. 1996; Brownlee 2001). These processes can lead to vascular damage but can also affect the generation of neurodegenerative disorder in the brain. Nevertheless, the effectiveness of tight glycemic control in the prevention of cognitive impairment is still controversial. The data from randomized control trial, the Action to Control Cardiovascular Risk in Diabetes-Memory in Diabetes (ACCORD-MIND) study, demonstrated that the declining rate of brain volume during 40 months was significantly lower in a group that received the intensive glycemic control targeting HbA1c to less than 6.0% (42 mmol/mol) than a group that received standard strategy targeting HbA1c to 7.0–7.9% (53–63 mmol/mol), but there was no clear difference in the cognitive function between the two groups (Launer et al. 2011). Recently, epidemiological evidence emerged to suggest that greater variability of blood glucose and postprandial plasma glucose excursions is associated with higher risk of cognitive decline (Rizzo et al. 2010; Abbatecola et al. 2006), which were reported to deteriorate endothelial dysfunction than a constant high concentration of blood glucose (Risso et al. 2001). Further research is warranted to determine the optimal blood glucose control.

2.4.3 Hyperinsulinemia

Insulin resistance and compensatory hyperinsulinemia are typical characteristics of the early stage of type 2 diabetes mellitus. Hyperinsulinemia is associated with impaired cognitive function, which is partially mediated by vascular disease. On the other hand, accumulated evidence has suggested that insulin and insulin receptors play important roles in the cognitive performance via modification of the activities of both excitatory and inhibitory postsynaptic receptors (e.g., NMDA and GABA receptors) and the activation of specific signaling pathways (e.g., insulin/IGF-1, Grb-r/SOS, Ras/Raf, and MEK/MAP kinases) (Zhao and Alkon 2001; Zemva and Schubert 2011; 44. Salkovic-Petrisic et al. 2009). Insulin receptors are abundantly expressed in several specific brain regions, including the hippocampus and the

cortex (Zhao and Alkon 2001), but prolonged hyperinsulinemia decreases the expression of insulin receptors at these brain regions and consequently induces an impaired response to insulin (Moloney et al. 2010). These changes could cause deficits in learning and memory formation, probably due to a neuroglial energy crisis (Zhao and Alkon 2001). Additionally, patients with Alzheimer's disease show disruptions in brain insulin sensitivity, such as lower insulin levels in cerebrospinal fluid, higher plasma insulin levels, and drastically reduced densities of insulin receptor in the brain as compared with healthy adults (Craft et al. 1998). Higher levels of plasma insulin provoke amyloid accumulation by limiting the degradation of amyloid beta protein via the direct competition for the insulin-degrading enzyme, which degrades both insulin and amyloid beta protein (Biessels et al. 2006; Craft and Watson 2004). Additionally, insulin and insulin-like growth factor-1 stimulate the transportation of amyloid beta carrier proteins such as albumin and transthyretin into cerebrospinal fluid and the elimination of amyloid beta protein from the brain. However, lower insulin levels in cerebrospinal fluid and the impaired response to insulin and insulin-like growth factor-1 inhibit the transportation of these carrier proteins and decrease the clearance of amyloid beta protein (Craft and Watson 2004).

2.4.4 Inflammation

Chronic inflammation is thought to be involved in the initiation of insulin resistance and the development of diabetes mellitus (Nesto 2004; Doi et al. 2005; Schmidt et al. 1999). Diabetic patients also tend to show chronic systemic inflammation (Lee et al. 2009). Several cross-sectional studies have investigated the associations between inflammatory markers and cognitive impairment and decline in community-dwelling elderly (Schram et al. 2007; Alley et al. 2008). There is evidence of an activated inflammatory response in microglial cells obtained from the brains of dementia patients (Rogers et al. 2007). It has been reported that the levels of interleukin-1, interleukin-6, tumor necrosis factor-α, C-reactive protein, granulocyte macrophage colony-stimulating factor, and eotaxin are high in brain tissue from patients with Alzheimer's disease (Fuster-Matanzo et al. 2013). Macrophage inflammatory protein-1α has also been detected in reactive astrocytes nearby Aβ plaques in the brain of Alzheimer's disease (Xia and Hyman 1999). A cross-sectional study showed that elevated circulating levels of inflammatory markers were associated with worse cognitive ability in diabetic patients (Marioni et al. 2010). These findings raise the possibility that chronic inflammation may play a role in accelerated cognitive impairment, either by a direct effect on the brain or by influencing the development of vascular disease. However, the evidence of a causal association between inflammation and cognitive function remains limited.

2.4.5 *Hypoglycemic Episode*

Several longitudinal studies suggested that severe hypoglycemia may be also a risk factor for cognitive impairments in patients with type 2 diabetes. Patients with recurrent severe hypoglycemia episode have a 1.5–2.0 times greater risk of the development or deterioration of cognitive impairment (Whitmer et al. 2009; Lin and Sheu 2013; de Galan et al. 2009). Severe hypoglycemia can induce the permanent neurological sequelae including neuronal cell death (Fanelli et al. 2004) and increase in platelet aggregation and fibrinogen formation (Wright and Frier 2008), which may accelerate cognitive impairments. Older patients are thought to have less brain reserve or brain plasticity than younger patients (Artola et al. 2002; Gispen and Biessels 2000). Therefore, it is plausible that hypoglycemia could cause neurological changes in the elderly.

2.5 Conclusions

Despite the methodological limitations of the observational studies, there is convincing evidence of an increased risk of dementia in community-dwelling elderly with diabetes mellitus. Notably, diabetes mellitus is a significant risk factor for not only vascular dementia but also Alzheimer's disease. The etiology of cognitive dysfunction in subjects with type 2 diabetes mellitus is probably multifactorial, but the mechanisms underpinning this association are not yet fully clarified. Since the pathophysiological processes of dementia begin many years before any symptoms appear, the optimal management of risk factors as early as possible in the life cycle may be important to prevent late-life dementia in subjects with diabetes mellitus. Nevertheless, the standard therapeutic strategies may be insufficient to prevent the cognitive decline completely. Therefore, further research should attempt to explore novel therapeutic strategies to prevent or reduce the development of dementia in subjects with diabetes mellitus.

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Chapter 3
Molecular Pathophysiology of Insulin Depletion, Mitochondrial Dysfunction, and Oxidative Stress in Alzheimer's Disease Brain

Yusaku Nakabeppu

Abstract Accumulating clinical data indicates that insulin resistance and diabetes mellitus (DM) are major risk factors for Alzheimer's disease (AD); however, the exact mechanisms on how insulin resistance and DM act as risk factors for AD remain unclear. Recent progress in gene expression profiling of AD brains revealed that brain insulin production and insulin signaling are significantly impaired, indicating that AD brain exhibits a feature of brain diabetes with depletion of brain insulin, which causes mitochondrial dysfunction with increased oxidative stress, thereby increasing sensitivity to peripheral diabetes. Such diabetic condition in early stage of AD brain can be exacerbated by peripheral diabetes, namely, through hyperglycemia, hyperinsulinemia, or impaired insulin response. In this chapter, I reviewed mitochondrial dysfunction and oxidative stress in AD brain and discussed how those events are involved in AD pathogenesis.

3.1 Introduction

About 50 million people worldwide suffer from dementia, with 10 million new cases every year. Sporadic Alzheimer's disease (AD) (also known as late-onset AD) is the most common dementia subtype, accounting for 60–70% of all dementia cases (WHO 2017). AD is characterized by the accumulation in the brain of both senile plaques containing aggregated amyloid β (Aβ) and neurofibrillary tangles (NFTs) consisting of aggregated highly phosphorylated TAU protein and

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by neuronal loss mainly in the cortex and hippocampus. About 1% of AD cases develop as a result of mutations to any of three specific genes for the amyloid precursor protein (APP) and the presenilin 1 and presenilin 2 proteins, with the latter two regulating APP processing through their effects on γ secretase (an enzyme that cleaves APP). Individuals with mutations in any of these three dominantly inherited genes tend to develop AD symptoms before the age of 65, sometimes as early as age 30, and it has been shown that Aβ plaques can be present for more than 20 years before the onset of dementia in patients with such inherited mutations (Alzheimer's Association 2015; Bateman et al. 2012). The vast majority of individuals with sporadic AD have late-onset disease, occurring at age 65 or later, and similar to other chronic diseases, sporadic AD develops as a result of multiple factors including lifestyle rather than just from a single cause (Arenaza-Urquijo et al. 2015). Especially, factors that impede or alter brain growth during early life could render certain brain regions or networks selectively vulnerable to the onset, accumulation, or spread of AD-related pathology during later life (Seifan et al. 2015).

It has been shown by epidemiologic studies that insulin resistance and diabetes mellitus (DM) are risk factors for pathogenesis of dementia including AD (Bedse et al. 2015; de la Monte 2014; Diehl et al. 2017; Hao et al. 2015; Matsuzaki et al. 2010; Ohara et al. 2011; Talbot et al. 2012). Moreover, it was demonstrated through brain imaging by positron-emission tomography (PET) with use of ^{18}F-fluorodeoxyglucose (FDG) and Pittsburgh compound B (PIB) (FDG-PET and PIB-PET, respectively) that a significant decrease in cerebral glucose use in the precuneus region (known to be an area of early deposition of Aβ in both sporadic AD and inherited AD cases) was detected in mutation carriers 10 years before the onset of the expected symptom (Bateman et al. 2012). Though these data suggest that insulin resistance and DM may lead to the disturbance of glucose metabolism in the brain, the exact mechanisms on how insulin resistance and DM acts as risk factors for AD remain unclear.

In this chapter, I consider that AD brain exhibits a feature of brain diabetes with depletion of brain insulin, which causes mitochondrial dysfunction with increased oxidative stress, thereby increasing sensitivity to peripheral diabetes.

3.2 Altered Expression of Diabetes-Related Genes in Alzheimer's Disease Brains

Genome-wide gene expression profiling of postmortem brains from sporadic AD patients have revealed altered expressions of neurological and immunological genes, genes encoding inflammatory molecules and metabolic enzymes (Bossers et al. 2010; Brooks et al. 2007; Castillo et al. 2017; Colangelo et al. 2002; Hokama et al. 2014; Parachikova et al. 2007; Tan et al. 2010).

Colangelo et al. reported altered gene expression profile supporting the hypothesis of widespread transcriptional alterations, misregulation of RNAs involved in metal ion homeostasis, transcription factor signaling deficits, decreases in neurotrophic support, and activated apoptotic and neuroinflammatory signaling in moderately affected AD hippocampal CA1 (Colangelo et al. 2002). Brooks et al. reported that 15 out of 51 members of the glycolytic, tricarboxylic acid cycle, oxidative phosphorylation, and associated pathways are statistically significantly downregulated in the hippocampus in AD brain, thus suggesting altered glucose metabolism in AD brain (Brooks et al. 2007). Parachikova et al. reported that upon assessment using microarray analysis, the hippocampus of AD cases with mild/moderate dementia had increased gene expression of the inflammatory molecule major histocompatibility complex (MHC) II, compared to non-demented high-pathology controls (Parachikova et al. 2007). Bossers et al. reported the results of a systematic search for global gene expression changes in the prefrontal cortex during the course of AD using Braak staging. They identified a number of genes involved in the processing of amyloid precursor protein and Aβ (*PSEN2*, *RER1*, *ZNT3*, *PCSK1*, *SST*, *PACAP*, and *EGR1*) that were initially upregulated in Braak stages I–III but were significantly downregulated in the late Braak stages V–VI (Bossers et al. 2010). Moreover, Tan et al. reported a significantly altered AD transcriptome (5485 genes) in the neocortex, characterized by synaptic dysfunction, perturbed neurotransmission, and activation of neuroinflammation (Tan et al. 2010).

We have examined gene expression profiles in postmortem human brains donated for the Hisayama study (Castillo et al. 2017; Hokama et al. 2014). The hippocampi of AD brains showed the most significant alteration in gene expression profile. In AD brains, 143 from the top 200 transcript clusters were markedly downregulated in the hippocampus beyond the expected level based on the cell population change. Among the top 200 transcript clusters, 145 genes were eligible for generating functional gene networks. The most relevant network included downregulated genes such as MET, PCSK1, PTPN3, SERPINF1, and VEGFA and upregulated genes such as AEBP1 and TXNIP, all known to be involved in insulin production and signaling, as discussed in the next session. Adipocyte enhancer-binding protein 1 (AEBP1) is known to activate inflammatory responses via the NF-kappaB (NF-κB) pathway in macrophages and regulate adipogenesis in preadipocytes (Majdalawieh et al. 2007); on the other hand, NF-κB is known to suppress *PCSK1* expression in pancreatic β-cells (Cardozo et al. 2001). In normal human brains, AEBP1 protein mainly detected in the perikarya of hippocampal pyramidal neurons and its expression was elevated in the pyramidal neurons and some astrocytes in AD hippocampi (Shijo et al. 2018). Moreover, certain AEBP1-positive neurons in AD brains exhibit increased nuclear NF-κB. Comparison of AD and non-AD cases suggested a positive correlation between the expression level of AEBP1 and the degree of Aβ pathology (Shijo et al. 2018). These findings imply that increased expression of AEBP1 protein has a role in the progression of AD pathology, through suppressing *PCSK1* expression via NF-κB activation.

The second-most relevant network consisted of the genes encoding GABA receptors (GABRA1, GABRA4, GABRA5, GABRG2), synaptotagmin members, syntaxin, potassium channels, and regulators of G protein signaling. Expression of all of these genes was markedly decreased in the AD hippocampus (Hokama et al. 2014), in agreement with the loss of functional $GABA_A$ receptors and impaired homeostasis between excitation (glutamate) and inhibition (GABA) in the AD brain (Abbas et al. 2016; Limon et al. 2012). Since insulin signaling leads to a rapid increase in the cell surface accumulation and function of postsynaptic $GABA_A$ receptors (Luscher et al. 2011), decreased expression of $GABA_A$ receptors in AD brain may result in insulin refractoriness. The third-most relevant network consisted of genes regulated by insulin signaling pathways (*IL12RB2*, *PRKCB*, *WIPF3*, *NRN1*, *ENC1*, *SATB1*, *PHACTR1*, *ELAVL4*, *FABP3*, *AACS*, *LARGE*, *SPTBN2*, *YWHAG*), and their expression was significantly decreased in AD hippocampus (Hokama et al. 2014), indicating that insulin signaling is largely impaired in AD brain. The alterations in the expression levels of the genes constituting these three networks were well preserved in the temporal cortex and to a lesser extent in the frontal cortex of AD brains. Comparative analyses of expression changes in the brains of AD patients and a mouse model of AD (3xTg-AD), which express mutant human APP_{Swe} and $MAPT_{P301L}$ together with mutant mouse $PSEN1_{M146V}$ (Oddo et al. 2003), were also performed, and genes involved in noninsulin-dependent DM and obesity were commonly altered in both AD brains and the AD mouse model, as were genes related to psychiatric disorders and AD.

Importantly, we found that the alterations in the expression profiles of DM-related genes in AD brains are independent of peripheral DM-related abnormalities, indicating that the altered expression of genes related to DM in AD brains resulted from AD pathology, which may thereby be exacerbated by peripheral insulin resistance or DM (Hokama et al. 2014).

3.3 Insulin Depletion, Impaired Insulin Signaling, and Mitochondrial Dysfunction in AD Brain

There are common alterations of gene expression in AD brains from two independent studies (the Oxford Project to Investigate Memory and Ageing and the Hisayama study) (Hokama et al. 2014). Our study (Hokama et al. 2014) and that of Bosser et al. (2010) and Tan et al. (2010) all showed that expression of the *PCSK1* gene is reproducibly and most significantly downregulated in the late stages of disease in AD brains. Moreover, our data showed that the extent of *PCSK1* downregulation was most significant in the hippocampi of AD brains, with downregulation occurring to a lesser extent in the temporal cortex and to an even lesser extent in the frontal cortex, in accordance with the pathological severity.

PCSK1, encoding proprotein convertase subtilisin/kexin type 1, is essential together with PCSK2 for proinsulin processing (Schechter et al. 1992; Seidah and

Chretien 1999; see Chap. 1 in this book). In both human and mouse brains, PCSK1 protein is highly expressed in hippocampal neurons, and its expression is significantly decreased in both AD patient and 3xTg-AD mouse brains (Abolhassani et al. 2017; Hokama et al. 2014). Moreover, PCSK2 protein level was also decreased in AD hippocampi (Hokama et al. 2014). These results indicated for the first time that hippocampal neurons in human brain are equipped with enzymes for proteolytic maturation of insulin precursor expressed in these neurons, and thus decreased expression of PCSK1 and PCSK2 in AD brain is expected to cause impaired processing of proinsulin resulting in insulin depletion in the brain.

We found that expression of *MET* gene encoding a receptor for hepatocyte growth factor (HGF) was significantly decreased in AD patients (Hamasaki et al. 2014; Hokama et al. 2014). Expression of *MET* gene has been shown to be upregulated by VEGF and HGF (Gerritsen et al. 2003), and we also found that the expression level of *VEGF* is significantly decreased in AD brains (Hokama et al. 2014), thus suggesting that the downregulation of *MET* gene in AD brains is likely to reflect reduced expression of VEGF, whose expression is known to be upregulated by insulin (Miele et al. 2000). Importantly, Fafolios et al. (2011) reported that MET is essential for an optimal hepatic insulin response by directly engaging IR to form a MET-IR hybrid complex, culminating in a robust signal output. They also found that the HGF-MET system restores insulin responsiveness in a mouse model of insulin refractoriness. In human brain, MET protein is mainly expressed in neurons in the cortex and hippocampus as well as in astrocytes, and its expression in neurons is significantly decreased in AD brain, suggesting impaired insulin/HGF signaling in these neurons and astrocytes (Hamasaki et al. 2014).

Astrocytes express insulin receptor (IR) and respond to insulin and/or IGF-1 (Garwood et al. 2015). Astrocytes contain glycogen, an energy buffer, which can bridge the local short-term energy requirements of the brain. Glycogen levels reflect a dynamic equilibrium between glycogen synthesis and glycogenolysis (Belanger et al. 2011). In astrocytes cultured in vitro, stimulation with insulin and/or IGF-1 promotes glucose uptake and glycogen storage (Fernandez et al. 2017; Heni et al., 2011; Muhic et al. 2015), thus suggesting that depletion of brain insulin might decrease glucose uptake and glycogen storage in astrocytes. Glycogen is the largest energy reserve of the brain and has been found to be almost exclusively localized in astrocytes in the adult brain (Belanger et al. 2011); therefore decrease in glycogen storage in astrocyte causes severe energy failure in AD brain.

A large amount of energy, in the form of ATP, is required to maintain basic brain functions, such as maintenance or re-establishment of membrane potential, signaling, and essential cellular activities. This ATP is supplied by consuming oxygen and glucose via oxidative phosphorylation in the mitochondria. An adult human brain typically weighs only about 2% of the body weight; however, a resting brain consumes more than 20% of all the oxygen consumed in the whole body, thus indicating a tenfold greater energy requirement than other tissues. Thus, the brain utilizes a large amount of glucose (Chen and Zhong 2013; MacKenna et al. 2012).

Insulin depletion and impaired insulin signaling in AD brain are strongly related to brain glucose hypometabolism that can be observed potentially decades prior to the development of AD symptoms (Neth and Craft 2017). Indeed, brain imaging with FDG-PET tracer revealed that brain glucose uptake is significantly decreased in temporal-parietal cortex in AD brain, and its occurrence precedes cognitive dysfunction and pathological alterations decades earlier (Bateman et al. 2012; Cerami et al. 2015; Chen and Zhong 2013; Cunnane et al. 2011; Dukart et al. 2013; Mosconi et al. 2014). In AD brains, two essential glucose metabolic pathways in mitochondria, Krebs cycle and oxidative phosphorylation, are known to be distressed. Abnormal Krebs cycle or/and oxidative phosphorylation cause(s) not only glucose hypometabolism but also the increased generation of reactive oxygen species (ROS), oxidative damage, and programmed cell death such as apoptosis (Chen and Zhong 2013). Because mitochondria are also the main location that suffers from ROS, oxidative stress further exacerbates mitochondrial dysfunction, and this vicious cycle is more prone to occur and has been demonstrated to be an event occurring before the appearance of senile plaques and the onset of clinical manifestations (Bhat et al. 2015; Yan et al. 2013).

The gene expression profiles in AD brains revealed that *NEUROD6* encoding the neurogenic basic helix-loop-helix transcription factor, which has been shown to confer tolerance to oxidative stress by triggering an antioxidant response and sustaining mitochondrial biomass (Uittenbogaard et al. 2010), is significantly downregulated in AD brains (Fowler et al. 2015; Hokama et al. 2014). Interestingly, expression of NEUROD6, whose variants were also found to be associated with AD, can be upregulated by 2-deoxy-glucose (Fowler et al. 2015), suggesting a causative connection among decreased glucose uptake, mitochondrial dysfunction, and increased oxidative stress in AD brain.

Thus, AD brain exhibits diabetic condition in the brain, with insulin depletion, insulin refractoriness, glucose hypometabolism, and mitochondrial dysfunction resulting in energy failure in the brain. Such diabetic condition in early stage of AD brain can be exacerbated by peripheral diabetes, namely, through hyperglycemia, hyperinsulinemia, or impaired insulin response (Fig. 3.1).

3.4 Increased Accumulation of Oxidized DNA Lesions and Altered Defense System in AD Brain

The increased oxidative stress in AD brains is demonstrated by increased accumulation of various oxidized molecules in lipids, proteins, and nucleic acids detected mostly in the neurons (Cobb and Cole 2015; de la Monte et al. 2000; Lovell et al. 2011; Nunomura et al. 2001; Wang et al. 2006). Among those, 8-oxoguanine (8-oxoG), an oxidized form of guanine, accumulates in both nuclear and mitochondrial DNA and is recognized as the most pronounced marker for oxidative stress in AD brains (Bradley-Whitman et al. 2014; Gabbita et al. 1998; Lyras et al. 1997;

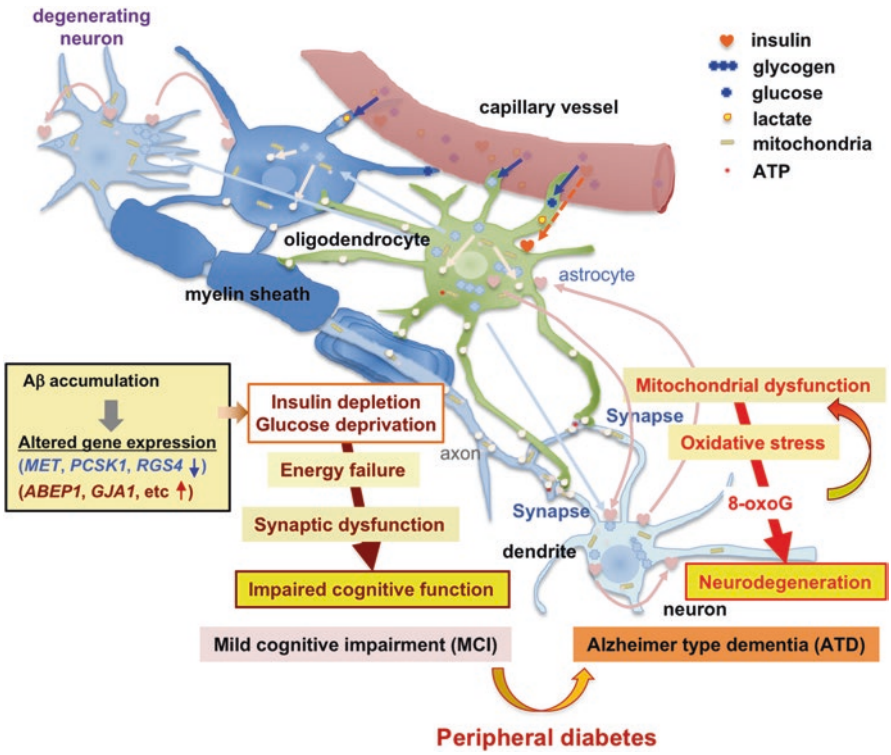

Fig. 3.1 Diabetic condition in early stage of AD brain can be exacerbated by peripheral diabetes. In early stage of AD, Aβ accumulation in brain alters gene expression profiles and causes depletion of brain insulin and impaired insulin signaling; thus, patient brain with mild cognitive impairment (MCI) exhibits a feature of brain diabetes with hypometabolism of glucose and energy failure. Such condition may result in synaptic dysfunction with impaired cognitive function. Diabetic condition in early stage of AD brain can be exacerbated by peripheral diabetes, namely, through hyperglycemia, hyperinsulinemia, or impaired insulin response, and thus aggravate mitochondrial dysfunction with increased oxidative stress, which in turn increases oxidative DNA damage such as accumulation of 8-oxoguanine (8-oxoG) in both neurons and microglia. Persistent vicious cycle of mitochondrial dysfunction may exacerbate neurodegeneration, as seen in patients with Alzheimer-type dementia (ATD)

Mecocci et al. 1994; Wang et al. 2005, 2006). Immunohistochemical examination of postmortem AD brains revealed that cytoplasmic accumulation of 8-oxoG is evident in hippocampal CA1 and CA3 pyramidal neurons (Song et al. 2011), and in neurons of the temporal cortex (de la Monte et al. 2000), where Aβ is also highly accumulated. Accumulation of 8-oxoG in the AD brain is an early event, occurring before the onset of dementia (Coppede and Migliore 2015; Lovell and Markesbery 2007).

Many mouse models for familial AD have been established (Puzzo et al. 2015), and increased cytoplasmic immunoreactivity for 8-oxoG has been observed in the

brains of some models (Aliev et al. 2003; Duffy and Holscher 2013; Oka et al. 2016; Song et al. 2011; Xiong et al. 2011). 8-OxoG is mostly likely to be detected in mitochondrial DNA or cytoplasmic RNA. These observations support that oxidative stress is increased in mouse models of AD, similar to those observed in postmortem AD patient brains. Recently, we examined the effects of human mitochondrial transcriptional factor A (hTFAM) on the pathology of a mouse model of AD (3xTg-AD), because TFAM is known to protect mitochondria from oxidative stress through maintenance of mitochondrial DNA (Kang and Hamasaki 2005; Oka et al. 2016). Expression of hTFAM significantly improved cognitive function, reducing accumulation of both 8-oxoG in mitochondrial DNA and intracellular Aβ in 3xTg-AD mice. Furthermore, we found that AD model neurons derived from human-induced pluripotent stem cells carrying a mutant $PSEN1_{(P117L)}$ gene exhibited mitochondrial dysfunction, accumulation of 8-oxoG and single-strand breaks in mitochondrial DNA, and impaired neuritogenesis. Extracellular treatment with recombinant hTFAM effectively suppressed these deleterious outcomes (Oka et al. 2016), thus demonstrating that Aβ induces mitochondrial dysfunction and oxidative stress, which further accelerate Aβ accumulation, resulting in the mitochondria-mediated vicious cycle of AD.

8-OxoG accumulation in cellular genomes causes either spontaneous mutagenesis or cell death (Nakabeppu 2017; Nakabeppu et al. 2007a; Ohno et al. 2014). The buildup of 8-oxoG in DNA is caused by direct oxidation of guanine in DNA itself or through the incorporation of 8-oxoG from nucleotide pools in which 8-oxo-2′-deoxyguanosine triphosphate (8-oxo-dGTP) is generated under oxidative condition. 8-oxo-dGTP can be utilized by DNA polymerases as a precursor for DNA synthesis; consequently, 8-oxoG is incorporated into the nascent strand opposite adenine and cytosine in the template with almost equal efficiency. In counteracting the accumulation of 8-oxoG in DNA of human and rodent cells, three enzymes, MTH1, OGG1, and MUTYH, play important roles (Nakabeppu 2017). MutT homolog (MTH1, also known as NUDT1), an oxidized purine nucleoside triphosphatase, efficiently hydrolyzes 8-oxo-dGTP accumulated in nucleotide pools to 8-oxo-dGMP and pyrophosphate, thereby avoiding incorporation of 8-oxoG into DNA (Nakabeppu 2001a, 2017). OGG1 with 8-oxoG DNA glycosylase activity excises 8-oxoG opposite cytosine in DNA, thereby preventing the accumulation of 8-oxoG in DNA (Boiteux and Radicella 2000; Nakabeppu 2017; Nishioka et al. 1999). Adenine inserted opposite 8-oxoG in template DNA (8-oxoG:A) are excised by MutY homolog (MUTYH) with adenine DNA glycosylase (Nakabeppu 2017; Ohtsubo et al. 2000). MTH1 and OGG1 thus avoid accumulation of 8-oxoG in DNA, however, if too much 8-oxoG accumulated in DNA, BER initiated by MUTYH causes DNA strand breaks, thus initiating programmed cell death to eliminate damaged cells (see next session) (Oka and Nakabeppu 2011). All three enzymes are known to function both in nuclei and mitochondria (Nakabeppu 2001b, 2017).

We have shown that MTH1 protein is most highly expressed in the stratum lucidum of the CA3 hippocampal subfield corresponding to mossy fiber synapses, followed by perikarya of granular neurons of the dentate gyrus and pyramidal neu-

rons of the entorhinal cortex, in control postmortem human brains (Furuta et al. 2001), and weakly expressed in the cytoplasm of CA1 and CA3 pyramidal neurons (Song et al. 2011). In AD brains, MTH1 synaptic expression in CA3 as well as cytoplasmic expression in CA1 and CA3 neurons was significantly decreased, whereas increased expression was observed in the entorhinal cortex (Furuta et al. 2001; Song et al. 2011). It is noteworthy that decreases in the MTH1 levels in CA1 and CA3 neurons correlate with an increased 8-oxoG levels in these neurons (Song et al. 2011). It has been also shown that substantial levels of both nuclear and mitochondrial forms of OGG1 are expressed in frontal, temporal, and parietal lobes and cerebellum in control human brains (Shao et al. 2008). In contrast, the protein levels of nuclear OGG1 in the frontal lobes from patients with late-stage AD were significantly decreased, and nuclear OGG1 in temporal lobe and cerebellum from patients with mild cognitive impairment (MCI) were significantly increased. There was no significant difference in mitochondrial OGG1 levels among control, MCI, and late-stage AD cases. Irrespective of the alteration in OGG1 protein levels in MCI or late-stage AD brains, 8-oxoG DNA glycosylase activity was significantly decreased in nuclear fractions and to a lesser extent in mitochondrial fractions from MCI and late-stage AD brains (Shao et al. 2008). It has been reported that both nuclear and mitochondrial forms of OGG1 are modified by 4-hydroxynonenal, a neurotoxic by-product of lipid peroxidation in aged brains (Shao et al. 2008). This modification of mitochondrial OGG1 is likely to be elevated in MCI, perhaps underlying the decreased mitochondrial OGG1 activity in MCI. We have reported that the mitochondrial form of OGG1 (OGG1-2a) is strongly expressed in the superior occipital gyrus, orbitofrontal gyrus, and entorhinal cortex; is at much lower levels in CA1, CA3, and CA4; and is absent from the dentate gyrus in control human brains. In late-stage AD brains, OGG1-2a was detected as associated with NFTs, dystrophic neurites, and reactive astrocytes, suggesting highly increased oxidative stress in mitochondria (Iida et al. 2002). Mutations in *OGG1* (C796 deletion, Ala53Thr, Ala288Val) specific to AD patients have previously been reported (Mao et al. 2007). Mutant OGG1-1a protein with the C756 deletion has an altered carboxy-terminal sequence (267aa to 345aa), resulting in the complete loss of 8-oxoG DNA glycosylase activity. The two other missense mutations (Ala53Thr and Ala288Val), which are likely to be rare polymorphic variants, conferred significantly reduced repair capacity to OGG1-1a, as well as reduced binding capacity to its partner proteins, poly(ADP-ribose) polymerase 1 (PARP-1) and X-ray repair cross-complementing protein 1 (XRCC1) (Jacob et al. 2013). All three mutations also alter the amino acid sequence of OGG1-2a (C796 deletion alters 267aa to 424aa). This suggests that both the nuclear form (OGG1-1a) and the mitochondrial form (OGG1-2a) lose repair capacity. To date, no association of a *MUTYH* polymorphism or its altered expression in AD brain has been reported.

In the transgenic (Tg)-*APP*$^{Arc/Swe}$ mouse model, there is a transient increase of at least fourfold *Ogg1* mRNA levels in the hippocampus, frontal cortex, cerebellum, and other regions in 4-month-old mice compared with the levels found in 6-week-old Tg-*APP*$^{Arc/Swe}$ and wild-type mice, and the levels are two- to threefold higher

than those found in 4-month-old wild-type mice. The *Ogg1* mRNA levels in 12-month-old Tg-*APP*$^{Arc/Swe}$ mouse brains were significantly decreased in all the brain regions examined and are equivalent to the levels in 6-week-old mouse brains (Lillenes et al. 2013). The Tg-*APP*$^{Arc/Swe}$ model has early-onset senile plaque formation (4–6 months) and increased intraneuronal Aβ aggregation (1 month) prior to extracellular Aβ deposition, suggesting that the increased expression of *Ogg1* is likely to be a protective response to oxidative damage caused by the accumulation of intraneuronal Aβ aggregation, as seen in preclinical AD brains. Such a protective response is likely to be diminished in late stages of AD pathology, as found in late-stage AD patient brains. While MTH1 and MUTYH have not yet been investigated in any AD mouse model, it would be interesting to examine their expression levels and to determine whether the progression of AD pathology in the AD mouse can be altered with MTH1 or MUTYH deficiency.

3.5 8-Oxoguanine Accumulated in DNA May Be Involved in AD Pathology

8-OxoG accumulation in AD brain is likely to be a result of increased oxidative stress and impaired defense system, namely, decreased expression of MTH1 and OGG1, in the brain. Observations in neurodegenerated postmortem brains (Bradley-Whitman et al. 2014; Coppede and Migliore 2015; Lovell and Markesbery 2007; Lovell et al. 2011; Nakabeppu et al. 2007b) and studies using animal models for various neurodegenerative diseases have shown that 8-oxoG accumulation in nuclear or mitochondrial DNA in neurons under oxidative conditions causes neurodegeneration and that MTH1 or OGG1 protects neurons by preventing 8-oxoG accumulation (Cardozo-Pelaez et al. 2012; De Luca et al. 2008; Liu et al. 2011; Miller-Pinsler et al. 2015; Sheng et al. 2012; Ventura et al. 2013; Yamaguchi et al. 2006).

We have shown that accumulation of 8-oxoG in nuclear and mitochondrial DNA triggers two distinct cell death pathways that are independent of each other (Oka et al. 2008). Both pathways are initiated by the accumulation of MUTYH-generated single-strand breaks (SSBs) in nuclear or mitochondrial DNA. When 8-oxoG accumulates to high levels in nuclear DNA, poly(ADP-ribose) polymerase (PARP) binds to the SSBs generated by MUTYH-initiated base excision repair (BER) on 8-oxoG:A pair, from which MUTYH excises adenine (A) base. This increases poly(ADP-ribose) polymer (PAR) resulting in nicotinamide adenine dinucleotide (NAD^+) and ATP depletion followed by nuclear translocation of apoptosis-inducing factor (AIF). AIF then executes apoptotic cell death. On the other hand, 8-oxoG accumulated to high levels in mitochondrial DNA causes degradation of mitochondrial DNA through MUTYH-initiated BER, resulting in mitochondrial dysfunction and activation of calpains, which in turn cause lysosomal rupture and cell death (Oka and Nakabeppu 2011).

In the early phase of 3-nitropropionic acid (3-NP)-induced striatal degeneration, MTH1 and/or OGG1-deficient medium spiny neurons accumulate high levels of 8-oxoG and SSBs in mitochondrial DNA in an MUTYH-dependent manner, resulting in calpain activation and neuronal damage. In the later phase, dead neurons or damaged neurons activate microglia, which produce ROS, and activated microglia accumulate high levels of 8-oxoG and SSBs in nuclear DNA. In activated microglia, SSBs accumulated in nuclear DNA cause activation of the PARP-AIF pathway in a MUTYH-dependent manner, thus exacerbating microgliosis and neurodegeneration (Sheng et al. 2012). Under oxidative conditions, 8-oxoG is highly accumulated in mitochondrial DNA but not in the nuclear DNA of neurons, and this accumulation in mitochondrial DNA is efficiently suppressed by the increased expression of MTH1. These observations indicate that the 8-oxoG accumulated in mitochondrial DNA is derived from the 8-oxo-dGTP accumulated in the nucleotide pool, but not from direct oxidation of guanine in DNA, under oxidative conditions, because only mitochondrial DNA and not nuclear DNA is replicating in postmitotic neurons. On the other hand, microglial proliferation can be induced under inflammatory responses in the brain with an increase production of ROS; therefore, microglia accumulate 8-oxoG in nuclear DNA (Sheng et al. 2012). Administration of a calpain or PARP inhibitor significantly ameliorated 3-NP-induced striatal degeneration and decreased microgliosis in MTH1/OGG1-deficient mice, indicating that calpain-dependent neuronal damage causes microgliosis and that microgliosis indeed exacerbates neurodegeneration (Sheng et al. 2012). It is noteworthy that activation of calpain and PARP is a hallmark of neurodegeneration under oxidative conditions, in both animal models and in AD brains (Kauppinen and Swanson 2007; Martire et al. 2015; Saito et al. 1993; Yamashima 2013), thus suggesting that 8-oxoG accumulated in AD brain triggers neurodegenerative process.

Recently, we isolated cortical neurons from adult wild-type and MTH1/OGG1-deficient mice and maintained them with and without antioxidants for 2–5 days and then examined their morphology and mitochondrial function. In the presence of antioxidants, both MTH1/OGG1-deficient and wild-type neurons exhibited efficient neurite extension and arborization. However, in the absence of antioxidants, the accumulation of 8-oxoG in mitochondrial DNA of MTH1/OGG1-deficient neurons was increased resulting in mitochondrial dysfunction. MTH1/OGG1-deficient neurons exhibited significantly poor neurite outgrowth with decreased complexity of neuritic arborization, indicating that MTH1 and OGG1 are essential for neuritogenesis or protection of nerve fibers under oxidative conditions. These observations indicate that mitochondrial dysfunction caused by oxidative damage in neurons results in degeneration of axons or dendrites, as well as neuronal death as discussed above, which may represent a part of early pathological features of AD brain. Such degenerating neurons may trigger microglial activation, thus resulting in neuronal loss by phagocytosis.

Now that many different mouse models of AD are available, whether the introduction of MTH1 or OGG1 deficiency exacerbates AD pathology or overexpression of MTH1 or OGG1 as transgene suppresses the progression of AD pathology should

be addressed. Such approach will shed light on the development of new therapeutic approaches for AD.

3.6 Conclusions

Aβ is known to cause various pathological changes including altered gene expression, insulin depletion, and mitochondrial dysfunction, thus increasing oxidative stress in AD brain. As a result, AD brain becomes vulnerable to peripheral DM, and oxidized DNA lesions such as 8-oxoG are highly accumulated in both mitochondrial DNA of neurons and nuclear DNA of microglia. Now, accumulating evidence suggests that such damages in neurons and microglia trigger neuronal dysfunction and microglial activation, both of which further exacerbate neurodegeneration and neuronal loss as seen in AD brain (Fig. 3.2).

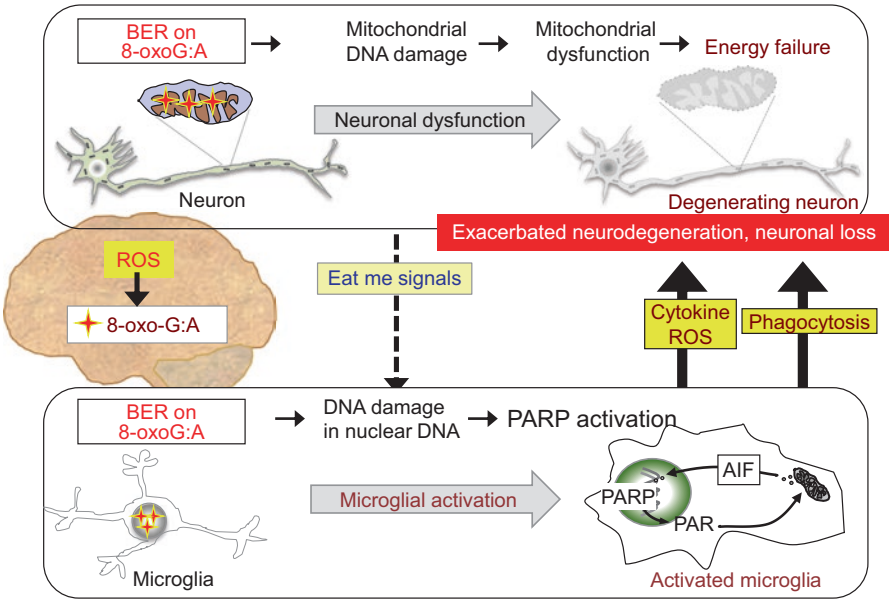

Fig. 3.2 8-oxoguanine accumulated in mitochondrial DNA of neuronal cells and nuclear DNA of microglia causes neurodegeneration. At the early stages of neurodegeneration with oxidative stress, high levels of 8-oxoG accumulate in mitochondrial DNA of neurons. As a result, the mitochondrial DNA is degraded in the process of BER initiated by MUTYH and is depleted; thus mitochondrial function is impaired. In such condition, synaptic dysfunction and neuronal degeneration can be induced. In the latter period, microglia are activated by eat-me signals such as nucleotides released from degenerating neurons. In activated microglia, high level of 8-oxoG accumulates in their nuclear DNA because ROS production is enhanced. Thereafter, DNA damage accumulates in nuclear DNA during the process of BER initiated by MUTYH. DNA damage accumulated in nuclear DNA of microglia induces activation of microglia, thus increasing production of cytokines and ROS, resulting in chronic microgliosis. Microgliosis exacerbates neuronal degeneration and neuronal loss by phagocytosis, as seen in AD brain

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Chapter 4
The Full Spectrum of Alzheimer's Disease Is Rooted in Metabolic Derangements That Drive Type 3 Diabetes

Suzanne M. de la Monte

Abstract The standard practice in neuropathology is to diagnose Alzheimer's disease (AD) based on the distribution and abundance of neurofibrillary tangles and Aβ deposits. However, other significant abnormalities including neuroinflammation, gliosis, white matter degeneration, non-Aβ microvascular disease, and insulin-related metabolic dysfunction require further study to understand how they could be targeted to more effectively remediate AD. This review addresses non-Aβ and non-pTau AD-associated pathologies, highlighting their major features, roles in neurodegeneration, and etiopathic links to deficits in brain insulin and insulin-like growth factor signaling and cognitive impairment. The discussion delineates why AD with its most characteristic clinical and pathological phenotypic profiles should be regarded as a brain form of diabetes, i.e., type 3 diabetes, and entertains the hypothesis that type 3 diabetes is just one of the categories of insulin resistance diseases that can occur independently or overlap with one or more of the others, including type 2 diabetes, metabolic syndrome, and nonalcoholic fatty liver disease.

Keywords Alzheimer's disease · White matter degeneration · Microvascular disease · Insulin resistance · Dementia · Amyloid · Neuroinflammation

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4.1 Alzheimer's Disease Fundamentals

4.1.1 Alzheimer's Disease: Definition and Diagnostics Overview

Alzheimer's disease (AD) is characteristically associated with progressive alterations in behavior, impairment of recent or short-term memory, and declines in executive and cognitive functions (McKhann et al. 2011). Structured longitudinal neuropsychological tests of memory, intellectual function, and language are used to render a diagnosis of possible or probable AD. However, to increase diagnostic accuracy, clinical and neuropsychological testing is supplemented with laboratory and neuroimaging assessments (McKhann et al. 2011), including assays of amyloid precursor protein-amyloid beta 1–42 peptide ($A\beta_{1-42}$) and phospho-Tau (pTau231) in cerebrospinal fluid (CSF) and serum (Blennow et al. 2015a; Olsson et al. 2016), magnetic resonance imaging (MRI) (Duncan et al. 2013; Pantano et al. 1999), functional MRI (fMRI), diffusion tensor imaging (DTI) (Amlien and Fjell 2014), single-photon emission computed tomography (SPECT), positron emission tomography (PET), and magnetic resonance spectroscopy (MRS) (Jones and Waldman 2004; Ewers et al. 2011).

4.1.2 Aging Versus Alzheimer's Disease

Aging leads to atrophy and reduced function of most organs throughout the body, including the brain (Double et al. 1996). Lifestyle choices have measurable positive and negative effects on aging such that healthful eating habits and regular physical and mental exercise help preserve cognitive function (Daly et al. 2015; Rolandi et al. 2016; Madsen et al. 2015), whereas poor lifestyle choices accelerate physical and functional aging (Beydoun et al. 2014; Moreira 2013). Furthermore, aging is the most consistent and dominant risk factor for neurodegeneration. One of the main differences between aging and neurodegeneration is that with aging, the brain exhibits modest degrees of atrophy and functional loss over a period of years, whereas in AD, the declines are swifter and relentless, driving formerly fully functioning people to eventual end-stage vegetative states. These concepts suggest that lifestyle measures that either curtail or exacerbate the aging process may also modulate risk and rates of developing AD as well as other neurodegenerative diseases.

4.1.3 Characteristic Neuropathology

Typically, neurodegeneration begins before it becomes clinically manifested, i.e., there is a pre-symptomatic period during which deficits are subtle or silent. Although the asymptomatic phase enables victims to continue functioning, the negative aspect is that the disease remains hidden during the period when it may be reversible. The potential for early intervention is further challenged by social and family pressures that cause afflicted individuals to remain guarded and secretive about their cognitive deficits. Postmortem studies have shown that brain structures hit earliest by AD, including medial temporal and orbitofrontal regions, are functionally linked to impairments in memory acquisition. With advancement of AD, neurodegeneration "spreads" to involve other brain regions, causing progressive destruction of the corticolimbic circuitry and eventually other pathways.

At the tissue or histopathological level, progressive loss of neurons and synaptic terminals, mediated by apoptosis, necrosis, oxidative stress, and neuroinflammation, represents fundamental cellular pathologies that correspond with atrophy of corticolimbic structures. What distinguishes neuronal loss in AD from non-degenerative disease processes is the co-accumulation of three major proteins including abnormally phosphorylated tau, $A\beta_{1–42}$, and ubiquitin (Nelson et al. 2012; Hyman et al. 2012; Montine et al. 2012). Tau is a major neuronal cytoskeletal protein that provides neurons with structure and enables them to form stable interconnections. Aberrant hyper-phosphorylation of tau through inappropriate activation of kinases such as glycogen synthase kinase-3β (GSK-3β) causes Tau fibrillization, aggregation, and ubiquitination, followed by stress activation of the unfolded protein response, loss of neuronal function, and ultimately cell death. Insoluble, fibrillary aggregates of hyper-phosphorylated and ubiquitinated Tau are major components of neurofibrillary tangles, dystrophic neurites, and neuropil threads which characteristically are present in AD and progressively accumulate with increasing severity of neurodegeneration (Serrano-Pozo et al. 2011). Their presence in the brain is detectable by immunohistochemical staining with antibodies to phospho-Tau or ubiquitin or by silver-based histochemical staining.

$A\beta_{1–42}$ is a ~4 kD peptide generated by secretase cleavage of amyloid beta precursor protein (AβPP). Under normal circumstances, AβPP cleavage products, including $A\beta_{1–42}$, are continuously cleared from the brain by transport into the general circulation (Ueno et al. 2014). In both aging and AD, $A\beta_{1–42}$ accumulates in cortical and leptomeningeal vessel walls, cortical and sub-cortical perivascular spaces, plaques, and as soluble oligomeric Aβ-derived diffusible ligands (ADDLs) which are neurotoxic fibrils (Kalaria and Ballard 1999; Viola and Klein 2015). Like hyper-phosphorylated tau, insoluble $A\beta_{1–42}$ deposits in vessels and plaques are ubiquitinated. $A\beta_{1–42}$ accumulations in the brain are readily detected by immunohistochemical staining for $A\beta_{1–42}$ or ubiquitin, light microscopic imaging of Congo red-stained sections under polarized light, or fluorescence microscopy of thioflavin-S-stained histological sections of the brain.

4.1.4 Clinical Neuroimaging and Laboratory Studies Detect $A\beta_{1–42}$ and pTau Accumulations in the Brain

Extensive postmortem investigations demonstrating progressive accumulations of pTau- and $A\beta_{1–42}$-associated lesions with advancing stages of AD-associated cognitive decline inspired the development of noninvasive tests to detect and monitor related abnormalities in living patients. Neuroimaging by positron emission tomography (PET) was developed to detect $A\beta_{1–42}$ and pTau using F18 isotopically labeled tracers (Fleisher et al. 2012; Cselenyi et al. 2012). PET imaging for Aβ emerged in about 2002. In 2012, after several iterations, its use as a diagnostic aid for AD won FDA approval (Yang et al. 2012). PET imaging with F18 isotopically labeled tracers for pTau (707 and 708) is used to detect pTau accumulations in the brains of people suspected of having cognitive impairment or dementia due to AD (Zhang et al. 2012; Declercq et al. 2016). Noninvasive PET imaging of Aβ and pTau accumulations in the brain provide objective data about the nature and distribution of neurodegeneration and opportunity to increase accuracy of the clinical diagnosis. Initially, those approaches drew tremendous excitement because abundant signals reflecting Aβ and pTau accumulations were detected in selected AD cases, whereas neuroimaging pathologies were virtually absent in healthy controls. Furthermore, the PET imaging for Aβ and pTau showed that the abnormal signals extended well beyond corticolimbic structures (Shin et al. 2011; Braskie et al. 2010; Barrio et al. 2008; Small et al. 2006; Rowe et al. 2013a, b), a phenomenon that could potentially explain occurrences of more global deficits as AD progresses.

Cerebrospinal fluid (CSF) assays for pTau and Aβ were also developed based on the characteristic presence, distribution, and abundance of related lesions in AD brains (Blennow et al. 2015a; Olsson et al. 2016). CSF levels of pTau increase with AD progression, whereas Aβ levels increase in the early stages of AD but subsequently decline as brain clearance declines and brain levels increase. Reduced brain clearance of Aβ is also marked by lower serum levels (Blennow et al. 2015b). Together with monitoring the clinical course and assessing longitudinal changes in neuropsychological performance (McKhann et al. 2011), a reasonably accurate diagnosis of AD can be made in most cases that are at intermediate to somewhat late stages of neurodegeneration.

4.1.5 Limitations and Concerns Regarding Aβ and pTau as Dominant Diagnostic and Therapeutic Targets

The predominant distributions of atrophy in corticolimbic structures and in the parietal and temporal lobes are not specific to AD since other forms of dementia including dementia with Lewy bodies and frontotemporal lobar degeneration often exhibit overlapping patterns of brain atrophy. Furthermore, AD variants and overlapping or complex forms of neurodegeneration can have nonstandard and asymmetric

distributions of atrophy. These factors limit the accuracy of AD diagnoses that are solely based on anatomical neuroimaging or macroscopic examination of the brain, justifying the need for histopathological studies, including the use of molecular marker-based analyses to distinguish among the various subtypes of neurodegeneration.

PET imaging to detect pTau and Aβ accumulations has become widely used as diagnostic aids for AD. However, postmortem studies have established that neither "biomarker" is specific for AD, as they both accumulate in several diseases (Hulette et al. 2009; Naasan et al. 2016; Jellinger 2003; Washington et al. 2016; Chandra 2015; Barrio et al. 2015). Correspondingly, with broadened use of F18-PET imaging of Aβ and pTau, significant positive signals have been detected in many conditions including other dementias (Engler et al. 2008; Berti et al. 2011), traumatic brain injury (Hong et al. 2014), and normal aging (Chetelat et al. 2013), indicating that Aβ and pTau accumulations are not specific for AD. Therefore, noninvasive assays restricted to these bio-indices may not confer the diagnostic accuracy needed for subject assignment in clinical therapeutic trials. Instead, the best diagnostic strategy may be to utilize neuroimaging data, including PET studies in conjunction with the clinical profile and formal neuropsychological testing. In many respects, this scenario tells us that major abnormalities unrelated to pTau and Aβ also have important roles in the pathogenesis and progression of AD.

4.2 Major Brain Abnormalities Unrelated to Aβ and pTau in AD

4.2.1 Overview of the Problem

Although diagnostic criteria for rendering a neuropathologic diagnosis of AD have been streamlined to semiquantitative assessments of neurofibrillary tangles and senile plaques in specific brain regions (Hyman et al. 2012), realistically, the nature and distribution of neurodegeneration are far broader. Major abnormalities not routinely considered despite their overwhelming presence in AD include neuronal loss; neuroinflammation; gliosis; oxidative and nitrosative stress; white matter degeneration; vascular degeneration, particularly in white matter (Brun et al. 1995; Vinters 2015); and blood-brain barrier disruption (Bridges et al. 2014; Grammas et al. 2011; Johanson et al. 2018). In addition, impairments in brain metabolism (glucose and oxygen utilization) (Hoyer 1982; de Leon et al. 1983; Faulstich 1991; Daulatzai 2017), although recognized for decades and frequently assessed, have not been incorporated into the cluster of AD biomarkers. Failure to consider these important aspects of AD limits opportunity to fully understand the nature of disease and therefore optimally strategize development of forward-looking therapeutic interventions. For example, ignoring the degenerative changes that occur in white matter and microvessels is problematic because these abnormalities occur

early and their progression can have greater overall negative impact on brain function than the burdens of neurofibrillary tangles and plaques. Limiting therapeutic targets to pTau and Aβ accumulations has already been demonstrated to be too restrictive and largely ineffective for providing significant and sustained disease remediation in AD.

4.2.2 Neuronal Loss and Degeneration

Neurodegeneration in AD is associated with loss of neurons, nerve terminals, and fibers beginning in the hippocampus, parahippocampal gyrus (entorhinal cortex), and medial temporal structures (Mizutani et al. 1990). However, what characteristically distinguishes AD from other disease processes is that neuronal loss is accompanied by progressive accumulations of neurofibrillary tangles, dystrophic neurites, neuritic plaques, and neuropil threads. These lesions mark loss of interneuronal connections, compromised neuronal plasticity, and cognitive impairment.

Neurofibrillary tangles are composed of aggregated twisted insoluble fibrillar proteins (paired helical filaments, PHF) whose main constituent is the hyperphosphorylated tau. Tau is a microtubule-associated protein. Microtubules provide structure and intracellular nutrient transport functions. Neuropil threads (Braak et al. 1986; Perry et al. 1991) and dystrophic (irregular, swollen) axonal neurites distributed in the neuropil and around plaques also contain PHF (Su et al. 1993). Over time (years), neurons continue to degenerate, disconnect, and die, while PHF-associated neuronal, axonal, and dendritic pathologies increase, progressively extending from medial temporal to cortical-limbic, followed by parietal and frontal regions and beyond (Serrano-Pozo et al. 2011). Neuronal death is ultimately mediated by several factors including oxidative (Gotz et al. 1994; Mancuso et al. 2007; Mangialasche et al. 2009; de la Monte and Wands 2006), endoplasmic reticulum (de la Monte 2012c), and nitrosative (Mangialasche et al. 2009; Swomley and Butterfield 2015; de la Monte et al. 2007) stress, apoptosis, mitochondrial dysfunction with energy failure (Kidd 2005; Gonzalez-Lima et al. 2014; Daulatzai 2017; de la Monte and Wands 2006), brain hypoperfusion (Aliev et al. 2003; Daulatzai 2017), neuroinflammation (McGeer and McGeer 2013), neurotoxic effects of $A\beta_{1-42}$, and impaired signaling through insulin and insulin-like growth factor (IGF) pathways that promote cell survival and energy metabolism (Steen et al. 2005; de la Monte and Wands 2008).

4.2.3 Synaptic Terminal Degeneration

Loss of cortical presynaptic terminals and dendritic spines and dystrophic deformation of axonal and dendritic spines correlate with severity of dementia and are better markers of disease severity than senile plaques (Masliah et al. 1989, 1991). Synaptic

disconnection due to degeneration and loss of nerve terminals is associated with reduced synaptophysin immunoreactivity (Masliah et al. 1989, 1991) and accompanied by loss of neuronal and neuritic sprouting in AD (Masliah 1995; Brun et al. 1995; Liu et al. 1996). Irregularly swollen, dystrophic cortical neurites are detectable by silver impregnation histochemical techniques and immunohistochemical staining for synaptophysin (Su et al. 1993) and ubiquitin (Wilson et al. 2001; Whatley et al. 2008). The histological correlate of neuritic dystrophy resulting from synaptic disconnection is cortical spongiosis manifested by vacuolation of the neuropil, especially in superficial layers of cerebral cortex.

Dystrophic neurites are often distributed along the periphery of $A\beta_{1-42}$ plaques (Wippold et al. 2008), a phenomenon that could be linked to the presence of trophic factors such as basic fibroblast growth factor within plaques, potentially drawing in disconnected sprouting neurites (Cummings et al. 1993). Furthermore, the finding in a genetic mouse model that anti-$A\beta_{1-42}$ therapy prevented synaptic degeneration (Buttini et al. 2005) suggests that the neurotoxic effects of $A\beta_{1-42}$ have causal roles in the impairment of synaptic plasticity. Subsequently, the finding that mitoxantrone inhibition of $A\beta_{1-42}$ oligomer fibril growth was neuroprotective in reducing the loss of cortical synapses in an experimental model of AD (Eleuteri et al. 2015) provided evidence that synaptic loss in AD is mediated by the neurotoxic effects of $A\beta_{1-42}$ oligomers. However, it should also be noted that cortical dystrophic neurites are often distributed independent of $A\beta_{1-42}$ deposits (Masliah et al. 1991), and in the brains of ApoE-ε4 allele carriers, the presence of abundant cortical senile plaques in AD does not contribute to synaptic pathology or loss of cholinergic function (Corey-bloom et al. 2000). Therefore, alternative mechanisms of synaptic disconnection should be evaluated.

4.2.4 Gliosis

Progressive loss of neurons, nerve terminals, and fibers in AD is associated with gliosis, characterized by proliferation and activation of astrocytic glia (Brun et al. 1995; de la Monte 1989) and deposition of extracellular matrix composed of glial fibrillary acidic protein (GFAP) in both gray and white matter structures (Chalmers et al. 2005). Combined neurodegenerative and reactive gliotic changes cause the underlying parenchymal architecture to become distorted. For example, instead of their normal laminar arrangements, cortical neurons become irregularly distributed and misoriented among hypertrophic astrocytes, plaques, microglia, and metabolic astrocytes. In addition, loss of nerve terminals and fibers combined with the proliferation of dystrophic neurites lead to collapse (shrinkage) and vacuolation of the neuropil. As neurodegeneration advances, hypertrophic, reactive astrocytes increase in abundance throughout the cortex but most prominently in layers III and V and at cortical-white matter boundaries. Gliosis is also evident throughout white matter and medial temporal structures, particularly the ventromedial amygdala.

The distribution and severity of gliosis are best revealed by immunohistochemical staining for GFAP (Fig. 4.1a–c), which typically shows that glial activation in AD is substantially more pronounced than pTau and Aβ pathologies. Astrocytic gliosis is not simply a scarring response to neurodegeneration since activated astrocytes have documented roles in mediating inflammatory and stress-associated tissue injury (Birch 2014; Garwood et al. 2017; Verkhratsky et al. 2014). Pro-inflammatory cytokines, chemokines, and reactive oxygen and nitrogen species can all damage synapses and disrupt neuronal plasticity (Agostinho et al. 2010). Therefore, once activated, gliosis can exacerbate neurodegeneration.

4.2.5 Neuroinflammation

Neuroinflammation in AD is largely mediated by microglia and astrocytes. In hematoxylin- and eosin-stained histological sections, activated microglia exhibit irregularly twisted rod-shaped cell bodies distributed in the neuropil and closely associated with senile plaques. Immunohistochemical staining with CD45 or Iba1 antibodies

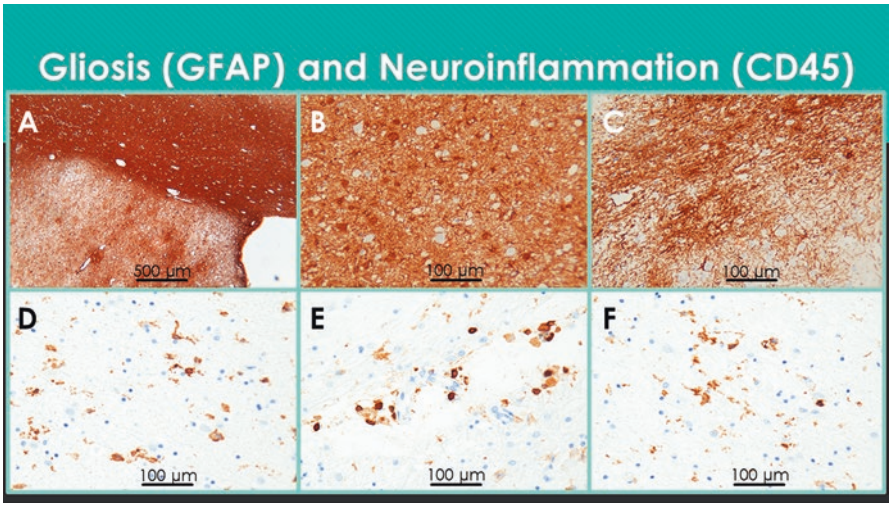

Fig. 4.1 Gliosis and neuroinflammation in AD. Formalin-fixed, paraffin-embedded (FFPE) sections of medial temporal structures including the amygdala from a postmortem human brain with AD were immunostained for (**a**–**c**) GFAP or (**d**–**f**) CD45 to detect reactive gliosis or microglia, respectively. Immunoreactivity was detected with HRP polymer-conjugated secondary antibodies and diaminobenzidine (DAB) as the chromogen (brown precipitate). The sections were counterstained with hematoxylin. Note (**a**) dense band of GFAP immunoreactivity in white matter (upper right) and diffuse labeling of the amygdala (lower left). Higher magnification images show (**b**) abundant hypertrophic astrocytes and (**c**) glial fibrils distributed throughout the amygdala. (**d**–**f**) Activated microglia (**d**) distributed throughout the neuropil, (**e**) surrounding small blood vessels, and (**f**) in white matter (**d**–**f**)

demonstrates microglia abundantly distributed in the cortical neuropil, subcortical nuclei, and white matter. Microglia infiltrate white matter diffusely, but also prominently surround vessels within the central, periventricular, and subcortical U-fiber zones (Fig. 4.1d–f), along with reactive astrocytes (gliosis). In addition, overlapping microgliosis and astrogliosis are abundantly present within both corticolimbic and more distant structures, indicating that their distributions extend well beyond the structures that are typically marred by neurofibrillary tangle and plaque pathologies.

Neuroinflammatory injury occurs via pro-inflammatory cytokine activation, chemokine and complement release, and increased generation of membrane fatty acids, eicosanoids, lipid peroxidation products, reactive oxygen species, and reactive nitrogen species (Piro et al. 2012; Agostinho et al. 2010; Singhal et al. 2014). Consequences of neuroinflammation include damage to nerve terminals, ultimately resulting in synaptic dysfunction followed by cognitive impairment (Agostinho et al. 2010). Neuronal injury and death linked to increased generation of fatty acids may be due to phospholipase activation and attendant hydrolysis of membrane phospholipids (Stephenson et al. 1999).

The sources of neuroinflammation are not well understood. One hypothesis stemming from the observation that microglial and reactive astrocyte-derived pro-inflammatory cytokines such as IL-1β, IL-6, interferon-gamma, and macrophage migration inhibitory factor, are increased around plaques was that Aβ promotes neuroinflammation (Mehlhorn et al. 2000; Dandrea et al. 2001). In addition, Aβ-activated microglia and reactive astrocytes could potentially cause neuronal injury and cholinergic dysfunction by increasing inducible cyclooxygenase, inducible nitric oxide synthase, and p38 MAPK activities (Giovannini et al. 2002). Alternatively, brain metabolic dysfunction linked to impaired insulin signaling may be the driving force of neuroinflammation, vasculopathy, and oxidative stress (Misiak et al. 2012; Samaras and Sachdev 2012; Gaspar et al. 2016).

4.2.6 Oxidative Stress

Oxidative stress is an important underlying mediator of neurodegeneration in AD (Agostinho et al. 2010; de la Monte 2012b, de la Monte et al. 2017a) due to its relationships to neuroinflammation, insulin resistance, lipid peroxidation, and cell death. Potential sources of stress and inflammation include increased levels of advanced glycation end products (AGE) and expression of the receptor for advanced glycation end products (RAGE) (Deane et al. 2003; Donahue et al. 2006; Lovestone and Smith 2014; Yamagishi et al. 2015), impaired insulin/IGF signaling through Akt pathways, lipid peroxidation linked to myelin breakdown, and ceramide accumulation. Neuroinflammation in AD is associated with increased pro-inflammatory cytokine expression in astrocytes and microglia (Agostinho et al. 2010; Piro et al. 2012; Singhal et al. 2014). Correspondingly, postmortem brain levels of AGE and 4-hydroxy-2-nonenal (4-HNE), a marker of lipid peroxidation, increase with AD

progression (Fig. 4.9). However, at earlier stages of disease, 4-HNE was found selectively increased in AD CSF, along with pTau and Aβ (Fig. 4.10), suggesting that stress-mediated white matter myelin degeneration marks the early stages of neurodegeneration.

4.2.7 White Matter Degeneration

4.2.7.1 Nature and Distribution

White matter mainly consists of myelinated axons together with glial cells, including oligodendrocytes and astrocytes, and vascular elements ranging from penetrating arteries and veins to capillaries and venules. Axons are long cytoplasmic extensions of neuronal cell bodies that serve to connect neurons in different regions of the CNS. Axonal structure is maintained by an elaborate cytoskeleton that is rich in neurofilament proteins and microtubule-associated proteins such as Tau. CNS myelin is composed of lipid-rich oligodendrocyte membranes that wrap around axons to provide insulation and ensure efficient conductivity. Loss of myelin or axons compromises neurotransmission and plasticity.

White matter degeneration is a major and consistent abnormality in AD. Its occurrence was initially characterized in 1986 by Brun and Englund (1986). Subsequently, it was demonstrated that white matter atrophy emerges early and in the preclinical stages of AD (de la Monte 1989). White matter atrophy can be quantified in relation to overall brain atrophy and cortical or subcortical nuclear atrophy using morphometric analysis (de la Monte 1989). With that approach, white matter atrophy in postmortem AD brains was shown to be most pronounced in the parietal and temporal lobes, followed by frontal lobes, whereas the occipital lobes were relatively spared (de la Monte 1989). In addition, the anterior commissure, fornix, and corpus callosum undergo atrophy, while the internal, external, and extreme capsules remain intact. The histopathological correlates of white matter atrophy in AD have been characterized mainly via histochemical staining with Luxol fast blue dye. Luxol fast blue reacts with phospholipids or lipoproteins and detects myelin loss. Silver impregnation, such by Bielschowsky staining which binds to neuronal cytoskeletal proteins, is used to characterize axonal pathology.

4.2.7.2 Associated Critical Pathologies

In AD, white matter atrophy is associated with loss of myelin and axons. Myelin loss, manifested by pallor of Luxol fast blue staining (Fig. 4.2), is associated with reduced populations of oligodendrocytes which are needed to maintain myelin, increased reactive gliosis (scarring) (Figs. 4.1 and 4.3), and degenerative vasculopathy (Brun and Englund 1986; de la Monte 1989; Brickman et al. 2008; Burns et al. 2005; Brilliant et al. 1995; Englund 1998; Sjobeck et al. 2003, 2005) (Fig. 4.4).

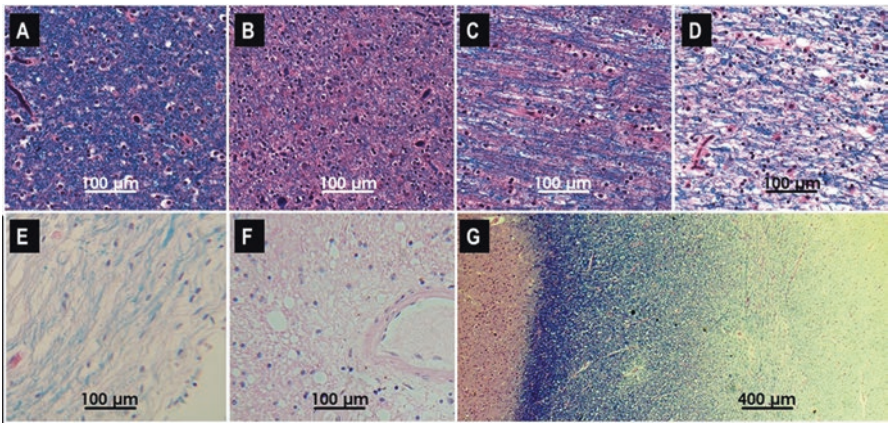

Fig. 4.2 Spectrum of white matter (WM) degeneration in AD. Sections of FFPE posterior cingulate gyrus with underlying WM from human postmortem brains with different Braak stage severities of AD were stained with Luxol fast blue (LFB) to show myelin integrity and counterstained with hematoxylin and eosin (LHE). High-intensity blue staining reflects intact myelin, and low-intensity staining indicates myelin loss. (**a**) Normal aged control WM with dense blue myelin staining. (**b**–**f**) Progressive reductions in WM LFB staining with increasing severity of AD: (**b**) Braak 2, (**c**) Braak 3, (**d**) Braak 4, (**e**) Braak 5, and (**f**) Braak 6. (**g**) Leukoaraiosis manifested by graded WM degeneration from subcortical U-fiber region (left dense blue band) to central WM (right) where LFB staining is minimal LFB staining

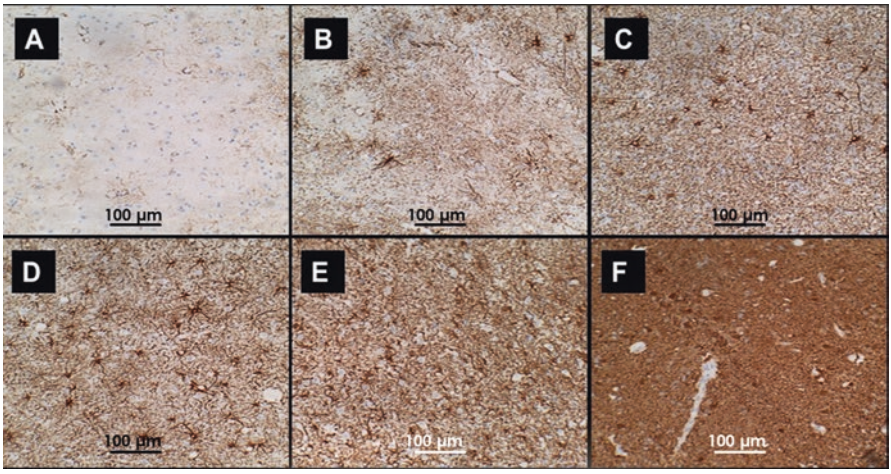

Fig. 4.3 WM gliosis increases with severity of AD. FFPE sections of posterior cingulate from brains with (**a**) normal aging or different Braak stage severities of AD: (**b**) Braak 2, (**c**) Braak 3, (**d**) Braak 4, (**e**) Braak 5, and (**f**) Braak 6 were immunostained for GFAP (see legend to Fig. 4.1). Higher intensities of GFAP immunoreactivity correspond to greater degrees of gliosis

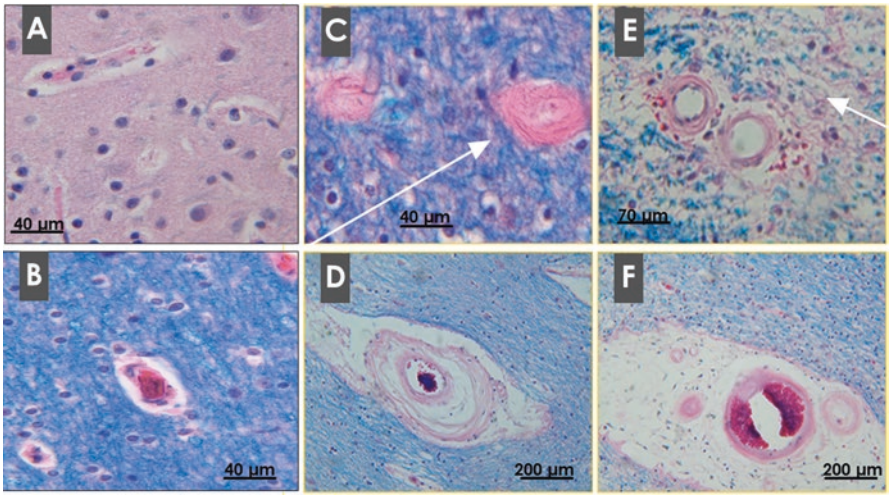

Fig. 4.4 Microvascular pathology in AD. FFPE sections of human postmortem parietal (**a**) control cortical, (**b**) control WM, and (**c**–**f**) AD WM were stained with LHE. Note delicate walls and plump, regularly spaced endothelial cells in control microvessels. In AD, WM vascular disease affects small arteries, arterioles, and capillaries and results in (**c**) severe fibrotic thickening of the walls with extreme narrowing of lumens (arrow), (**d**, **e**) degeneration of vascular smooth muscle and loss of perivascular tissue and increased perivascular inflammatory cells (arrow in **e**), and (**f**) extensive attrition of perivascular WM tissue resulting in loss of contact between vessels and WM parenchyma

White matter degeneration is most pronounced in periventricular and central regions, corresponding with the distribution of leukoaraiosis (Fig. 4.2) and white matter hyperintensities seen by MRI (Scheltens et al. 1995). White matter degenerative vasculopathy mainly impacts microvessels which exhibit mural thickening and fibrosis with narrowing of the lumens, damage to endothelial cells, and perivascular tissue attrition and fibrosis. Although the consequence of cerebral micro-vasculopathy, including micro-infarcts and atrophy, can be detected by MRI (Scheltens et al. 1995), the vasculopathy/vascular degeneration cannot be assessed directly using noninvasive neuroimaging tests.

4.2.7.3 Cell Types Affected

Despite their widespread use, histochemical stains, including Luxol fast blue, are relatively non-specific and offer little prospect for uncovering disease mechanisms. On the other hand, immunohistochemical staining provides an effective means of characterizing pathological processes. For example, GFAP immunoreactivity marks increased abundance and activation of reactive astrocytes, astrocytic fibrils, and glial fibrillary matrix (white matter scarring). Antibodies to pTau or neurofilament are used to demonstrate altered patterns and abundance of neuronal cytoskeletal

proteins in relation to axonal loss and degeneration. Myelin basic protein antibodies help assess the integrity of mature myelin. Oligodendrocytes express Olig transcription factors; therefore, immunohistochemical staining for Olig1, Olig2, and Olig3 could potentially be used to quantify the loss of oligodendrocytes that accompanies white matter atrophy and degeneration in AD.

4.2.7.4 Gliosis

In AD, white matter gliosis is associated with markedly increased GFAP fibrillar and astrocytic cytoplasm immunoreactivity (Figs. 4.1 and 4.3). Dense fibrillary gliosis is typically observed in periventricular zones. Central white matter exhibits prominently increased populations of reactive astrocytes in a background of variably increased GFAP-positive fibrils. Central white matter exhibits the most prominently increased populations of reactive astrocytes in a background of variably increased GFAP-positive fibrils. Next is severity of gliosis are the subcortical U-fiber zones and white matter cores within gyri. Gliosis is also evident in white matter fibers that are intrinsic to nuclei that exhibit neuronal degeneration, but least prominent in major sensory, motor, and cerebellar tract systems.

4.2.7.5 Neuroinflammation

Although the histopathology of white matter atrophy and degeneration in AD has been well characterized, the mechanisms remain unknown. Empirical studies showing that increased GFAP immunoreactivity overlaps with the distribution of microgliosis in white matter (Fig. 4.1d–f) suggest that gliosis and neuroinflammation may be interrelated. Increased generation of pro-inflammatory cytokines by microglia and astrocytes could potentially lead to oxidative injury and degeneration of myelin as well as axons. Although attractive, the underlying cause of neuroinflammation has not yet been determined. However, one potential consideration is that white matter degeneration is mediated by increased $A\beta_{1–40}$ and $A\beta_{1–42}$ accumulation and attendant neuroinflammation (Roher et al. 2002). Against this argument is that $A\beta_{1–40}$ and $A\beta_{1–42}$ do not accumulate in white matter except at cortical-white matter boundaries, and their increased immunoreactivity is not present in regions of white matter that exhibit the most severe myelin loss, fiber rarefaction, gliosis, and neuroinflammation.

4.2.7.6 Role of Ischemic Injury

One compelling hypothesis is that white matter degeneration is mediated by chronic ischemic injury secondary to microvascular disease (Brun and Englund 1986; Verny et al. 1991; Englund 1998; de la Monte et al. 2000; Van Der Vlies et al. 2012; Love and Miners 2015; Poliakova et al. 2016). Correspondingly, white matter fiber

attrition frequently occurs in perivascular distributions and is associated with vascular fibrosis and luminal narrowing (Jellinger 2002; Suter et al. 2002; Thal et al. 2003; Ervin et al. 2004). In addition, large areas of leukoaraiosis, characterized by ill-defined regions of myelin loss and incomplete infarction (Prencipe and Marini 1989), are nearly always associated with white matter vasculopathy in AD but regarded as unspecific since elderly controls and patients with vascular dementia have similar abnormalities by neuroimaging (Verny et al. 1991; Meyer et al. 1992). Furthermore, it is now well-recognized that white matter ischemic injury contributes to cognitive impairment in AD and that, if this aspect of AD were prevented or effectively treated, incident rates and severity of AD would decline (Etiene et al. 1998). Correspondingly, the recent decline in AD prevalence has been attributed to increased use of cerebrovascular and cardiovascular preventive and intervention measures in older individuals (Langa 2015).

4.2.7.7 Oligodendrocyte Dysfunction

Another potential mediator of white matter degeneration in AD is loss or impaired function of oligodendrocytes. Maintenance of oligodendrocytes is required for myelin homeostasis, and loss of myelin impairs neuronal conductivity and compromises the insulation of axons from the extracellular environment. Correspondingly, elevated levels of neurofilament light chain and myelin sulfatides were detected in CSF of patients with subcortical vascular dementia, even prior to significant onset of symptoms (Wallin et al. 2016a). Increased neurofilament and myelin sulfatides in CSF mark degeneration of white matter axons and myelin, reinforcing the concept that white matter degeneration occurs early in AD. Furthermore, myelin lipid breakdown can lead to oxidative damage via lipid peroxidation with attendant neuroinflammation and reactive gliosis. Previous studies have demonstrated major abnormalities in oligodendrocyte myelin-associated gene expression in both human and experimental models of AD (Love and Miners 2015; Tong et al. 2016; de la Monte 2017). Mechanistically, oligodendrocyte survival and function and myelin maintenance are supported through stimulation of insulin and insulin-like growth factor (IGF) signaling pathways (Barres et al. 1993; Carson et al. 1993; Chesik et al. 2008). Correspondingly, in experimental models of impaired insulin and IGF signaling in the brain, oligodendrocyte dysfunction with white matter atrophy accompanies AD-type pathology and cognitive impairment (de la Monte et al. 2006; Lester-Coll et al. 2006).

4.2.7.8 Current Limitations in Our Assessments of White Matter Degeneration in AD

The major barriers to incorporating indices of white matter degeneration into the diagnostic scheme for AD are that (1) practical tools and strategies for systematically characterizing white matter degeneration and quantifying changes over time

or responses to treatment remain limited, (2) the full spectrum of abnormalities including alterations in lipid composition has not been characterized, and (3) the mechanistic framework remains uncertain and under-studied. Another limitation is that neuroimaging approaches are not sufficiently refined to enable distinctions among the many causes of white matter degeneration. Finally, surrogate CSF or serum biomarkers of white matter degeneration have not been discovered. Fortunately, progress in the application of mass spectrometry and lipidomics (Han et al. 2002; Lam et al. 2014; Mendis et al. 2016; Tong et al. 2017) may help provide new insights into the nature and pathogenesis of white matter degeneration in AD.

4.2.8 Microvascular Degeneration

4.2.8.1 Role of Vascular Degeneration in Dementia

Progressive declines in cerebral blood flow, glucose metabolism, and oxygen utilization in AD have been recognized for decades and suggest that impairments in brain perfusion contribute to neurodegeneration (de la Torre and Mussivand 1993; de la Torre and Stefano 2000). However, the structural pathology that mediates deficits in cerebral blood flow and metabolism remains somewhat controversial. For example, in one postmortem study, vascular pathology was observed in over 80% of AD cases (Toledo et al. 2013), yet in other clinical and postmortem studies, dementia was linked to cases in which cerebrovascular disease overlapped with mild or moderate severity AD and not when it occurred in isolation (Nolan et al. 1998; Etiene et al. 1998). Correspondingly, although substantial losses in brain volume due to large or multiple small infarcts can lead to depression and cognitive impairment, they do not cause AD (Ballard et al. 2000). Perhaps the most compelling data concerning the interactive roles of cerebrovascular disease and AD was provided by the 14-year Gothenburg study in which 63% of the cases had dementia due to AD or mixed AD+vascular disease, another 23% had other forms of dementia, and only 14% had pure vascular dementia (Wallin et al. 2016b). Furthermore, the recent decline in AD incidence rates has been attributed to improved vascular care rather than recovery from AD (Scheltens et al. 2016), and supports the earlier hypothesis that cerebrovascular disease lowers the threshold for AD to become clinically manifested (Etiene et al. 1998).

4.2.8.2 Nature of Microvascular Disease in AD

Two types of vascular pathology are characteristically present in AD: Aβ-associated and Aβ-unassociated. Amyloid angiopathy affects cortical and leptomeningeal but not white matter vessels (Vinters et al. 1990; Joachim and Selkoe 1992). In the cortex, microvessels, including capillaries, contain Aβ deposits in their walls and in the

adjacent perivascular parenchyma (Vinters et al. 1996; Vinters 2015). The most clinically significant consequence of amyloid angiopathy is hemorrhage.

Non-Aβ vascular degeneration occurs in the cerebral cortex, white matter, and subcortical nuclei. The earliest descriptions of AD vasculopathy noted that the cortical microvessels, including capillaries, arterioles, and venules, exhibit thickened basement membranes and attrition of perivascular tissue (Fig. 4.4) (Scheibel et al. 1989). Pathophysiologically, non-Aβ vascular degeneration most frequently occurs in the settings of diabetes mellitus (Luchsinger 2012) and systemic arterial hypertension (Naderali et al. 2009; Middleton and Yaffe 2009). Blood vessels, particularly in white matter, become fibrotic with thickened walls and severely narrowed lumens, which together reduce vessel wall compliance, restrict brain perfusion, and impair responsiveness to metabolic demands (Farkas et al. 2000).

4.2.8.3 Consequences of Brain Microvascular Disease

Degeneration of vessel walls also causes them to weaken and become leaky, enabling circulating toxins and inflammatory mediators to enter the brain (Brun and Englund 1986; Englund 1998; Perlmutter and Chui 1990). Consequently, white matter tissue surrounding damaged, leaky vessels is vulnerable to injury and degeneration (de la Torre and Stefano 2000; Neltner et al. 2014; Kalaria et al. 2012; Chalmers et al. 2005; Jellinger 2002; Verny et al. 1991; Ferrer et al. 1990; Thal et al. 2003) with attendant ischemic atrophy, incomplete infarction, and leukoaraiosis (Brun and Englund 1986; Englund 1998). White matter vascular dysfunction and pathology are variably associated with dementia, but consistently correlated with slowness in mental processing, decline in executive function, and compromise of blood-brain barrier (BBB) integrity (Wallin et al. 2016a).

4.2.9 Blood-Brain Barrier Disruption in AD

The blood-brain barrier is critical for regulating brain exposures to substances in the peripheral circulation, including toxins. Metalloprotein-9 (MMP-9) regulates opening and activity of the BBB, while tissue inhibitor of metalloproteinase 1 (TIMP-1) counteracts this effect (Wallin et al. 2016a). Plasminogen activator inhibitor-1 (PAI-1), which is produced by endothelial cells, inhibits fibrinolysis as well as MMP activity (Wallin et al. 2016a). In AD and other dementias, white matter microvascular disease is associated with elevated CSF levels of MMP-9 (Wallin et al. 2016a), BBB dysfunction marked by increased permeability to albumin, and altered pro-inflammatory and pro-coagulation events that enhance microvascular occlusions and thereby promote ischemic injury (Grammas 2011).

In AD, BBB disruption could account for (1) neurotoxic injury leading to neurodegeneration (Mann 1985; Hoyer 1982), (2) dysregulation of the brain pool of Aβ

and its equilibrium status between cerebrospinal fluid and plasma (Johanson et al. 2018), and (3) neuroinflammation (Ott et al. 2018). Aβ homeostasis is regulated by influx of soluble Aβ across the BBB via interactions with RAGE and efflux via the low-density lipoprotein (LDL) receptor on brain endothelial cells. AD is associated with increased RAGE influx or decreased LDL receptor efflux, preventing Aβ clearance (Grammas 2011).

4.3 What Comes First?

As AD progresses from its pre-symptomatic stages to dementia, different aspects of disease emerge and evolve (Daviglus et al. 2010). Brain accumulations of Aβ due to reduced clearance (Zafari et al. 2015) and neuroinflammation increase during the pre-symptomatic period and peak early in the course of neurodegeneration (Serrano-Pozo et al. 2011). pTau accumulation begins later than Aβ, and the progressively increased levels associated with neurofibrillary tangle and dystrophic neurite pathologies correlate with cognitive decline, memory impairment, and hippocampal atrophy (Daviglus et al. 2010). However, the two abnormalities that correlate best with cognitive impairment and progressive dementia are hippocampal atrophy and impairment in glucose utilization. In addition, evidence suggests that, in contrast to senile plaque burden which does not correlate with dementia, Aβ-derived diffusible ligands (ADDLs) also increase in association with brain metabolic dysfunction and cognitive impairment through the late stages of AD (Viola and Klein 2015). Altogether, the data suggest that most of the bio-indices studied in relation to AD may be informative and carry diagnostic potential only during limited stages of disease. In contrast, brain metabolic dysfunction linked to deficits in glucose utilization reliably marks the course of progressive cognitive decline and neurodegeneration. ADDL accumulation may provide a supplementary index of neurotoxicity-mediated neurodegeneration in AD (Schuster and Funke 2016).

4.4 Brain Metabolic Dysfunction in AD

4.4.1 Impairments in Brain Glucose Utilization

The predictably consistent clinical, pathophysiological, and neuropathological abnormalities that characterize the progressive course of AD suggest the existence of a fundamental underlying process that drives neurodegeneration. In our reconceptualization of its etiopathic basis, it will be critical to link seemingly unrelated pathologies utilizing evidence-based approaches to determine how they are shared. Deficits in brain energy metabolism, particularly with respect to glucose utilization in AD, have been recognized for years, but more recent approaches such as PET imaging with (18)F-fluoro-deoxyglucose (FDG) have standardized its detection in

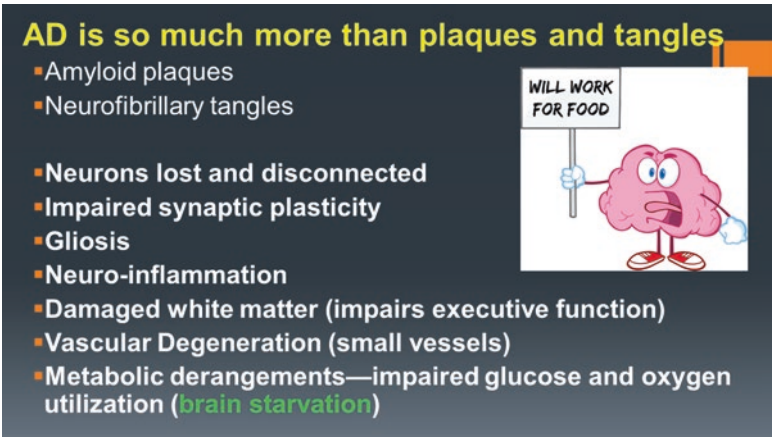

Fig. 4.5 The AD neuropathological spectrum includes an array of abnormalities linked to neurodegeneration and goes well beyond progressive accumulations of pTau and $A\beta_{1-42}$-associated pathologies. Most other major aspects of AD neurodegeneration stem from metabolic derangements linked to insulin deficiency and insulin resistance, which essentially produce states of brain starvation due to impaired glucose uptake and utilization

the early stages of neurodegeneration (Daulatzai 2012; Schaffer et al. 2015). Correspondingly, one of the most significant findings across multiple studies is that AD is associated with global reductions in brain glucose metabolism relative to normal healthy control brains (de Leon et al. 1983; Faulstich 1991; Waldron et al. 2015; Wurtman 2015). The importance of these observations is that glucose metabolism is critical for most brain functions, but particularly those related to cognition, behavior, and plasticity, which are most significantly impacted in AD. Metabolic derangements pertaining to glucose and oxygen utilization in the brain worsen with severity of AD. Since glucose and oxygen are the main fuels, deficits in their utilization effectively cause brain starvation (Fig. 4.5). A key mediator of brain metabolic dysfunction in AD is the progressive compromise of insulin's actions, starting in the earliest stages of disease (de la Monte 2012a, b, c; de la Monte et al. 2009a, 2011b).

4.4.2 Insulin and Insulin-Like Growth Factor (IGF) Functions in the Brain

Insulin and its cousin IGF-1 and their receptors are abundantly expressed in brain regions that are most vulnerable to AD neurodegeneration (de la Monte and Wands 2005; see Chap. 1 in this book). Insulin and IGF-1 signaling networks regulate neuronal survival, plasticity, growth, metabolism, and repair and mediate memory, cognition, motor functions, and behavior (de la Monte 2012b; de la Monte and Wands 2005). The findings that brain and cerebrospinal fluid (CSF) insulin levels are

reduced in the early and intermediate stages of AD (Lee et al. 2013) and that insulin administration improves working memory and cognition (Benedict et al. 2011; de la Monte 2013; Kidd 2008; Reger et al. 2008) highlight the etiopathic role of insulin-linked metabolic dysfunction in AD. In addition, counter-regulatory roles of insulin and Aβ have been suggested by a large number of experimental reports that are supported in part by human studies demonstrating co-occurrences of brain insulin and IGF-1 deficiencies with higher brain levels of Aβ and AGE levels (Lee et al. 2013; de la Monte and Tong 2014; Shuvaev et al. 2001) and enhancement of Aβ clearance with insulin administration (Reger et al. 2008). Since insulin and IGF-1 regulate neuronal and oligodendroglial cell functions including survival (de la Monte 2012b, de la Monte and Wands 2005), it is evident that deficiencies in these trophic factors or their receptor responsiveness would lead to pathology in both gray and white matter structures. Although there has been relatively little research linking impairments in insulin and IGF signaling to white matter and oligodendrocyte pathology in human cases of AD, there is ample evidence that both gray and white matter structures undergo atrophy and neurodegeneration with disease progression.

4.4.3 Lessons from Experimental Models of Brain Insulin Deficiency and Resistance

Experimental models have been instrumental in demonstrating that brain insulin deficiency and resistance impair learning and memory and mediate neurodegeneration (de la Monte et al. 2011a). The models included (1) silencing of brain insulin or IGF polypeptide or receptor expression, (2) intracerebral (i.c.) treatment with streptozotocin (STZ), and (3) diet-induced obesity-associated systemic insulin resistance. Selective silencing of brain insulin, IGF-1 or IGF-2 polypeptide, or receptor genes by i.c. administration of targeted short interfering RNA molecules caused significant atrophy of the hippocampus and temporal lobes with neuronal loss and impairments in spatial learning and memory (de la Monte et al. 2011a). Although STZ is a well-established pro-diabetes toxin, i.c. administration causes impairments in spatial learning and memory (Lester-Coll et al. 2006; Tong et al. 2016) and AD-type neurodegeneration characterized by temporal lobe and hippocampal atrophy with neuronal loss, gliosis, white matter degeneration, increased oxidative stress, and elevated levels of pTau, Aβ42, and ubiquitin (de la Monte et al. 2017b; Tong et al. 2016). Further analysis revealed that i.c. STZ disrupts brain insulin and IGF-1 signaling through their receptors and at multiple downstream points in the cascades, corresponding with increased activation of stress and pro-apoptosis mechanisms and inhibition of cell survival and metabolism pathways (de la Monte et al. 2017b, Tong et al. 2016). Therefore, the i.c. STZ model replicates most of the characteristic neuropathological findings in human AD, warranting the conclusion that AD is a brain metabolic disorder with diabetes-like abnormalities.

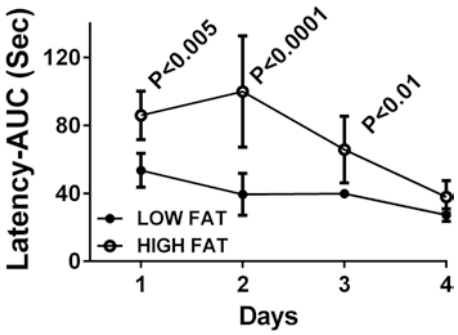

Fig. 4.6 Chronic high-fat diet-induced obesity with insulin resistance impairs spatial learning and memory in an experimental rat model. Adult male Long Evans rats were fed with low (LFD)- or high (HFD)-fat diets for 6 weeks, which resulted in steatohepatitis, peripheral insulin resistance, visceral obesity, and cognitive impairment (de la Monte et al. 2009c). The Morris water maze test was performed over a 4-day period with three trials per day. Performance on the first 2 days reflects learning and memory acquisition while the platform is visible, but entry points into the maze are varied, and performance on days 3 and 4 reflects memory consolidation when the maze platform is hidden, and entry points are varied. Area-under-the-curve (AUC) calculations for the latencies (seconds) required to locate and land on the platform were made for each of the three daily trials. Intergroup statistical comparisons were made with paired t-tests

The finding that experimental high-fat diet-induced obesity was associated with brain insulin resistance, cognitive impairment (Fig. 4.6), and increased brain levels of pTau, Aβ, and oxidative stress (Moroz et al. 2008; Lyn-Cook et al. 2009; Tong et al. 2010) was initially surprising. However, further investigations revealed that those models also had visceral obesity, steatohepatitis with hepatic insulin resistance, type 2 diabetes mellitus, and systemic inflammation (Lyn-Cook et al. 2009; Jiao et al. 2009). Two key findings were that steatohepatitis progressed in parallel with brain insulin resistance and was associated with increased liver and serum levels of ceramides due to dysregulated sphingolipid metabolism (Lyn-Cook et al. 2009). Since ceramides can be pro-inflammatory and inhibit insulin signaling through PI3K-Akt (Czubowicz and Strosznajder 2014; Zinda et al. 2001; de la Monte and Tong 2014), additional experiments determined whether ceramides, due to their lipid soluble nature, could cross the BBB and cause neurodegeneration. Those studies showed that ceramides can cross the BBB and exert neurotoxic/neurodegenerative effects manifested by increased levels of oxidative stress, Aβ, and pTau, pro-apoptosis pathway activation, and impairments in insulin signaling (Tong and de la Monte 2009). Therefore, these investigations provided a potential mechanism by which peripheral insulin resistance diseases could be linked to cognitive impairment, brain insulin resistance, and AD-type neurodegeneration.

4.5 Brain Diabetes and the Pathogenesis of AD

4.5.1 Primary Brain Insulin Deficiency and Resistance in AD: Type 3 Diabetes

To validate the roles of brain insulin and IGF deficiency and resistance, insulin, IGF, and corresponding receptor expression were measured in human postmortem brains that were diagnosed with different Braak stage severities of AD (de la Monte and Wands 2008; Steen et al. 2005; Rivera et al. 2005) (Fig. 4.7). Those investigations demonstrated significant and progressive disease-stage declines in insulin and IGF-1 signaling mechanisms, including through PI3K-Akt pathways that regulate energy metabolism, cell survival, and neuronal plasticity and inhibit cellular stress and apoptosis (de la Monte and Wands 2008; Steen et al. 2005; Rivera et al. 2005; Talbot et al. 2012). In addition, sustained deficits in brain insulin/IGF signaling were linked to reduced expression of choline acetyltransferase, which is needed to generate acetylcholine (de la Monte and Wands 2008, Steen et al. 2005, Rivera et al. 2005).

In accord with the experimental data showing causal roles of brain insulin and IGF-1 deficiency and resistance in the pathogenesis of AD-type neurodegeneration, it was important to determine whether related abnormalities occurred early during disease and could be detected in cerebrospinal fluid (CSF). The availability of paired clinical and postmortem CSF samples from confirmed cases of AD enabled us to

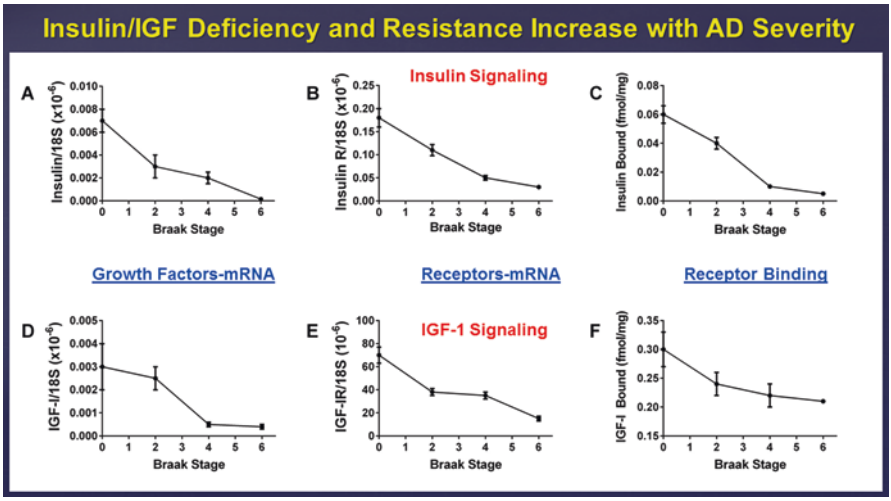

Fig. 4.7 Progressive declines in frontal lobe expression of (**a**) insulin and (**d**) IGF-1 polypeptide genes, (**b**) insulin and (**e**) IGF-1 receptor genes, and (**c**) insulin and (**f**) IGF-1 receptor binding with increasing Braak stage severity of AD. The mRNA levels were measured by qRT-PCR analysis, and ligand-receptor interactions were measured using competitive equilibrium binding assays. (Rivera et al. 2005)

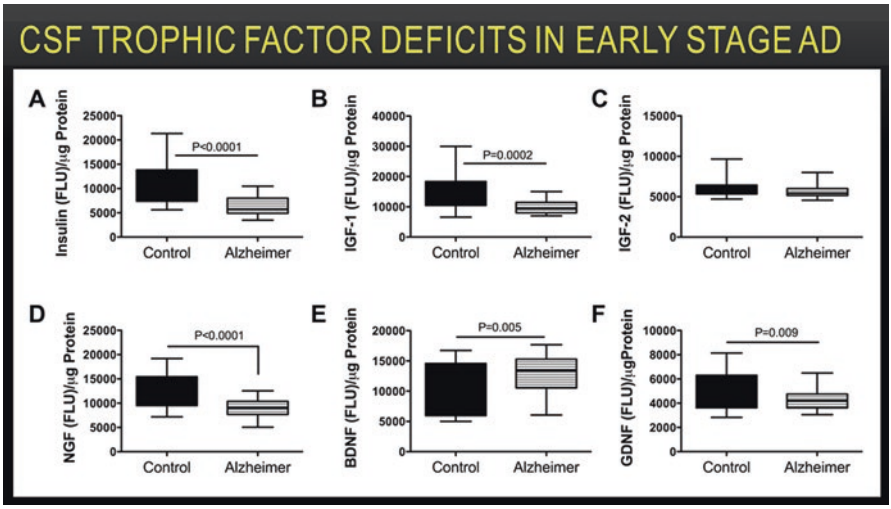

Fig. 4.8 Altered CSF levels of insulin, IGFs, and neurotrophins in early AD. Lumbar puncture CSF samples from controls ($N = 12$) and patients with early probable AD ($N = 16$) were used to measure (**a**) insulin, (**b**) IGF-1, (**c**) IGF-2, (**d**) nerve growth factor (NGF), (**e**) brain-derived neurotrophic factor (BDNF), and (**f**) glial-derived neurotrophic factor (GDNF) immunoreactivity by ELISA (Lee et al. 2013). Immunoreactivity is expressed in fluorescence light units (FLU) normalized to protein content. Data were analyzed with Student t-tests

demonstrate that insulin and IGF-1 levels in CSF are significantly decreased in the mild cognitive impairment stages of AD (Lee et al. 2013) (Fig. 4.8). In addition, CSF levels of nerve growth factor and glial-derived neurotrophic factor were also shown to be reduced in AD (Lee et al. 2013). Therefore, besides pTau and Aβ, indices of brain metabolic and neurotrophic dysfunction should be included in CSF screening panels to aid in earlier diagnosis of AD (Figs. 4.9 and 4.10).

4.5.2 Secondary Systemic Insulin Resistance Diseases and Cognitive Impairment

Epidemiological trend analyses showed that the rates of AD had increased sharply across all age groups, 50 years and above, over a period of several decades (de la Monte et al. 2009b). Importantly, those trends paralleled shifting rates of diabetes mellitus (de la Monte et al. 2009b), suggesting that the underlying cause factors might be related. Correspondingly, several human studies demonstrated that the risks of developing cognitive impairment and dementia were significantly elevated in overweight or obese people and diabetics relative to lean controls (Pedditizi et al. 2016, Alosco and Gunstad 2014, Luchsinger et al. 2007, Noble et al. 2012, Naderali et al. 2009; see Chap. 2 in this book). Moreover, inadequate medical control of type

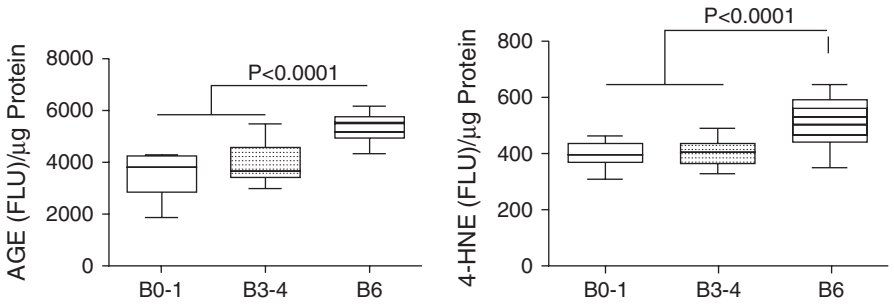

Fig. 4.9 Increased levels of cerebral oxidative stress with AD progression marked by Braak stage (B). Levels of (left) advanced glycation end product (AGE) and (right) 4-hydroxynonenal (4-HNE) lipid peroxidation markers were measured in postmortem frontal lobe homogenates by direct binding ELISA (Lee et al. 2013). B1–2 corresponds to control. B3–4 represents early- to intermediate-stage AD. B5–6 represents severe AD. Immunoreactivity was detected with horseradish peroxidase-conjugated secondary antibody and Amplex Red. Fluorescence light units (FLU) were measured (Ex 579 nm/Em 595 nm) in a SpectraMax M5, and results were normalized to protein content. Boxplots depict calculated group means (horizontal bars), 95% confidence limits (upper and lower borders of the boxes), and ranges (stems). Intergroup statistical comparisons were made by repeated measures one-way ANOVA with the post hoc Tukey test. Significant P-values are indicated over the bars

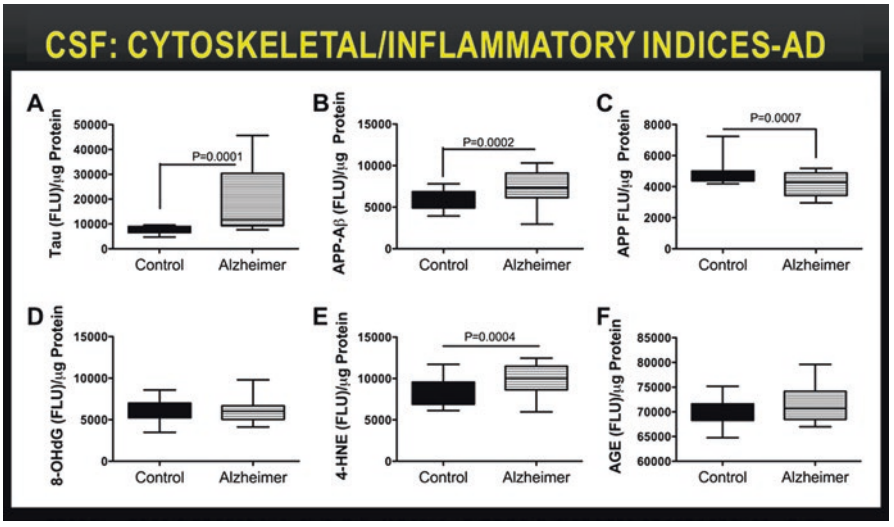

Fig. 4.10 Increased CSF indices of oxidative stress in early AD. Lumbar puncture CSF from controls ($N = 12$) and patients with early AD ($N = 16$) were used to measure (**a**) phosphorylated tau (Tau), (**b**) the Aβ fragment of amyloid precursor protein (APP-Aβ), (**c**) APP, (**d**) 8-hydroxy-2′-deoxyguanosine (8-OHdG), (**e**) 4-HNE, and (**f**) AGE by direct binding ELISA (Lee et al. 2013). Immunoreactivity was detected with horseradish peroxidase-conjugated secondary antibody and Amplex Red. Fluorescence light units (FLU) were measured (Ex 579 nm/Em 595 nm) in a SpectraMax M5, and results were normalized to protein content. Boxplots depict calculated group means (horizontal bars), 95% confidence limits (upper and lower borders of the boxes), and ranges (stems). Intergroup statistical comparisons were made with Student t-tests

1 and type 2 diabetes also increased risk for cognitive impairment (Drab 2009; Roriz-Filho et al. 2009; de la Monte 2012c, 2014; Fotuhi et al. 2012; Sridhar et al. 2015) and AD (Li et al. 2015). Still others linked various forms of peripheral insulin resistance (Kim and Feldman 2015; Cholerton et al. 2011) including prediabetes (Roriz-Filho et al. 2009), metabolic syndrome (Frisardi et al. 2010), and nonalcoholic fatty liver disease (de la Monte et al. 2009a; Nagoshi 2014) to cognitive decline. Finally, multivariate analysis of a late-onset AD international, multicenter cohort identified gene clusters associated with inflammation, diabetes, and obesity as pathologic processes linked to neurodegeneration (Meda et al. 2012). Altogether, evidence that peripheral insulin resistance diseases contribute to or cause cognitive impairment and neurodegeneration in humans is strong and corresponds well with data generated from experimental models.

4.5.3 Type 3 Versus Type 2 Diabetes

Because the human AD-associated abnormalities in insulin and IGF-1 signaling are highly reminiscent of the pathophysiological findings in both type 1 and type 2 diabetes mellitus, yet they selectively involve the brain, we coined the term "type 3 diabetes" (Table 4.1) (Steen et al. 2005; de la Monte and Wands 2008). Type 3 diabetes concisely conveys the concept that AD is a brain form of diabetes in which both ligand (insulin and IGF-1) deficiencies and receptor resistances coexist and mediate functional impairments in signaling pathways that mediate glucose

Table 4.1 Characteristic features of type 1, type 2 and type 3 diabetes

Target effects	Type 1 diabetes	Type 2 diabetes	Type 3 diabetes
Insulin ligand	Reduced	Increased	Reduced
Insulin receptor	Unaffected or Increased	Reduced Activation	Reduced activation and expression
Glucose utilization	Decreased	Decreased	Decreased
Primary tissue/organs	Pancreas (Brain)	Skeletal muscle, adipose tissue, blood vessels	Brain neurons and white matter
Secondary tissue/organs	Brain, retina, blood vessels, kidneys, kidneys, peripheral and autonomic nerves	Brain, retina, blood vessels, kidneys, peripheral and autonomic nerves	Brain satiety centers with increased proneness to obesity

Major consequences of diabetes include impaired glucose utilization, energy metabolism, alterations in the lipidome, inflammation, and oxidative stress. At the core of this complex dysregulated metabolic disease state is the inability of cells, tissues, and organs to utilize insulin signaling networks. In Type 1 diabetes, the primary problem stems from reduced insulin production. In Type 2 diabetes, insulin production is abundant, but the receptors have reduced responsiveness (insulin resistance). In Type 3 diabetes, the brain undergoes neurodegeneration due to combined effects of insulin deficiency and insulin resistance. The structures targeted by Types 1 and 2 diabetes are nearly identical. However, in Type 3 diabetes, the brain, including neurons, white matter, and micro-vessels, is the main target, but Type 3 diabetes is driven by most factors that lead to or result from Types 1 and 2 diabetes

utilization, metabolism, neuronal plasticity, cell survival, and a range of functions needed to maintain the integrity of the CNS. In "type 3 diabetes," we hypothesize that the brain is the main target of metabolic dysfunction since most people with typical AD have pathology limited to the brain and lack of clinical evidence of peripheral insulin resistance. On the other hand, it is impossible to ignore both human and experimental evidence that peripheral insulin resistance diseases in general are often associated with cognitive impairment and AD-type neurodegeneration. This phenomenon could account for the rapid increases in the incidence and prevalence rates of mild cognitive impairment (MCI) and AD. The good news is that the excess MCI/AD case burdens are potentially preventable and treatable using strategies like those employed to manage diabetes mellitus, metabolic syndrome, and nonalcoholic fatty liver disease.

Going forward, it is important to recognize that the severities of cognitive impairment and neurodegeneration which accompany peripheral insulin resistance diseases including type 2 diabetes tend to correspond to MCI or early AD, whereas in type 3 diabetes neurodegeneration progresses to end-stage dementia. However, another way to conceptualize the problem is to regard insulin resistance diseases as a single pathophysiological process that can afflict one or multiple organs and tissues in the same way that atherosclerosis can target one or more vessels and produce distinct manifestations of disease. Atherosclerotic damage to carotid vessels produces CNS deficits, whereas coronary atherosclerosis correlates with myocardial ischemic injury and infarction, and renal artery atherosclerosis leads to kidney disease, yet we regard the underlying pathologies as the same and largely mediated by hypertension and diabetes mellitus. Therefore, it would not be exceptional to suggest that insulin resistance diseases can preferentially attack different organ systems, either singularly or in combination, and with dominant or minor effects on function. Type 3 diabetes is the case in which insulin resistance disease dominantly attacks the brain and has mainly minor effects on other organs, whereas type 2 diabetes, metabolic syndrome, and nonalcoholic steatohepatitis represent peripheral insulin resistance diseases that have variable to modest adverse effects on CNS function.

4.6 Broadening the Therapeutic Options for AD

Nearly all pathologies in AD, including $A\beta_{1-42}$ deposits; phospho-tau-containing, paired helical filament-associated pathologies; and the broader array of disease processes linked to metabolic dysfunction, neuroinflammation, cellular stress, synaptic disconnection, aberrant proliferation of dystrophic neurites (reflecting loss of neuronal plasticity), cell death, white matter atrophy and degeneration, and microvascular disease, could be attributed to impairments in brain insulin and IGF signaling. Therefore, going forward, therapeutic interventions should include measures that increase insulin supply, insulin/IGF receptor responsiveness, downstream signaling through IRS, and appropriate modulation of target gene expression. Therefore, therapeutic interventions for AD should be multipronged to address all components of neurodegeneration at various stages of AD rather than focused only on reducing

burdens of $A\beta_{1–42}$ and pTau. Potential strategies for therapeutic targeting of brain metabolic dysfunction and associated or cofactor pathologies are summarized below.

4.6.1 Lifestyle Modifications

Although proven effective for restoring and preserving insulin sensitivity, implementing healthful lifestyle changes through diet and physical activity remains challenging because they are difficult to maintain. In addition, it has been difficult to assess the full benefits of caloric restriction and physical activity on long-term cognitive function. A third concern is that lifestyle measures may be ineffective once neurodegeneration advances to intermediate stages or if systemic insulin resistance diseases cannot be controlled. Most likely, lifestyle interventions will be coupled with medical interventions to more effectively halt progression of neurodegeneration.

4.6.2 Anti-inflammatory/Anti-oxidant Treatments

Neuroinflammation and cellular stress (oxidative, nitrosative, and endoplasmic reticulum) are associated with broad activation of cytokines and chemokines (de la Monte et al. 2017a; Ott et al. 2018) that are largely generated in microglia and astrocytes (Dickson et al. 1993; Mrak et al. 1995; Mrak 2009; Agostinho et al. 2010) or from systemic sources (de la Monte et al. 2017a; Ott et al. 2018). Furthermore, neuroinflammation and cellular stress are linked to major AD-associated neuropathological lesions, including $A\beta_{1–42}$ deposits and PHF-associated neurofibrillary tangles, dystrophic neurites, tau hyper-phosphorylation, cell death, and loss of synaptic terminals (Du Yan et al. 1997; Agostinho et al. 2010; de la Monte and Tong 2014). However, clinical trials have failed to demonstrate that anti-inflammatory and anti-oxidant agents alone can remediate cognitive impairment and neurodegeneration, suggesting that neuroinflammation has a cofactor rather than causal role in AD progression.

4.6.3 Insulins, Incretins, and Beyond

Insulin has positive effects on neurocognitive function in people with MCI or early-stage AD (de la Monte 2017). Mechanistically, insulin stimulates glucose utilization in the brain (Jauch-Chara et al. 2012; Reger et al. 2008; Stockhorst et al. 2004; Talbot et al. 2012). Nasal administration of long-acting or ultralong-acting insulins has been shown to benefit subsets of MCI or AD patients (de la Monte 2017). Nasal delivery of insulin penetrates the blood-brain barrier enabling CNS targeting while minimizing risk of hypoglycemia (de la Monte 2012b). Incretins, particularly long-acting synthetic analogues, are attractive alternatives to insulin because they

stimulate insulin secretion (Yamamoto et al. 2003; Freeman 2009; Irwin et al. 2010) and can be administered one or two times per week and stability of long-acting forms ensures predictable levels of insulin release (de la Monte 2017). Furthermore, using experimental models of AD, investigators have shown that incretins can clear a broad range of AD pathologies, including neuroinflammation, Aβ accumulations, and dysregulated lipid metabolism (Duffy and Holscher 2013; Holscher 2014; McClean and Holscher 2014). However, the insulinotropic effects of incretins can decline over time, possibly due to exhaustion or resistance of insulin-producing cells (Meier and Nauck 2010).

4.6.4 Insulin Sensitizers

Peroxisome proliferator activator receptors (PPARs) are nuclear hormone receptors that have both insulin-sensitizing and anti-inflammatory effects in response to agonist binding (Collino et al. 2008; Dunn et al. 2010; Kalinin et al. 2009). Delta is the most abundantly expressed PPAR isoform in the brain (de la Monte and Wands 2006), and its downregulation in AD brains (de la Monte and Wands 2006) has been implicated in the pathogenesis of neuroinflammation and oxidative stress. This concept is supported by the findings that experimental depletion of PPAR-delta increases neuroinflammation, gliosis, oxidative stress, Aβ deposition, and PHF-tau (Barroso et al. 2013), while PPAR-delta agonist treatments reduce neuroinflammation and Aβ deposition in AD models (Kalinin et al. 2009; de la Monte et al. 2017b). PPAR agonists offer potentially excellent opportunities for treating insulin resistance diseases in general, and brain diabetes specifically, because insulin resistance worsens as disease progresses. Insulin resistance begins at the cell surface receptor which is problematic because eventually insulin therapy will have reduced effectiveness. However, PPAR agonists target nuclear hormone receptors to broadly activate target genes. Moreover, PPAR agonists can activate both insulin- and IGF-1-regulated pathways and suppress neuroinflammation (de la Monte et al. 2017b). Although several studies using PPAR-γ agonists provided mixed results, future treatment strategies should consider the need to target PPAR-δ, which in the CNS is far more abundantly expressed than PPAR-γ (de la Monte and Wands 2005). Experimental data generated in AD models treated with PPAR-δ or hybrid PPAR-δ/γ agonists strongly support the conclusion that disease remediation can be achieved by proper targeting of PPAR subtypes in the brain (de la Monte et al. 2006, 2017b).

4.7 Conclusions

AD should be regarded as a form of brain metabolic dysfunction in which insulin resistance and deficiency develop primarily in the brain (type 3 diabetes). However, similar but generally less severe forms of AD-type neurodegeneration often accompany systemic insulin resistance diseases such as type 2 diabetes mellitus, metabolic

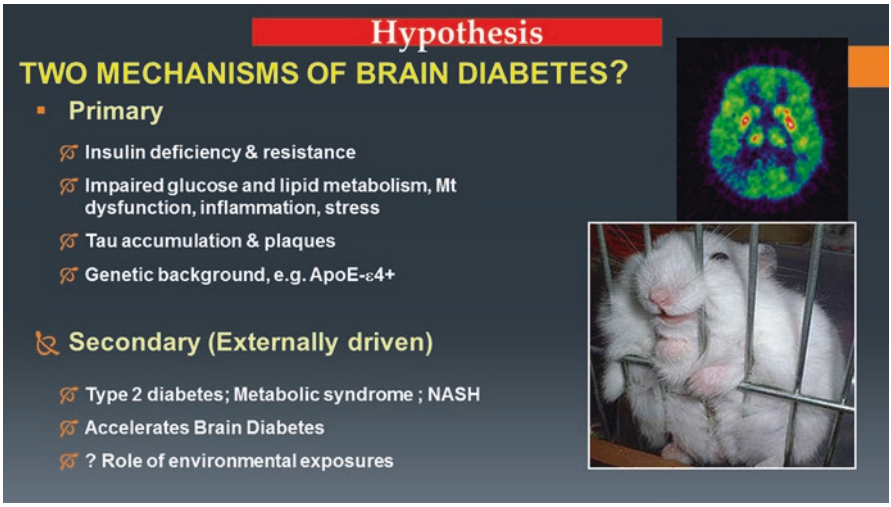

Fig. 4.11 Two proposed mechanisms of brain insulin resistance and cognitive impairment. In the primary disease model, brain insulin resistance is an early dominant and progressive metabolic abnormality that leads to end-stage AD dementia and usually occurs independent of clinically manifested systemic insulin resistance diseases. In the secondary (extrinsic factor) disease model, insulin resistance mainly targets peripheral organ systems and has modest impact on the brain compared with primary brain insulin resistance and results in mild cognitive impairment or early- to moderate-stage AD. However, secondary brain insulin resistance can exacerbate underlying primary brain insulin resistance and accelerate the course of AD. Growing evidence indicates systemic/secondary brain insulin resistance diseases are linked to obesogenic diets and sedentary lifestyles. In addition, experimental data highlight the role of chronic low-dose nitrosamine exposures as potential mediators of the array of insulin resistance diseases. (de la Monte et al. 2009c, 2011b; Tong et al. 2010; Yalcin et al. 2015; Lester-Coll et al. 2006)

syndrome, and nonalcoholic fatty liver disease. Given the recent striking increases in rates of AD, type 2 diabetes, metabolic syndrome, obesity, and nonalcoholic fatty liver disease and growing evidence that people with systemic insulin resistance diseases have significantly higher risks of developing cognitive impairment, it is likely that the underlying factors causing these diseases are either identical or closely related (Fig. 4.11). These concepts suggest that effective treatment and preventive strategies for insulin resistance diseases, including AD, could substantially overlap with one another, although tissue-/organ-specific targeting of pharmaceuticals may be required to optimize outcomes.

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Chapter 5
The Roles of Apolipoprotein E, Lipids, and Glucose in the Pathogenesis of Alzheimer's Disease

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Abstract Although the mechanisms by which Alzheimer's disease (AD) occurs remains unclear, it is widely accepted that both genetic and nongenetic components contribute to the pathogenesis of AD, especially the sporadic form of the disease. Nongenetic risk factors include diabetes and dyslipidemia, which are associated with impaired glucose and lipid metabolism, respectively. Apolipoprotein E (ApoE), one of the major lipid carriers in the brain, is the strongest genetic risk factor for late-onset AD. Several studies indicate that ApoE isoforms differentially affect not only lipid metabolism but also glucose metabolism or related pathways, suggesting that these risk factors contribute to the pathogenesis of AD through some common mechanisms. In this chapter, we discuss the roles of ApoE, lipids, and glucose in the pathogenesis of AD by considering their potential interactions.

Keywords Alzheimer's disease · Diabetes · Dyslipidemia · ApoE · Aβ · Tau · Glucose · Lipids · Cholesterol · Cognitive dysfunction · Neurodegeneration · Cerebrovascular damage · Insulin signaling · Neuroinflammation

Abbreviations

AD	Alzheimer's disease
AMPK	AMP-activated protein kinase
ApoE	Apolipoprotein E
APP	Amyloid precursor protein
Aβ	β-amyloid

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BACE1	β-site APP-cleaving enzyme 1
BBB	Blood-brain barrier
CAA	Cerebral amyloid angiopathy
F-FDG	[18F]-fluorodeoxyglucose
GSK3β	Glycogen synthase kinase-3β
HDL	High-density lipoprotein
IDE	Insulin-degrading enzymes
JNK	c-Jun N-terminal kinase
LDL	Low-density lipoprotein
LRP1	LDL receptor-related protein 1
MCI	Mild cognitive impairment
NFTs	Neurofibrillary tangles
PP2A	Protein phosphatase 2A

5.1 Introduction

In 2016, 47 million people worldwide had dementia, and the number is expected to increase by more than 130 million by 2050 (Prince et al. 2016). Alzheimer's disease (AD) is the most prevalent form of dementia. More than 99% of all AD patients have a sporadic form of the disease. The neuropathological hallmarks of the disease are the accumulation of senile plaques, composed of β-amyloid (Aβ); the formation of neurofibrillary tangles (NFTs), composed of hyperphosphorylated tau protein; and the neuronal loss and neuroinflammation that accompany those processes. Although it is widely believed that Aβ initiates the pathogenesis of AD, the failure of "anti-Aβ" therapies in clinical trials has highlighted the need to re-evaluate the pathogenesis of AD (Burns 2009).

Epidemiological studies have indicated that diabetic patients have an elevated risk of developing AD (Ott et al. 1999; Kopf and Frolich 2009; Maher and Schubert 2009; Matsuzaki et al. 2010). Additionally, diabetes in midlife is associated with mild cognitive impairment (MCI), and dysglycemia increases disease progression to dementia in subjects with MCI (Morris et al. 2014; Roberts et al. 2014b). Through vicious cycles, diabetes and AD may cooperate to cause neurodegeneration (Shinohara and Sato 2017).

Dyslipidemia, especially the impairment of cholesterol metabolism, appears to be associated with the risk of AD. Indeed, a high midlife serum cholesterol level is a risk factor for the incidence of AD or AD-related pathology, as confirmed by a meta-analysis (Anstey et al. 2008). Despite such strong clinical evidence, the mechanisms by which impairment of glucose metabolism and lipid metabolism increases the risk of AD remain to be clarified (Sato and Morishita 2015).

The apolipoprotein E (*APOE*) gene has been established as the strongest genetic risk factor for late-onset sporadic AD. One ε4 allele of *APOE* (*APOE4*) increases the risk of AD by three- to fourfold, while one ε2 allele of *APOE* (*APOE2*) decreases the risk of AD by half, compared with the common ε3 allele of *APOE* (*APOE3*).

ApoE forms lipoprotein particles and regulates the transport of lipids, especially cholesterol. While ApoE can directly modulate Aβ metabolism, increasing evidence has indicated that ApoE also affects cognitive function through Aβ-independent pathways by regulating neuronal function, lipid metabolism, and possibly glucose metabolism or related pathways (Bu 2009; Liu et al. 2013; Zhao et al. 2017, 2018).

In this chapter, we discuss how ApoE and an imbalance of glucose metabolism (especially diabetes) or lipid metabolism (especially cholesterol) modify AD pathogenesis and potentially interact with each other by reviewing evidence regarding their effects on Aβ metabolism, tau metabolism, cognitive function, neurodegeneration, and cerebrovascular damage.

5.2 Effects on Aβ Metabolism

Neuropathological studies have shown that, compared with *APOE3* carriers, *APOE4* carriers have greater Aβ accumulation (i.e., senile plaques), while *APOE2* carriers have less Aβ accumulation (Schmechel et al. 1993; Polvikoski et al. 1995). Notably, the *APOE4* allele is associated with increased levels of Aβ40, most of which accumulates in the brain as the characteristic amyloid deposits of cerebral amyloid angiopathy (CAA) (Beffert et al. 1999; Fryer et al. 2005; Shinohara et al. 2016b). However, the mechanism whereby ApoE specifically affects Aβ40 rather than Aβ42 is not well elucidated, although in vitro and animal studies have reported that ApoE may affect Aβ aggregation by directly binding to Aβ or regulate Aβ clearance through competing receptor-mediated Aβ clearance pathways (Tai et al. 2013; Verghese et al. 2013; Shinohara et al. 2017). Differences in the lipidation status or quantity of ApoE isoforms might determine their effects on Aβ metabolism (Riddell et al. 2008; Kim et al. 2011; Shinohara et al. 2013: Hu et al. 2015). Moreover, high levels of LDL cholesterol and low levels of high-density lipoprotein HDL cholesterol in plasma are associated with higher amyloid-PET indices likely independent of the *APOE* genotypes (Reed et al. 2014). This result may be partially explained by an in vitro experiment in which cholesterol loading increased Aβ secretion by cultured neurons (Marquer et al. 2014). Consistently, statins (HMG-CoA reductase inhibitors), which can lower the level of LDL cholesterol in the blood, also reduce Aβ accumulation in the brain by modulating Aβ production or clearance pathways (Shinohara et al. 2010, 2014; Sato et al. 2012).

It has been reported that diabetes/hyperglycemia affects Aβ accumulation in the brains of wild-type animals (Sparks et al. 1994) and animal models of AD that overexpress amyloid precursor protein (APP) with familial mutations (Refolo et al. 2000; Ho et al. 2004; Takeda et al. 2010). Hyperglycemia may increase Aβ production by increasing the synaptic release of Aβ (Macauley et al. 2015) or modulating APP processing and metabolism (Son et al. 2012) through β-secretase 1 (BACE1) (Guglielmotto et al. 2012), glycogen synthase kinase-3β (GSK3β) (Phiel et al. 2003; Sereno et al. 2009; Sofola et al. 2010; Jaworski et al. 2011), or insulin-degrading enzyme (IDE) (Vekrellis et al. 2000). Notably, in the Hisayama study, one of the

best-known community-based studies in Japan, insulin resistance in midlife was associated with an elevated incidence of neuritic plaques later in life. Moreover, the effect on neuritic plaques was further increased in *APOE4* carriers (Matsuzaki et al. 2010). Despite these results, clinical evidence showing that diabetes increases Aβ deposition in humans is very limited (Kalaria 2009; Tomita et al. 2013; Roberts et al. 2014a). Previous animal studies have demonstrated that diabetes increases CAA but not parenchymal Aβ deposits (Takeda et al. 2010), while CAA is classified into several subtypes and confounded by gender and *APOE4* genotype (Shinohara et al. 2016b). Thus, more detailed neuropathological analyses might be required to determine how diabetes and the impairment of glucose metabolism affect Aβ metabolism, which might provide clues to address whether ApoE-/lipid-mediated Aβ accumulation interacts with an imbalance of glucose metabolism.

5.3 Effects on Tau Metabolism

Normal tau promotes the assembly and stabilization of microtubules; however, hyperphosphorylated tau sequesters normal tau and disrupts microtubules, forming NFTs (Iqbal et al. 1994, 2009). In mice expressing mutant human tau, cellular cholesterol levels were elevated in neurons affected by tau pathology (Glockner and Ohm 2014). Although the Hisayama study did not observe positive associations between impaired peripheral cholesterol metabolism and NFT neuropathology (Matsuzaki et al. 2011), impaired cholesterol metabolism was shown to induce tau hyperphosphorylation in animal models (Michikawa 2006; Ohm and Meske 2006; Maccioni et al. 2010). Statins also suppressed tau hyperphosphorylation induced by excess cholesterol in the rodent brain (Lu et al. 2010) and were shown to reduce NFTs in a tau pathology model (Boimel et al. 2009). Moreover, inhibition of cholesterol metabolism by blocking acyl-coenzyme A:cholesterol acyltransferase 1 activity reduced the amount of mutant human tau in the neurons of triple transgenic mice, which overexpress mutant forms of human APP and tau in the presence of mutant mouse presenilin-1 (Shibuya et al. 2015). Although the number of clinical studies that report the effects of *APOE* genotypes on tau accumulation is limited (Verghese et al. 2011), a recent study showed that the ApoE4 isoform exacerbated tau-mediated neurodegeneration in a model of tauopathy (Shi et al. 2017), which appears to be consistent with a previous neuropathological study (Ohm et al. 1999). These studies demonstrate that the regulation and dysregulation of cholesterol metabolism and ApoE affect tau pathology in the brain, although these effects should be further clarified, especially in clinical cohorts.

Tau phosphorylation was increased in animal models of both type 1 (Clodfelder-Miller et al. 2006; Jolivalt et al. 2008;Ke et al. 2009; Qu et al. 2011; Morales-Corraliza et al. 2016) and type 2 diabetes (Kim et al. 2009; El Khoury et al. 2016; Guo et al. 2016), potentially through the dysregulation of c-Jun N-terminal kinase

(JNK), AMP-activated protein kinase (AMPK), and protein phosphatase 2A (PP2A) (Mairet-Coello et al. 2013; El Khoury et al. 2016). Consistently, tau phosphorylation at the sites implicated in AD pathogenesis is increased in the brains of diabetic patients (Liu et al. 2009). However, several neuropathological studies concluded that the number of NFTs in the brain at autopsy was not affected by the presence of diabetes (Arvanitakis et al. 2006; Kalaria 2009; Matsuzaki et al. 2010; Abner et al. 2016; Pruzin et al. 2017), and diabetes/hyperglycemia did not affect tau accumulation in human tau transgenic mice (Gratuze et al. 2016). These studies indicate that diabetes does not exacerbate NFTs at later stages of AD, although the possibility remains that diabetes may promote tau phosphorylation in the early stages of AD or during the aging processes. Thus, further studies would be required to address whether ApoE and imbalanced lipid or glucose metabolism affects tau metabolism in a similar way.

5.4 Effects on Cognitive Dysfunction

ApoE and cholesterol may affect age-related cognitive changes. *APOE4* worsens age-related cognitive decline, while *APOE2* protects against decline (Helkala et al. 1996; Hyman et al. 1996; Wilson et al. 2002). Notably, several studies have shown that these effects can be independent of AD neuropathology (Berlau et al. 2009; Kantarci et al. 2012; Shinohara et al. 2016a). Although cholesterol is a critical component of the brain and particularly facilitates synaptogenesis in neuronal membranes (Mauch et al. 2001), it remains unknown how cholesterol contributes to cognitive changes during aging. Cholesterol appears to be reduced in an age-dependent manner in the brain, suggesting that cognitive decline during aging is accompanied by brain cholesterol loss (Ledesma et al. 2012; van Vliet 2012). This may explain the adverse effects of statins on cognitive function in elderly people (Shinohara et al. 2014). However, conflicting evidence shows that the reduction of cholesterol levels in aged neurons can increase signaling potency through receptor clustering at lipid rafts and promote cell survival under stress conditions (Sodero et al. 2011; Ledesma et al. 2012). This may explain why the *APOE4* allele worsens age-related cognitive decline, which is associated with increased cholesterol levels, while *APOE2* protects against decline and is associated with reduced cholesterol levels in the brain (Shinohara et al. 2016a). Therefore, further studies are necessary to address the mechanism by which ApoE and cholesterol modify cognitive function during aging.

Cognitive dysfunction progresses more rapidly in diabetic patients than in non-diabetic people independently of AD status, (Weinstein et al. 2015; Redondo et al. 2016). Importantly, subjects with diabetes and substantial AD-related pathological changes exhibited lower cognitive function than subjects with the pathological changes alone (Abner et al. 2016). Moreover, individuals with a history of diabetes

who are carriers of familial AD mutations exhibit greater cognitive decline after the onset of dementia (Aguirre-Acevedo et al. 2016). Transient hyperglycemia and hypoglycemia also affect cognitive function. Holmes et al. elegantly showed that attention and fine motor skills changed on the basis of altered glucose levels in diabetic patients during hypoglycemia and hyperglycemia induced by an artificial insulin/glucose infusion system (Holmes et al. 1983). Although the use of antidiabetic treatments might reduce the risk of dementia (Ng et al. 2014; Heneka et al. 2015), their intensive application increases the incidence of hypoglycemia (Moore et al. 2013) and possibly cognitive dysfunction (Whitmer et al. 2009; Yaffe et al. 2013; Pilotto et al. 2014). These results indicate that diabetes and the impairment of glucose metabolism provoke cognitive dysfunction independent of AD neuropathology and that such cognitive dysfunction can be accelerated by AD neuropathology. Such effects might be similar to those regarding ApoE/cholesterol metabolism, at least in terms of potential independence of AD neuropathology. Further studies would be needed to address whether ApoE and imbalanced lipid or glucose metabolism affect cognitive dysfunction through their mechanistic interactions.

5.5 Effects on Brain Structures

Clinical studies have illustrated that diabetes is associated with reduced brain volume (Sato and Morishita 2014), including reduction in the volumes of the hippocampus (Kerti et al. 2013; Moran et al. 2013; Roberts et al. 2014b; Hirabayashi et al. 2016), gray matter (Garcia-Casares et al. 2014; Li et al. 2016), and white matter (Moran et al. 2013). In a 3-year follow-up study, an increased rate of brain atrophy was associated with an increased decline in cognitive performance despite a lack of progression of cerebrovascular lesions (van Elderen et al. 2010), suggesting a role of nonvascular factors in neurodegeneration in diabetic patients. Notably, brain glucose hypometabolism is associated with brain atrophy and cognitive dysfunction in elderly people, including AD patients, while hyperglycemia is associated with reduced brain volume even in young adults (Ossenkoppele et al. 2014; Weinstein et al. 2015).

APOE4 carriers also have reduced hippocampal or entorhinal volume from a young age, while *APOE2* carriers have greater volume in these regions (Shaw et al. 2007; Chang et al. 2016); however, another study reported no difference among *APOE* genotypes in middle age (Suri et al. 2013), suggesting that the effect of ApoE isoforms on brain structural changes independent of AD neuropathology has yet to be determined. Imbalance of lipid metabolism also appears to affect brain structure (Solomon et al. 2009; Hughes et al. 2013; Srinivasa et al. 2015). However, as the results in these areas are somewhat controversial, more evidence would be needed to address the potential interaction among ApoE isoforms, lipid metabolism, and glucose metabolism in brain structural changes.

5.6 Effects on Glucose Metabolism and Insulin Signaling in the Brain

In an AD cohort, whole-brain [18F]-fluorodeoxyglucose (FDG) uptake was lower in MCI patients with diabetes than in those without diabetes (Li et al. 2016). An AD-like FDG pattern can also appear in cognitively normal individuals with the *APOE4* genotype (Langbaum et al. 2010; Knopman et al. 2014). These results indicate that both diabetes and ApoE isoforms affect glucose metabolism in the brain.

The brain has an abundance of the glucose transporter GLUT3, whose glucose uptake is independent of insulin, while some GLUT4, an insulin-dependent glucose transporter, is also present. In addition to glucose uptake, insulin signaling in the brain plays also important roles in neuronal function and viability by regulating insulin signaling pathways, where the interaction between insulin and insulin receptors triggers phosphorylation of phosphatidylinositol 3-kinase (PI3K) and protein kinase B (AKT) and activates other downstream pathways (Sun et al. 1991; Sutherland et al. 1993; Cross et al. 1995; Karen et al. 2008). Importantly, levels of molecules related to insulin signaling pathways, such as PI3K and AKT, in the brain are decreased in diabetic patients (Liu et al. 2011). Moreover, the impairment of brain insulin signaling has been reported in AD patients (Talbot et al. 2012) and in animal models of AD with diabetes (Takeda et al. 2010; Sato et al. 2011; Morales-Corraliza et al. 2016; Sajan et al. 2016). The ApoE4 isoform also affects insulin signaling in the mouse brain and in cultured neurons, while the ApoE2 isoform protects against this process (Ong et al. 2014; Chan et al. 2015, 2016; Keeney et al. 2015). The effects of the ApoE4 isoform were recently shown to be mediated by direct interference with the insulin receptor (Zhao et al. 2017, 2018).

Taken together, these results suggest that the impairment of glucose metabolism and/or insulin signaling in the brain caused by diabetes and ApoE isoforms might be a key to understanding the mechanism of neurodegeneration in AD.

5.7 Effects on Cerebrovascular Damage

AD patients often have cerebrovascular damage due to age and age-related disorders (Richard and Pasquier 2012). Cerebrovascular damage by itself is associated with cognitive dysfunction (Iadecola et al. 2009; Dickstein et al. 2010; Richard and Pasquier 2012; Sato and Morishita 2013; Neltner et al. 2014) and brain structural changes (Barnes et al. 2013).

Diabetes causes altered vascular reactivity (Caballero et al. 1999; Pasquier et al. 2006), microangiopathy (Muris et al. 2012), cerebrovascular lesions, and infarcts (Tanizaki et al. 2000; Arvanitakis et al. 2006; Roberts et al. 2011). Consistently, cerebrovascular damage was observed more frequently in AD patients with diabetes than in those without diabetes (Kalaria 2009). Similar effects were observed in AD animal models with diabetes (Takeda et al. 2010).

Atherosclerosis, one such type of vascular lesion, is caused by the accumulation of LDL cholesterol (Adibhatla and Hatcher 2008). *APOE4* carriers have elevated plasma levels of LDL cholesterol, which is associated with elevated incidence of stroke (Saidi et al. 2007). Animal and cellular studies also demonstrated that ApoE3 induces the phosphorylation of the tight junction protein occludin in endothelial cells to preserve blood-brain barrier (BBB) integrity (Nishitsuji et al. 2011), while ApoE4 is associated with BBB dysfunction, likely through activation of pro-inflammatory pathways (Nishitsuji et al. 2011; Bell et al. 2012; Alata et al. 2015).

These results might indicate that the impairment of glucose and lipid metabolism as well as the presence of the ApoE4 isoform might provoke neurodegenerative processes during AD pathogenesis at least in part through cerebrovascular damage.

5.8 Summary and Perspective

In this chapter, we have discussed how ApoE and the impairment of glucose and lipid metabolism contribute to the pathogenesis of AD. The disruption of homeostasis in lipid and glucose metabolism might exacerbate neurodegeneration and/or cognitive dysfunction through the accumulation of Aβ and tau and/or impairments of neuronal integrity, insulin signaling, and vascular function, and the effects of ApoE isoforms may act through some of the same mechanisms in the pathogenesis of AD (Fig. 5.1). Recent large, long-term, randomized controlled trials suggest that a multidisciplinary intervention, including exercise and diet, could improve or maintain cognitive function in at-risk elderly people (Ngandu et al. 2015). Exercise and diet could alter glucose and lipid metabolism in the brain and periphery. A more integrated understanding of the interactions among lipids, glucose, and ApoE is necessary to elucidate the pathogenesis of AD and to develop next-generation therapeutics.

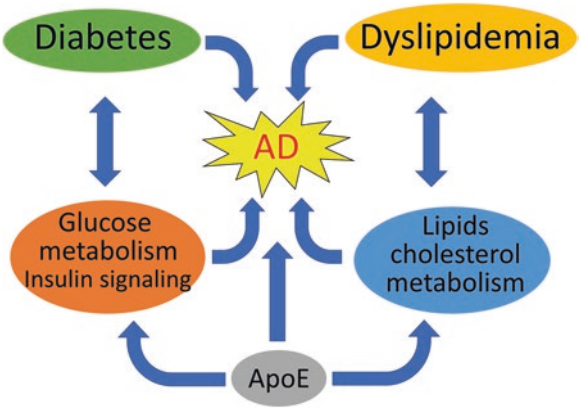

Fig. 5.1 Roles of ApoE, glucose metabolism, and lipid metabolism in the pathogenesis of AD. Impairments in glucose metabolism and lipid metabolism, associated with diabetes and dyslipidemia, respectively, contribute to AD pathogenesis by mechanisms that might be shared with ApoE

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Chapter 6
Molecular Connection Between Diabetes and Dementia

Yanxing Chen, Qian Yu, and Cheng-Xin Gong

Abstract Type 2 diabetes mellitus (T2DM) and Alzheimer's disease (AD) are both serious global health problems with high prevalence. These two diseases have some common features, including risk factors, age-associated disease onsets, insulin resistance, impaired glucose metabolism, deregulation of O-GlcNAcylation, chronic oxidative stress, and inflammation. Some of these features, such as insulin resistance, impaired glucose metabolism, and deregulation of O-GlcNAcylation, may serve as molecular links between T2DM and AD. Research on these molecular links is reviewed and discussed in this chapter. Understanding of these molecular links will help uncover the disease mechanisms and design therapeutic strategies to prevent and treat these two devastating diseases.

Keywords Alzheimer's disease · Brain insulin signaling · Brain glucose metabolism · Diabetes · O-GlcNAcylation · Dementia

6.1 Introduction

Both diabetes mellitus (DM) and dementia are serious global health problems with high prevalence, imposing increasing burden on the families, caregivers, and modern societies. The prevalence of diabetes has been increased markedly during the last decades and reaches nearly 10% of the adult population now (Control and Prevention 2014). There are three main types of DM: type 1 (T1DM), type 2

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(T2DM), and gestational diabetes. Approximately 90% of all diabetes cases are T2DM, which is caused and characterized by insulin resistance, a condition in which cells fail to respond to insulin adequately. Similar to dementia, the risk for developing T2DM increases with age, and T2DM also increases the risk for dementia. Thus, this chapter restricts the scope of diabetes to T2DM.

Dementia is a severe impairment or loss of intellectual capacity and personality integration that can be caused by a broad category of brain diseases. It is a long-term and often gradual decrease in the ability to think and remember, which is great enough to affect a person's daily functioning. About 10% of people develop dementia at some point in their lives (Loy et al. 2014). The most common type of dementia is Alzheimer's disease (AD), which makes up 50–70% of all dementia cases (Burns and Iliffe 2009). Thus, this chapter will focus mainly on the molecular connection between T2DM and AD.

AD is a devastating neurodegenerative disorder that ends up with dementia and death. The hallmark brain lesions of AD include the formation of extracellular amyloid plaques and intracellular neurofibrillary tangles (NFT) and synaptic/neuronal loss. The amyloid plaques are mainly composed of the aggregated amyloid β-peptides (Aβ) that are derived from Aβ precursor proteins (APP) through its cleavage by β-secretase and γ-secretase (Chow et al. 2010). NFTs consist of abnormally hyperphosphorylated tau proteins aggregated into paired helical filaments and straight filaments (Grundke-Iqbal et al. 1986). It has been widely recognized that the accumulation and aggregation of both Aβ and hyperphosphorylated tau are involved mechanistically in the pathogenesis and development of AD (Iqbal et al. 2016; Selkoe and Hardy 2016).

A key and early change of AD is a decrease in brain glucose uptake and metabolism, which worsens with the progression of the disease, suggesting its active role in the disease mechanism. This brain glucose metabolic impairment is recently found to be associated with deficient brain insulin activity or brain insulin resistance (Liu et al. 2011). Thus, the insulin resistance and impaired glucose metabolism appear to be the common feature of T2DM and AD, despite they occur primarily in the periphery in the former case and in the brain in the latter case. In addition, O-GlcNAcylation, a common dynamic posttranslational modification of nucleocytoplasmic and mitochondrial proteins by O-linked β-*N*-acetylglucosamine (O-GlcNAc), is a known sensor of intracellular glucose metabolism (Hart et al. 2007). The possible involvement of O-GlcNAcylation in both T2DM and AD was found (Lefebvre et al. 2010; Liu et al. 2009b). Therefore, deficient insulin signaling, impaired glucose metabolism, and deregulated O-GlcNAcylation may become the molecular links between T2DM and AD. These common links may help explain why these two disorders are the risk to each other. In this chapter, we discuss these molecular links, which will help us understand the molecular mechanisms and develop the disease-modifying treatment for these two diseases.

6.2 Common Features Between T2DM and AD

Although T2DM is primarily a peripheral metabolic syndrome and AD is a brain disorder, both diseases have several common features. They are both of very high prevalence, and both share several common risk factors, of which aging is the most important risk factor. The prevalence of both diseases increases remarkably with age, though T2DM usually starts at middle age, whereas sporadic AD usually starts after 60 years old. Other common risk factors include diet, overweight and obesity, chronic stress, and lack of physical activity (Steyn et al. 2004; Daviglus et al. 2011).

Epidemiological studies have indicated clear association between T2DM and AD. Longitudinal studies have shown that T2DM increases the risk of developing dementia, particularly AD by 1.3- to 2.3-fold (Ott et al. 1996, 1999; Leibson et al. 1997; Peila et al. 2002; Arvanitakis et al. 2004; Luchsinger et al. 2001; Okereke et al. 2008; Baumgart et al. 2015). Diabetic patients with positive apolipoprotein E (*APOE*) ε4 allele, the known risk factor for AD, had a 5.5-fold risk for AD compared to those with neither risk factor (Peila et al. 2002). A recent meta-analysis of large GWAS data identified eight common genetic loci for both T2DM and AD (Wang et al. 2017a, b), which provide novel insight into the molecular connection between T2DM and AD.

The key feature of T2DM is insulin resistance and impaired glucose metabolism in the periphery. This feature is also present in the brain in AD. Actually, the impairment of brain glucose uptake and metabolism has been established for decades and occurs much earlier than the onset of AD symptoms (Hoyer 2000; Mosconi et al. 2008). Because this impairment precedes the AD pathology and symptoms and worsens with the progression of the disease, it is likely that the brain glucose metabolism impairment may lead to or mechanistically involves in AD, rather than to be a consequence of the disease. Recent studies suggest that similar insulin resistance may also occur in the brains of individuals with T2DM (Liu et al. 2011). These findings provide some mechanistic insight how T2DM increases the risk for AD. In consistent to this, animal models of T2DM show AD-like brain pathologies (Li et al. 2007; Jung et al. 2013; Kim et al. 2009). Induction of T2D-like metabolic changes with high-fat diet also exacerbates AD pathologies (Ho et al. 2004).

Another common feature of T2DM and AD is their chronic and progressive nature and the involvement of chronic oxidative stress and inflammation in the disease progression (De Felice and Ferreira 2014). Unfortunately, neither disease is curable at present. Understanding the common features of these two devastating diseases will help reveal their molecular connection and search for the effective therapies for both conditions.

6.3 Brain Insulin Signaling

6.3.1 The Insulin Signaling Pathway

Insulin is the most important hormone for the regulation of glucose homeostasis. It stimulates glucose uptake in the liver, muscle, and fat and inhibits hepatic glucose production. It also promotes the synthesis and storage of carbohydrates, lipids, and proteins while inhibiting their degradation (Saltiel and Kahn 2001). In addition to its role in metabolism, insulin also regulates cell growth, cell differentiation, and gene expression (Potter et al. 2001; Han et al. 2015).

Insulin executes its function by binding to insulin receptor (IR) that in turn activates the insulin signaling transduction pathway (Fig. 6.1). IR belongs to a subfamily of receptor tyrosine kinases (Saltiel and Kahn 2001). Binding of insulin to IR leads to autophosphorylation of the receptor at tyrosine residues and induces a conformational change of the receptor that further increases its activity. The activated IR then recruits and phosphorylates the intracellular substrates, such as insulin receptor substrate (IRS) proteins and Cb1, which in turn promote the recruitment and activation of the proteins containing SH2 (Src-homology-2) domains, including phosphatidylinositol 3-kinase (PI3K) and the growth factor receptor-bound protein 2 (Grb2). The downstream signaling pathways are diverse. The two main pathways mediated by AKT/GSK and Ras/MEK are the best characterized. The PI3K/AKT pathway is the major pathway that mediates the action of insulin on glucose metabolism (Lochhead et al. 2001; Fisher and White 2004). The Ras/MEK pathway has no effects on the metabolic actions of insulin (Lazar et al. 1995), but it is important in insulin-mediated regulation of cell growth (Boulton et al. 1991). Recent studies indicate that the activation of these pathways is also involved in the biological processes in the brain and mediates the neuroprotective and neurotrophic actions of insulin (Nakamura et al. 2001; Schmidt et al. 2003; Haas et al. 2016; Hölscher 2014).

6.3.2 Recognition of Insulin's Roles in the Brain

The brain was previously considered an insulin-insensitive organ. The observation that intracisternally injected insulin induced a significant drop of glucose level both in the CSF and blood of dogs (Chowers et al. 1961) led scientists to assume that insulin might act in the brain. The presence of insulin in the brain was later verified by Havrankova et al. (1978), who reported 10- to 100-time higher concentration of insulin in the brain than in the peripheral. The existence of insulin in the brain was also reported in other studies, though with controversies concerning the exact concentration (Plata-Salamán 1991).

It is now well recognized that insulin does act in the brain in addition to the periphery. The majority of insulin in the brain appears to come from the periphery. Insulin can cross the blood-brain barrier (BBB) by a saturable, receptor-mediated

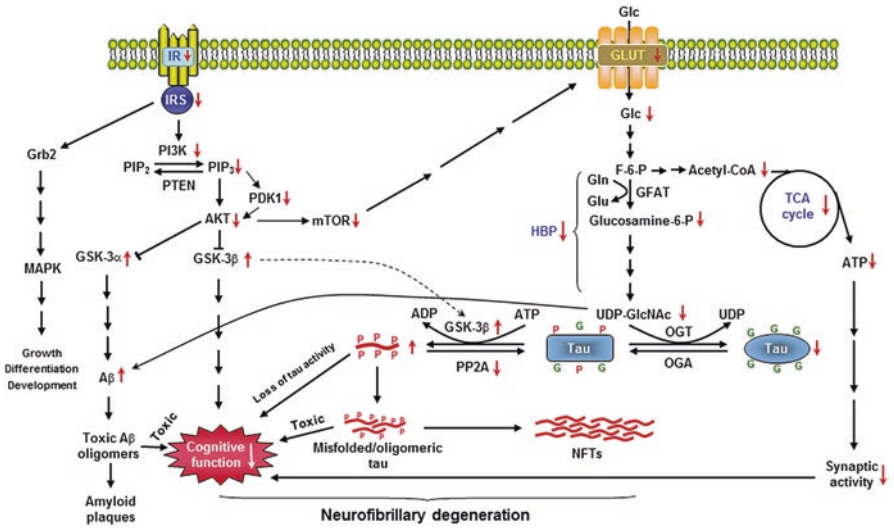

Fig. 6.1 The insulin signaling pathway and possible mechanisms through which deficient brain insulin signaling contributes to AD. The insulin signaling pathway starts from the binding of insulin to the insulin receptor (IR) and ends with various effectors mainly through regulating the activities of GSK-3 and MAPK (left half). This diagram demonstrates the possible pathways through which the deficient brain insulin signaling can promote Alzheimer hallmark pathologies and cognitive impairment. The vertical red arrows indicate the changes resulted from brain insulin resistance, as seen in AD. The right half of the diagram shows glucose metabolism to form UDP-GlcNAc through the hexosamine biosynthetic pathway (HBP). UDP-GlcNAc is a potent activator of OGT activity, which catalyzes protein O-GlcNAcylation. As a result of decreased intracellular UDP-GlcNAc level, downregulation of tau O-GlcNAcylation can promote its hyperphosphorylation, and the formation of NFT and of APP O-GlcNAcylation can promote its amyloidogenic processing to form Aβ and amyloid plaques. *Aβ* amyloid β-peptide, *ADP* adenosine diphosphate, *AKT* protein kinase B, *ATP* adenosine triphosphate, *F-6-P* fructose-6-phosphate, *Glc* glucose, *GlcNAc* β-N-acetylglucosamine, *Gln* glutamine, *Glu* glutamate, *GLUT* glucose transporter, *Grb2* Growth factor receptor-bound protein 2, *GSK-3* glycogen synthase kinase-3, *IR* insulin receptor, *IRS* insulin receptor substrate, *MAPK* Mitogen-activated protein kinases, *mTOR* mammalian target of rapamycin, *NFTs* neurofibrillary tangles, *OGA* O-GlcNAcase, *OGT* O-GlcNAc transferase, *PDK1* phosphoinositide-dependent kinase 1, *PI3K* phosphoinositide 3-kinase, *PIP2* phosphatidylinositol (3,4)-bisphosphate, *PIP3* phosphatidylinositol (3,4,5)-trisphosphate, *PP2A* protein phosphatase 2A, *PTEN* phosphatase and tensin homolog, *TCA* tricarboxylic acid cycle, *UDP* uridine diphosphate. (Reproduced from Chen et al. 2014a with permission)

transport mechanism (Banks et al. 1997; Duffy and Pardridge 1987), which takes place at euglycemic levels (Banks et al. 1997). The specific receptors for insulin in the microvessels of the brain are similar to IR in the peripheral tissue (Pardridge et al. 1985; Frank and Pardridge 1981).The permeability of insulin varies among different brain regions, with highest in the pons-medulla and hypothalamus but none in the midbrain or occipital cortex (Banks and Kastin 1998). In addition, insulin can also be synthesized inside of the brain. The expression of preproinsulin I and II and insulin mRNA has been identified in animal brains (Devaskar et al. 1993, 1994; Young 1986) as well as cultured neurons (Singh et al. 1997). Inhibition of

protein synthesis significantly decreased the number of insulin-immunoreactive neurons, suggesting the synthesis of insulin in neurons (Clarke et al. 1986). The synthesis of insulin may be confined to a subset of neurons like the pyramidal neurons in the hippocampus, prefrontal cortex, entorhinal cortex, and olfactory bulb, but not by glial cells (Clarke et al. 1986).

The role of insulin in the brain was further confirmed by the identification of IR in the brain. The distribution density of IR in the brain varies among different brain regions by differences of five to ten times. The highest IR density occurs in regions of olfactory bulb, cerebral cortex, hippocampus, hypothalamus, and cerebellum (Hill et al. 1986; Werther et al. 1987). The distribution of IR is not related to either vascularity or cell density. Abundant IRs are found in regions that contain dendritic fields receiving rich synaptic input (Werther et al. 1987). In addition, IRS is found to be co-expressed with IR in neurons of the hippocampus and olfactory bulb (Baskin et al. 1994). Other downstream members of the insulin signaling pathway, such as PI3K, AKT, and GSK-3, also reveal a similar expression pattern to that of IR in the brain (Hörsch and Kahn 1999; Moss et al. 1990; Leroy and Brion 1999). All these evidences suggest an active insulin signaling transduction in the brain regions closely related to synaptic function and cognition.

6.3.3 Functions of Insulin in the Brain

One of the first recognized functions of insulin in the brain is its role in the regulation of food intake and body weight control (Brief and Davis 1984; Foster et al. 1991; Honda et al. 2007). Insulin affects the neuronal activity of the hypothalamus that is involved in food intake and weight regulation. Hypothalamic insulin signaling is required for inhibition of peripheral glucose production (Obici et al. 2002b). Intracerebroventricular infusion of insulin induces a significant decrease in food intake and body weight in various species of animals (Brief and Davis 1984; Foster et al. 1991; Honda et al. 2007). Blocking or decreasing insulin activity with insulin antibodies, IR gene disruption, or decreased IR expression leads to elevation of body weight and food intake (McGowan et al. 1992; Obici et al. 2002a; Brüning et al. 2000).

A close relationship between insulin and brain glucose metabolism has been observed in human studies. Greater insulin resistance is associated with lower cerebral glucose metabolic rate in brain regions related to learning and memory (Baker et al. 2011). Inhibiting insulin signaling leads to reduced hippocampal energy metabolism during cognitive activity (Emmanuel et al. 2013). Insulin may directly regulate neuronal energy substrate uptake as it occurs in the periphery. Intracerebroventricular infusion of insulin increases the concentration of phosphocreatine (PCr) in the hippocampus (Henneberg and Hoyer 1994). The brain relies completely on glucose for energy, which cannot be synthesized or stored in neurons. Glucose is transported across the BBB via glucose transporter1 (GLUT1), which is highly expressed in the endothelial cells of the BBB (Schubert 2005). Then, the

major neuronal GLUT, GLUT3, mediates glucose uptake from extracellular space into neurons (Dwyer et al. 2002). Because GLUT1 and GLUT3 are insulin-insensitive, it was previously thought that insulin's effects on cognition could not be due to its regulation on glucose metabolism. However, other studies have shown that insulin can regulate glucose uptake by these transporters via influencing their surface expression (Pankratz et al. 2009; Ferreira et al. 2005). Furthermore, the insulin-sensitive GLUT4 has been found in brain regions involved in memory and cognition, such as the hippocampus and temporal cortex (Watson and Craft 2004). Intracerebroventricular injection of insulin stimulates the translocation of GLUT4 to the hippocampal plasma membrane that mirrors the increases in glucose uptake during hippocampal-dependent tasks (Grillo et al. 2009), suggesting that insulin might also influence memory in part through GLUT4-mediated glucose uptake.

Brain insulin is also involved in the central regulation of reproduction (Arias et al. 1992; Dong et al. 1991). Insulin stimulates the secretion of luteinizing hormone-releasing hormone (LHRH) from the hypothalamus in the brain (Arias et al. 1992). Insulin deficiency leads to decreased release of gonadotropin-releasing hormone (GnRH) and the responsiveness of pituitary LH-releasing cells to GnRH (Dong et al. 1991). Insulin is recognized as a neurotrophic factor because it plays a role in neuronal proliferation (Heni et al. 2011), differentiation (Wozniak et al. 1993), and neurite growth (Wozniak et al. 1993; Recio-Pinto and Ishii 1984). Moreover, insulin can protect neurons from apoptosis and against various insults like oxidative stress (Picone et al. 2011; De Felice et al. 2009). Insulin is capable of protecting neurons from death occurring either by necrosis or apoptosis, which is mainly mediated through the PI3K pathway (Ryu et al. 1999). Prolonged reduction of insulin level can result in neuronal loss and cognitive impairment (Li et al. 2002).

The more studied function of insulin in the brain may be its roles in neural plasticity and cognition. Insulin has been reported to be involved in cortical and hippocampal synaptic plasticity with the modulation of glutaminergic and GABAergic transmission, thus affecting memory and learning. The conversion of silent synapses into functional ones is dependent on the delivery of AMPAR to the synapse, which is of major importance in activity-dependent, developmental plasticity (Plitzko et al. 2001). Chronic addition of insulin has been shown to accelerate this process (Plitzko et al. 2001). In the mature brain, insulin decreases the number of AMPA receptor in the plasma membrane through accelerating its endocytosis, which results in LTD of AMPA receptor-mediated synaptic transmission in the hippocampal CA1 neurons (Man et al. 2000). Insulin can also increase the tyrosine phosphorylation of the NR2A and NR2B subunits of NMDA receptors (Christie et al. 1999) and potentiate hippocampal NMDA receptor activity (Chen and Leonard 1996). Apart from the phosphorylation regulation of NMDAR, insulin also promotes the delivery of NMDAR to the cell surface by exocytosis (Skeberdis et al. 2001), facilitating excitatory synaptic plasticity, including LTP. In addition, GABAergic neurotransmission plays a role in insulin-associated learning and memory. Insulin increases the expression and translocation of functional GABA receptors to the postsynaptic plasma membrane, thereby increasing the amplitudes of miniature inhibitory postsynaptic currents mediated by the GABA receptor (Wan

et al. 1997). Furthermore, insulin influences cognitive function by modulating the production and uptake of other neurotransmitters, such as acetylcholine (Kopf and Baratti 1999) and norepinephrine (Figlewicz et al. 1993).

Intracerebroventricular administration of insulin directly into the central nervous system improves memory in animals in a dose-dependent manner (Park et al. 2000; Haj-Ali et al. 2009). Intranasal administration of insulin, which bypasses the BBB and delivers insulin into the brain directly (Born et al. 2002; Dhuria et al. 2010), also improves cognitive function of rodents (Haas et al. 2016). Clinical trials employing intranasal delivery have shown beneficial effects of insulin on memory in both healthy adults and AD patients (Claxton et al. 2015; Benedict et al. 2004; Reger et al. 2006, 2008; Craft et al. 2012). This approach has been reported to increase the resting regional cerebral blood flow (rCBF) in the insular cortex and the putamen (Craft et al. 2012) and enhance brain energy in healthy men (Jauch-Chara et al. 2012). Intranasal administration of insulin at various doses improves declarative memory and attention in adults with MCI and AD (Reger et al. 2008; Craft et al. 2012). Patients receiving long-acting insulin detemir have better verbal working memory and visuospatial memory (Claxton et al. 2015). Interestingly, the beneficial effects of insulin appear to differ according to the apolipoprotein E (*APOE*) genotype, a genetic risk factor for sporadic AD. An earlier study showed improved declarative memory with intranasal insulin treatment only in APOE-ε4-negative MCI or AD patients (Reger et al. 2006). However, a recent study revealed that only *APOE*-ε4-positive MCI or mild to moderate AD patients exhibit improved verbal memory with intranasal insulin detemir (Claxton et al. 2015). Therefore, the effect of *APOE4* genotype on the therapeutic outcome of intranasal insulin remains elusive.

The molecular mechanisms that underlie the effects of insulin on cognition are not well understood. Brain regions that are responsible for the formation and consolidation of memory, such as the hippocampus and cerebral cortex, have abundant expression of IR and downstream effectors, suggesting the potential role of insulin signaling in memory and cognition. Upregulation of IR protein levels and enhanced IR sensitivity in hippocampal synaptic membrane are found in animals after being trained with water maze (Zhao et al. 1999; Dou et al. 2005). Changes in the downstream molecules, such as upregulation of IRS-1 and Akt in the synaptic membrane, accumulation of Shc and Grb-2 proteins in hippocampal synaptic membrane, and activation of MAPK, are also observed after long-term memory formation (Dou et al. 2005). These studies suggest that insulin signaling pathway is actively involved in learning and memory, the action of which might be mediated through the regulation of glucose metabolism, energy utilization, synaptic transmission, and/or plasticity.

Peripheral insulin may also affect brain functions indirectly. Intraperitoneal injection of insulin is reported to impair retention performance in a time- and dose-dependent manner (Kopf et al. 1998; Kopf and Baratti 1996). These effects

can be prevented by simultaneous administration of glucose (Kopf et al. 1998), suggesting that the memory impairment induced by peripheral insulin may be due to decreased brain glucose availability subsequent to hypoglycemia. This is consistent to other studies showing that intravenous insulin infusion using hyperinsulinemic-euglycemic clamp method could improve memory performance and attention in humans (Kern et al. 2001; Craft et al. 2003).

6.4 Deregulation of Brain Insulin Signaling and Its Role in AD

6.4.1 Brain Insulin Deficiency in AD

Because of the increased risk for AD in T2DM patients, possible contribution of insulin resistance to AD pathologies has been explored. Hyperinsulinemia and hyperglycemia caused by peripheral insulin resistance are associated with AD-related pathological changes (Matsuzaki et al. 2010; Baker et al. 2011). Clinical studies have shown that the peripheral insulin resistance is associated with poorer performance in intellectual functioning, verbal memory and psychomotor efficiency (Yau et al. 2010), lower hippocampal volume (Rasgon et al. 2011), higher amyloid deposition in frontal and temporal areas of the brain (Willette et al. 2015), and reduced cerebral glucose metabolism in the frontal, parietotemporal, and cingulate regions (Baker et al. 2011).

Insulin resistance is also found in the brains of AD cases and is proposed to contribute to the pathogenesis of the disease. Deregulation of insulin signaling in AD brain is characterized by the reduced amount of insulin (Moloney et al. 2010), reduced levels of insulin receptor binding (Rivera et al. 2005), and decreased responsiveness of the downstream effectors to the activation of insulin receptor (Talbot et al. 2012) in the brain. Because of this reason, de la Monte names AD as type 3 diabetes (de la Monte and Wands 2008). We also found decreased levels and activities of several components of the insulin signaling in AD brain (Liu et al. 2011). The serine phosphorylation of IRS-1, a signature of insulin resistance, is increased progressively with the severity of AD in the hippocampus (Talbot et al. 2012). Unlike in control brains the distribution of IR throughout the neuronal cell soma and dendrites, IR is concentrated intracellularly in AD brain (Moloney et al. 2010). Research evidence has shown that brain insulin resistance may promote AD through increased accumulation and reduced clearance of Aβ, increased hyperphosphorylation of tau, and reduction in glucose metabolism and energy utilization (Fig. 6.1).

6.4.2 Brain Insulin and Aβ

One of the hallmark brain lesions of AD is the presence of extracellular amyloid (senile) plaques that consist predominantly of amyloid-β (Aβ) peptides. The amyloid cascade hypothesis of AD suggests that the accumulation and oligomerization/aggregation of Aβ are the leading cause and central to the pathogenesis of AD (Selkoe and Hardy 2016). According to this hypothesis, any factors that lead to overproduction, decreased clearance, or oligomerization of Aβ would promote AD.

It has been reported that insulin promotes APP metabolism and increases the secretion of soluble APP in a PI3K-dependent manner (Solano et al. 2000). Insulin also reduces intraneuronal Aβ by stimulating APP/Aβ trafficking from the trans-Golgi network to the plasma membrane (Gasparini et al. 2001). Insulin can inhibit Aβ oligomer formation, abolish Aβ oligomer-induced oxidative stress and synaptic spine loss by blocking its neuronal binding (De Felice et al. 2009), and ameliorate Aβ-induced suppression of LTP (Lee et al. 2009). Insulin may modulate extracellular degradation of Aβ via insulin-degrading enzyme (IDE) (Kurochkin and Goto 1994; Qiu et al. 1998), a metalloprotease that also catabolizes insulin. The Aβ degrading activity, the mRNA, and the protein level of IDE are all decreased in AD brain, and these decreases correlate negatively with Aβ level (Pérez et al. 2000; Cook et al. 2003; Zhao et al. 2007). The reduced IDE level correlates with deficient brain insulin signaling found in AD patients and in AD transgenic mice (Zhao et al. 2004). It has been shown that insulin can increase the expression of IDE via the activation of PI3K. Therefore, deregulation of brain insulin signaling may lead to reduced IDE expression and thus reduced Aβ degradation, which contributes to the accumulation of Aβ.

On the other hand, Aβ oligomers can bind to IR and trigger the removal of IR from the plasma membrane, resulting in reduction of the surface IR and responsiveness to insulin (De Felice et al. 2009; Zhao et al. 2008). Unlike the distribution of insulin throughout the neuronal cell soma and dendrites in control brains, IR is concentrated inside of intracellular compartment in AD brain (Moloney et al. 2010). Aβ oligomers can also increase the serine phosphorylation of IRS1, leading to insulin resistance (Arvanitakis et al. 2006).

6.4.3 Brain Insulin and Tau

The second hallmark brain lesion of AD is neurofibrillary tangles composed of the aggregated and abnormally hyperphosphorylated microtubule-associated protein tau protein (Grundke-Iqbal et al. 1986). Many studies have shown that abnormal hyperphosphorylation and aggregation of tau are crucial to neurodegeneration in AD (Iqbal et al. 2016). During normal brain development, insulin acts as a neurotrophic factor and can regulate tau phosphorylation through the PI3K/AKT/GSK-3 signaling pathway, which is believed to contribute to the neuronal development and

plasticity (Hong and Lee 1997; Lesort and Johnson 2000; Lesort et al. 1999). However, under pathologic conditions where there is brain insulin resistance, tau is abnormally hyperphosphorylated. Diabetic monkeys with brain insulin resistance, as evidenced by increased level of serine phosphorylation of IRS1, exhibit widespread increase in the phosphorylated tau in the brain (Morales-Corraliza et al. 2016). The obesity-induced peripheral insulin resistance is also associated with brain insulin resistance and tau hyperphosphorylation (Špolcová et al. 2014). Brain/neuron-specific knockout of insulin receptor results in an increase in tau phosphorylation in mice (Schubert et al. 2004). IRS-2 knockout mice develop neurofibrillary tangles containing hyperphosphorylated tau in the hippocampus (Schubert et al. 2003). We have shown that inhibition of brain insulin signaling by intracerebroventricular administration of streptozotocin also induces hyperphosphorylation of tau at multiple sites associated with AD and reduces tau's ability to bind to microtubules in rodents (Chen et al. 2013; Deng et al. 2009). It also exacerbates tau pathology in a triple transgenic AD mouse model, the 3xTg-AD mice (Chen et al. 2014b). These findings suggest that brain insulin resistance is involved in the hyperphosphorylation of tau in AD brain. Indeed, the levels and activities of several components of the insulin signaling pathway are found to correlate negatively with the level of tau phosphorylation in AD brain (Liu et al. 2011).

6.5 O-GlcNAcylation in T2DM and AD

O-GlcNAcylation is a common dynamic posttranslational modification of nuclear, cytoplasmic, and mitochondrial proteins (Dias and Hart 2007). O-GlcNAc cycling is regulated by two enzymes: O-GlcNAc transferase (OGT) and O-GlcNAc hydrolase (O-GlcNAcase or OGA) (Butkinaree et al. 2010). OGT catalyzes the transfer of GlcNAc from UDP-GlcNAc to the serine or threonine residues of proteins, whereas OGA removes the O-GlcNAc from proteins (Fig. 6.1). UDP-GlcNAc is the end product of the hexosamine biosynthetic pathway (HBP), which consumes about 2–5% of glucose that enters the cell (Buse 2006). The activity of OGT is very sensitive to the level of UDP-GlcNAc, which respond rapidly to the metabolic pathways like glucose metabolism (Haltiwanger et al. 1990). Alteration in the HBP flux due to altered cellular glucose availability can lead to changed UDP-GlcNAc concentration and, subsequently, increased/decreased protein O-GlcNAcylation. Downregulation of O-GlcNAcylation of proteins induced by fasting can be reversed by refeeding (Li et al. 2006). Therefore, O-GlcNAcylation is regarded as an intracellular sensor of glucose metabolism and is regulated by insulin signaling.

The dynamic interplay between O-GlcNAcylation and phosphorylation of proteins is extensive (Wang et al. 2007). Inhibition to GSK-3β, a key kinase involved in the insulin signaling pathway, increases O-GlcNAcylation of at least 10 proteins and decreases O-GlcNAcylation of 19 other proteins (Wang et al. 2007). Overexpression of OGT increases the overall level of O-GlcNAc and reduces proline-directed phosphorylation on many proteins (Slawson et al. 2005). Reciprocal

occupancy of the two modifications could occur at the same serine or threonine residues or at proximal sites (Hart et al. 2011). The relationship between the two post-translational modifications is not simply reciprocal. O-GlcNAcylation and phosphorylation could also occur simultaneously at distant sites or even on completely different subpopulations of the molecules (Omary et al. 1997; Ball et al. 2006).

6.5.1 O-GlcNAcylation and T2DM

T2DM is characterized by peripheral insulin resistance and hyperglycemia. The transcription factors, PDX-1 and NeuroD1, which control insulin synthesis, are modified by O-GlcNAcylation (Andrali et al. 2007; Gao et al. 2003). O-GlcNAcylation of these proteins is positively correlated with the secretion of insulin from the β-cells of the pancreas. Under hyperglycemia, O-GlcNAc modification of NeuroD1 promotes its translocation from cytosol into the nucleus and enhances transcription of the insulin gene (Andrali et al. 2007). Similarly, increased O-GlcNAcylation of PDX-1 results in enhanced DNA binding activity and insulin secretion (Gao et al. 2003). However, long-term elevation of overall protein O-GlcNAcylation appears to be deleterious and associated with insulin resistance. Overexpression of OGT in skeletal muscle or liver induces insulin resistance and hyperglycemia (McClain et al. 2002; Dentin et al. 2008), while overexpression of OGA reversed OGT-induced hyperglycemia (Dentin et al. 2008). Elevation of O-GlcNAc levels by pharmacological approaches and OGA inhibition also results in insulin resistance (Vosseller et al. 2002; Arias et al. 2004). O-GlcNAcylation may play a pivotal role in the mechanism of insulin resistance by downregulating the insulin signaling pathway (Yang et al. 2008). The components of the insulin signaling pathway like the β chain of the insulin receptor, IRS1/2, the p110α unit of PI3-kinase, AKT, PDK1, and GSK-3 have been shown to be modified by O-GlcNAc (Gandy et al. 2006; Park et al. 2005; Lubas and Hanover 2000; Patti et al. 1999; Yang et al. 2008). However, pharmacological administration of OGA inhibitors, which increase cellular O-GlcNAcylation, failed to induce insulin resistance in cultured adipocytes and in rodents (Macauley et al. 2008, 2010a, b). Therefore, the exact role of O-GlcNAcylation in insulin resistance and diabetes remains elusive.

Several studies reported that O-GlcNAcylation may also contribute to the development of many complications seen in T2DM, like contractile defects (Yetik-Anacak and Catravas 2006), atherosclerosis (Federici et al. 2002), and cardiac dysfunction (Clark et al. 2003; Hu et al. 2005). Among them, diabetic cardiomyopathy is the major cause of morbidity and mortality in patients with diabetes (Bugger and Abel 2014). Elevation of O-GlcNAcylation levels by exposure to high glucose concentration, incubation with glucosamine, or overexpression of OGT in cardiomyocytes results in perturbation in calcium loading (Clark et al. 2003), which can be reversed by overexpression of OGA. Overexpression of OGA in STZ-induced diabetic mice also improves calcium transients and contractility (Hu et al. 2005).

These studies suggest that O-GlcNAcylation in the diabetic heart contributes to cardiac myocyte function and the development of diabetic cardiomyopathy, and reduction in O-GlcNAcylation benefits diabetic cardiac function.

6.5.2 O-GlcNAcylation and AD

An altered O-GlcNAcylated protein in AD was first reported by Yao and Coleman (1998), who found a marked reduction of O-GlcNAcylated clathrin assembly protein-3 (AP-3) in postmortem AD brain tissue. AP-3 is a synapse-specific protein that may play an important role in synaptic vesicle recycling (Maycox et al. 1992). However, the specific role of O-GlcNAc modification in the function of AP-3 remains unknown.

Because brain glucose uptake and metabolism are impaired in AD, which could theoretically result in downregulation of O-GlcNAcylation, we therefore determined the O-GlcNAcylation level of two independent cohorts of postmortem AD and control brains using an immuno-dot-blot assay with antibodies RL2 against O-GlcNAcylated proteins and found significant reduction of global protein O-GlcNAcylation in AD (Liu et al. 2004, 2009a). The decrease in O-GlcNAcylation correlates negatively to the phosphorylation level of tau in AD (Liu et al. 2009a), suggesting a link between these two. Similar decrease in protein O-GlcNAcylation is also seen in the brains of individuals with T2DM (Liu et al. 2009b). However, a recent study reported increased O-GlcNAcylation in AD brain instead (Förster et al. 2014). It is currently unclear why this study observed this opposite change in AD brain. The use of different brain areas, sample preparation, and analysis methods may underlie the observed discrepancies between these studies.

Numerous proteins are modified by O-GlcNAcylation in the mammalian brain (Alfaro et al. 2012). Several proteins involved in the possible mechanisms of AD, including APP, tau, and synaptic proteins, are modified by O-GlcNAc. Deregulation of O-GlcNAcylation of these AD-related proteins may mediate the roles of protein O-GlcNAcylation in AD (Iqbal et al. 2016; Gong et al. 2016).

APP was first reported to be modified with O-GlcNAc in 1995 (Griffith et al. 1995). However, the effect of this modification on APP processing and its function in neurodegenerative diseases including AD have not been investigated until the recent years. Jacobsen et al. found that increasing the level of APP O-GlcNAcylation with pharmacological approach or OGA knockdown switches APP processing toward the non-amyloidogenic pathway by increasing the secretion of sAPPα fragment and thus decreases Aβ production (Jacobsen and Iverfeldt 2011). The O-GlcNAc-promoted non-amyloidogenic processing of APP is probably facilitated by increasing the trafficking rate of APP from the trans-Golgi network to the plasma membrane and decreasing the endocytosis rate of APP (Chun et al. 2015). Reduced Aβ production through lowering γ-secretase activity is observed both in vitro and in 5xFAD mice after the treatment with OGA inhibitor, leading to a rescue of memory impairment (Kim et al. 2013). The same study also identified the O-GlcNAcylation

at Ser708 of nicastrin, a component of γ-secretase complex. The beneficial effects of elevated O-GlcNAc levels on cognition and Aβ production were also confirmed in another AD transgenic mouse model with the treatment of another OGA inhibitor (Yuzwa et al. 2014b). Furthermore, the forebrain-specific loss of OGT in adult mice leads to increased production of amyloidogenic Aβ-peptides and memory deficits (Wang et al. 2016).

Tau protein was first reported to be extensively modified by O-GlcNAc in 1996 by Hart and his colleagues (Arnold et al. 1996). They found that bovine tau is modified by O-GlcNAc at several serine/threonine residues. Later, we isolated tau from postmortem human brains and found that human brain tau is also modified by O-GlcNAc (Liu et al. 2004). To date, at least five O-GlcNAc sites on tau have been mapped. They are Thr123, Ser208, Ser238, Ser400, and one of Ser409/412/413 (Yuzwa et al. 2011, 2012; Smet-Nocca et al. 2011).

Regulation between tau phosphorylation and O-GlcNAcylation has been reported in several studies. Treatment of human neuroblastoma cells with phosphatase inhibitor okadaic acid induces tau hyperphosphorylation accompanied by decreased O-GlcNAcylation (Lefebvre et al. 2003). We also observed a reciprocal relationship between global O-GlcNAcylation and phosphorylation of tau in AD brains (Liu et al. 2004, 2009a). O-GlcNAcylation regulates tau phosphorylation site-specifically and largely negatively both in vitro and in vivo. It has been shown that the phosphorylation of Ser396 and Ser404 decreases Ser400 O-GlcNAcylation, while Ser400 O-GlcNAcylation reduces Ser404 phosphorylation induced by CDK2/cyclinA3 kinase and interrupts the sequential phosphorylation at Ser396 and Ser404 by GSK-3β (Smet-Nocca et al. 2011). Hyperphosphorylated tau purified from AD brain contains fourfold less O-GlcNAc than the non-hyperphosphorylated tau (Liu et al. 2009a). Downregulation of O-GlcNAcylation by OGT knockdown leads to increased phosphorylation of tau in cultured cells (Liu et al. 2009a). Forebrain-specific loss of OGT in adult mice leads to increased level of hyperphosphorylated tau and memory deficits (Wang et al. 2016). Decreased tau O-GlcNAcylation and concurrent hyperphosphorylation of tau at most phosphorylation sites were observed in fasting mice, which is reversible after refeeding (Li et al. 2006). Thus, the decreased brain glucose metabolism might have contributed to abnormal hyperphosphorylation of tau through downregulation of O-GlcNAcylation in AD (Fig. 6.1; Gong et al. 2016). O-GlcNAcylation of tau not only impacts its phosphorylation level but also may influence its aggregation. O-GlcNAcylation of tau at Ser356 could greatly slow down the aggregation of the fourth microtubule-binding repeat of tau (Yu et al. 2008).

On the basis of findings discussed above, whether elevating brain O-GlcNAcylation can be a therapeutic approach for treating AD has been investigated in several preclinical studies. Vocadlo's group was the first to explore this approach by treating the JNPL3 tau transgenic mice with thiamet-G, a specific BBB-permeable OGA inhibitor, for 36 weeks. They found that the treatment increases tau O-GlcNAcylation, hinders formation of tau aggregates, and decreases the number of NFTs and neuronal cell loss (Yuzwa et al. 2012). Surprisingly, this study did not find reduction of

tau hyperphosphorylation in the mouse brain after the chronic treatment, which is in contrast to previous observations with acute elevation of protein O-GlcNAcylation under various conditions (Liu et al. 2004, 2009a; Yuzwa et al. 2008). Later, the same group found that O-GlcNAc modification of tau leads to decreased aggregation propensity while not affecting either the local or global conformation of tau protein (Yuzwa et al. 2014a). This approach was also tested in two additional mouse models of tauopathies, Tau.P301L mice and TAPP mice. Chronic treatment of old Tau.P301L mice increased brain O-GlcNAcylation, mitigated the loss in body weight, and improved motor deficits and survival (Borghgraef et al. 2013). Cognitive decline is prevented in TAPP mice after the treatment with thiamet-G for 36 weeks (Yuzwa et al. 2014b). This treatment also reduced Aβ levels and the number of amyloid plaques in the brain but did not appear to alter APP processing. In addition, attenuation of Aβ accumulation, neuroinflammation, and memory impairment are seen in 5xFAD mice after treatment with another OGA inhibitor, NButGT (Kim et al. 2013). Importantly, the chronic use of the OGA inhibitor appears to be safe because no toxicity was observed in these studies.

6.6 Molecular Links Between T2DM and AD

Recent studies have demonstrated the roles of brain insulin resistance, impaired brain glucose metabolism, and deregulation of brain O-GlcNAcylation in AD. It is clear that sporadic AD is also a metabolic disorder, in which the deregulation of metabolic homeostasis occurs in the brain (Suzanne and Tong 2014). As insulin resistance is the center of and O-GlcNAcylation is also critical to T2DM, insulin and O-GlcNAcylation appear to be the major molecular links between T2DM and AD.

The exact molecular mechanisms/pathways by which brain insulin signaling regulates multiple brain functions still remain largely elusive. However, deficient brain insulin signaling can promote and contribute to several aspects of AD (Fig. 6.1) because it cross-talks with several other signaling pathways and regulates brain metabolism, neuroplasticity, and cognition. In AD brain, deficient insulin signaling (Steen et al. 2005; Liu et al. 2011) can lead to decreased PI3K-AKT signaling activity via decreased IR activation, resulting in over-activation of GSK-3. GSK-3β overactivation not only can lead to tau hyperphosphorylation directly but also cause cognitive impairments via other pathways. Insulin deficiency can also lead to decreased GLUT expression/function and thus decreased glucose uptake/metabolism in the brain. Decreased intraneuronal glucose metabolism can lead to a reduction of ATP generation through the TCA cycle and thus impaired synaptic activity and cognitive function. It can also result in decreased level of UDP-GlcNAc via HBP and, consequently, decreased O-GlcNAcylation of APP and tau, which can facilitate Aβ production and tau hyperphosphorylation. Aβ overproduction and tau hyperphosphorylation promote the formation of toxic oligomers of them and eventually leads to the deposits of amyloid plaques and neurofibrillary tangles in the

brain. On the other hand, activation of GSK-3α can also promote overproduction of Aβ through regulating APP cleavage (Phiel et al. 2003).

Oxidative stress and chronic inflammation occur in both T2DM and AD and may also serve as molecular links between the two conditions. Accumulation of oxidatively damaged proteins, lipids, and nucleic acids is implicated in the pathogenesis of both diseases (Reddy et al. 2009). The production of advanced glycation end products (AGEs) and its interaction with receptors for AGEs (RAGEs) trigger signaling cascade, leading to the cellular stress, apoptosis, and formation of inflammatory cytokines (Maczurek et al. 2008; Yan et al. 2008). Increased accumulation of AGEs in diabetes is associated with hyperglycemia and age (Mitsuhashi et al. 1993; Nogueira-Machado and Chaves 2008). AGE modification of islet amyloid polypeptide (IAPP) also promotes the formation of amyloid deposition in the islet (Kapurniotu et al. 1998). In AD, aggregated Aβ and tau can lead to mitochondrial dysfunction and oxidative stress (Ahmad 2013). High level of AGEs is present in amyloid plaques and NFTs and closely associated with the formation of these two pathologies (Vitek et al. 1994; Ko et al. 1999). RAGE is also a receptor for Aβ, which mediates Aβ-induced neuroinflammation and disruption of LTP (Origlia et al. 2008; Du Yan et al. 1996). Besides, oxidative stress can lead to the activation of JNK (Ma et al. 2009), and consequently insulin resistance, which is also seen in AD brain.

Chronic inflammation is associated with the development of insulin resistance and T2DM. Circulating inflammatory markers and cytokines, such as C-reactive protein (CRP) and interleukins (IL-1β and IL-6), predict the development of T2DM (Freeman et al. 2002; Pradhan et al. 2001; Spranger et al. 2003). The overproduction of IL-1β and IL-6 can cause β-cell dysfunction, apoptosis in pancreatic islets, reduced insulin secretion, and insulin resistance (Arafat et al. 2007; Fève and Bastard 2009). Tumor necrosis factor-α (TNF-α), produced and secreted by adipose tissue, can induce insulin resistance through its effects on metabolism, decreasing the peripheral uptake of glucose in response to insulin (Hotamisligil et al. 1993). Similarly, neuroinflammation is also thought to contribute to the progression of AD (Hong et al. 2016). The activation of microglial cells and astrocytes by toxic substances, such as Aβ, gives rise to the release of various inflammatory mediators, leading to the suppression of LTP, reduced production and release of various neurotrophic factors such as BDNF, and neuronal loss (Heneka and O'Banion 2007). Increased levels of proinflammatory cytokines, such as TNF-α, IL-1β, and IL-6, are observed at all stages of AD (Mrak and Griffin 2005). These cytokines may also promote the formation of Aβ deposits and NFTs (Heneka and O'Banion 2007).

Animal studies have implicated inflammation as the possible link between AD and T2DM (Mushtaq et al. 2015). BBB-permeable proinflammatory factors induced by T2DM could attribute to the neuronal dysfunction in aged brain, which is more susceptible to peripheral inflammatory responses (Franceschi et al. 2000), leading to the increased risk of developing AD.

It is likely that protein O-GlcNAcylation also mediates the links between oxidative stress or chronic inflammation and T2DM or AD, because it appears to regulate

both oxidative stress and inflammation. Our recent proteomic studies found that O-GlcNAc modifies proteins involved in oxidative stress or neuroinflammation in both mouse and human brains (Alfaro et al. 2012; Wang et al. 2017a, b). Elevation of O-GlcNAcylation attenuates oxidative stress and apoptosis in cardiomyocytes and following contrast-induced acute kidney injury in rats (Ngoh et al. 2011; Hu et al. 2017). Several studies have shown the impact of O-GlcNAcylation on inflammation, but the exact roles and mechanisms are largely not understood (Baudoin and Issad 2015).

6.7 Conclusions

As discussed above, brain insulin resistance, impaired brain glucose metabolism, and deregulation of brain O-GlcNAcylation may be important molecular links between T2DM and AD. Although insulin resistance in AD is restricted to the brain and in T2DM affects primarily the periphery, it occurs at very early stage and progresses with the development of the diseases, contributing to the development of the two diseases. Restoring insulin sensitivity has been the major strategy to treat T2DM. Restoring or boosting insulin signaling in the brain is now under active investigation for AD drug discovery. Several FDA-approved drugs for the treatment of T2DM have been studied and are continuing to be studied for their efficacies for treating AD (Yarchoan and Arnold 2014; Chen et al. 2016). Increasing the brain insulin level by intranasal delivery of insulin has been proven effective in promoting the memory and attention in MCI and AD patients (Hölscher 2014; Shemesh et al. 2011). Animal studies have revealed that intranasal insulin may decrease the hyperphosphorylation of tau through upregulation of tau phosphatase and downregulation of tau protein kinases (Chen et al. 2014c). Intranasal insulin can also ameliorate Aβ pathologies in AD transgenic mice by shifting APP processing to the non-amyloidogenic pathway (Mao et al. 2016). These studies also show that intranasal insulin not only can reduce AD pathologies but also enhances synaptic plasticity and neurogenesis in the brain. Other antidiabetic drugs, including analogues of incretins, dipeptidyl peptidase IV inhibitors, thiazolidinediones, and metformin, have been shown to reduce the levels of Aβ and tau phosphorylation, attenuate neuroinflammation and oxidative stress, promote neurogenesis and synaptic plasticity, and benefit the cognitively impaired animals (Chen et al. 2016). Clinical trials are under way to evaluate the efficacy of these drugs for the treatment of MCI and AD patients. Thus, understanding the molecular link between T2DM and AD will help develop strategies to prevent and treat both disorders.

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Conflict of Interest C.-X.G. serves on the scientific advisory board of Alectos Therapeutics and filed a patent application dealing with O-GlcNAcylation treatment for ischemic brain injury. Y.C. and C.-X.G. hold a patent on the prevention of anesthesia-induced memory loss by using intranasal insulin. The other author confirms that this article content has no conflicts of interest.

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Chapter 7
Type II Diabetes Mellitus Accelerates Age-Dependent Aβ Pathology in Cynomolgus Monkey Brain

Nobuyuki Kimura

Abstract Accumulating evidence suggests that diabetes mellitus (DM) is one of the strongest risk factors for developing Alzheimer's disease (AD). However, it remains unclear how DM accelerates AD pathology in the brain. Cynomolgus monkey (*Macaca fascicularis*) is one of the nonhuman primates used for biomedical research, and we can observe spontaneous formation of AD pathology, such as senile plaques (SPs) and neurofibrillary tangles (NFTs), with the advance of aging. Furthermore, obesity is occasionally observed and frequently leads to development of type II DM (T2DM) in laboratory-housed cynomolgus monkeys. These findings suggest that cynomolgus monkey is a useful species to study the relationship between T2DM and AD pathology. In T2DM-affected monkey brains, SPs were observed in frontal and temporal lobe cortices almost 5 years earlier than healthy control monkeys. Moreover, age-related endocytic pathology, such as intraneuronal accumulation of enlarged endosomes, was exacerbated in T2DM-affected monkey brains. Since accumulating evidences suggest that endocytic dysfunction is involved in Aβ pathology, T2DM may aggravate age-related endocytic dysfunction, leading to the acceleration of Aβ pathology.

Keywords Alzheimer's disease · Aβ pathology · Cynomolgus monkey · Endocytic dysfunction · Type II diabetes mellitus

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7.1 Introduction

Alzheimer's disease (AD) is the most common cause of dementia and is characterized by two major pathological hallmarks such as senile plaques (SPs) and neurofibrillary tangles (NFTs) (Selkoe 1991; Mattson 2004; Armstrong 2009). It is widely accepted that β-amyloid protein (Aβ), the major component of SPs, is a key molecule underlying AD pathogenesis; however, it remains unclear why aging causes AD (Hardy and Selkoe 2002; Goedert et al. 1991). Several epidemiological/clinical studies have shown that diabetic mellitus (DM) patients are significantly more likely to develop cognitive dysfunction and exhibit increased susceptibility to AD (Leibson et al. 1997; Arvanitakis et al. 2004; Frisardi et al. 2010; Daviglus et al. 2011; Crane et al. 2013), in consistent with the original Rotterdam study (Ott et al. 1999). Recent findings also showed that there are several pathogenic connections between AD and DM patient brains, especially for defective neuronal insulin signaling (De Felice and Ferreira 2014). In the brain, insulin has a pivotal role in neuronal functions by regulating energy metabolism, growth, survival, and differentiation via insulin signaling (Bingham et al. 2002; Zhao et al. 2004; Huang et al. 2005; Duarte et al. 2006; Lacroix et al. 2008; Kuwabara et al. 2011). Hence, insulin resistance causes the alteration in insulin signaling pathway, leading to an AD-like pattern of reduced cerebral glucose metabolic rate in the brain (Salkovic-Petrisic et al. 2006; Baker et al. 2010). Moreover, accumulating evidence showed that the experimental induction of DM enhanced AD pathology even in rodents (Ho et al. 2004; Li et al. 2010; Plaschke et al. 2010; Takeda et al. 2010; Bitela et al. 2012; Currais et al. 2012; Maesako et al. 2012; Son et al. 2012; Yamamoto et al. 2012; Chen et al. 2013; Yang et al. 2013; Mehla et al., 2014). However, it remains unclear how DM physiologically accelerates AD pathology in the brain. Here, I summarize our recent finding that DM accelerates age-dependent Aβ pathology in the brain of nonhuman primates.

7.2 Cynomolgus Monkey as an Animal Model for Spontaneous AD Pathology

Cynomolgus monkey (*Macaca fascicularis*) is one of the nonhuman primates used for biomedical research. Although there is no criteria for dementia of nonhuman primates, both SPs and NFTs are observed spontaneously in brains of cynomolgus monkeys with advancing age (Fig. 7.1) (Nakamura et al. 1998; Oikawa et al. 2010). In addition, the amino acid sequence of Aβ of cynomolgus monkeys is completely consistent with that of humans (Podlisny et al. 1991). These advantages make this species a useful model to study age-dependent AD pathophysiology.

Intriguingly, as with humans, obesity occasionally occurs in adult, middle-aged monkeys, and it can result in the development of type II DM (T2DM) (Wagner et al. 2001, 2006). These monkeys have a period of insulin resistance and hyperinsulinemia

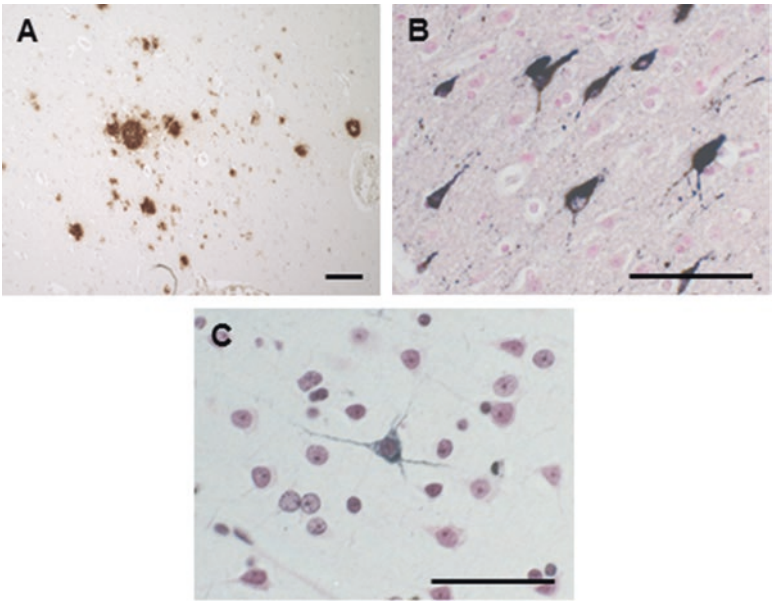

Fig. 7.1 AD pathology in aged cynomolgus monkey brains. Images of temporal lobe sections from aged cynomolgus monkeys (**a–c**). The section of 33-year-old monkey was immunostained with anti-Aβ antibody (82E1; IBL, Gunma, Japan) (**a**). The section of 36-year-old monkey was immunostained with anti-phosphorylated Tau antibody (AT8; Thermo, Rockford, IL) (**b**). A neuron with Gallyas-silver-positive structure in 36-year-old cynomolgus monkey (**c**). Scale bars, 100 μm

before developing overt T2DM, which is then accompanied by deficiency in pancreatic insulin production (Wagner et al. 2001, 2006; Bauer et al. 2011). The pathological changes in the pancreatic islets are also similar to human diabetics, such as the deposition of islet amyloid polypeptide (Koh et al. 2005; Kuwabara et al. 2011; Lacroix et al. 2008). In addition, gestational diabetes has been also reported in female cynomolgus monkeys (Wagner et al. 2001, 2006; Bauer et al. 2011).

In Japan, Tsukuba Primate Research Center (TPRC) maintains a large breeding and rearing colony of cynomolgus monkeys for high-quality production of nonhuman primate models and biomedical investigations, and it has accumulated clinical data for more than 40 years. In the TPRC colony, cynomolgus monkeys are bred within a closed colony. Intriguingly, some adult monkeys are spontaneously affected with T2DM for various reasons, such as pregnancy history and environmental factors. Generally, the normal blood glucose level for female monkeys is in the range of 24–74 mg/dL, and for male monkeys the range is 24–76 mg/dL. Normal blood triglyceride levels are in the range of 8–85 mg/dL for females and 6–52 mg/dL for males. On the other hand, T2DM-affected monkeys exhibit obvious hyperlipidemia and hyperglycemia, and histopathological analyses also confirmed DM-related pathology such as hyalinized islets with severe amyloid deposits, fatty degeneration of the liver, and atheromatosis (Okabayashi et al. 2015). These findings strongly

suggest that cynomolgus monkeys are a useful species to investigate not only age-dependent AD lesions but also the relationship between DM and AD pathology.

7.3 T2DM Accelerates Aβ Pathology in Cynomolgus Monkey Brain

In cynomolgus monkey brains, SP depositions are observed in the brains of aged monkeys, but not in those of normal adult monkeys younger than 20 years of age (Kimura et al. 2005; Leibson et al. 1997). However, strikingly, we apparently observed diffuse Aβ-immunopositive SPs in brains of T2DM-affected adult monkeys younger than 20 years old, even though they were very small quantities as compared to aged monkey brains (Fig. 7.2a, b) (Okabayashi et al. 2015). In aged cynomolgus monkey brains, cerebral amyloid angiopathy (CAA) lesions are also observed, and NFTs are observed over 32-year-old monkey brains (Kimura et al. 2005, 2009). Although abnormally phosphorylated tau accumulation was not

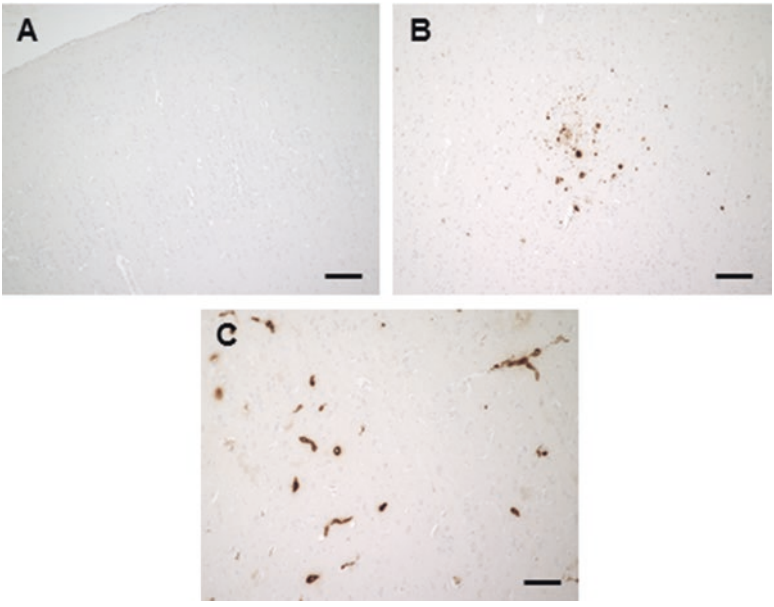

Fig. 7.2 Accelerated Aβ pathology in T2DM-affected monkey brains. Images of temporal lobe (TL) sections from normal cynomolgus monkeys (**a**) and cynomolgus monkeys with T2DM (**b**, **c**). Sections were immunostained with anti-Aβ antibody and counterstained with hematoxylin. In normal adult monkey brains (21-year-old), we did not observe Aβ-immunopositive structures (**a**). By contrast, we did observe small but obvious Aβ-immunopositive senile plaques (SPs) in the frontal and temporal cortices of DM-affected adult monkeys (21-year-old) (**b**). Moreover, we observed severe CAA lesions in T2DM-affected aged monkey brains as compared to normal aged monkeys (**c**). Scale bars, 100 μm

apparently observed, we found much severe CAA in the brains of aged monkeys with T2DM (Fig. 7.2c) (Okabayashi et al. 2015). These findings are consistent with the previous studies showing that T2DM-related conditions induce amyloidogenesis and Aβ pathology in rodent models (Duarte et al. 2006; Falkenburger et al. 2010; Frisardi et al. 2010; Goedert et al. 1991; Grbovic et al. 2003; Hardy and Selkoe 2002; Harold et al. 2009; Ho et al. 2004; Huang et al. 2001, 2005; Jordens et al. 2005; Kamada et al. 1992). Moreover, these findings suggest that T2DM can induce not only parenchymal Aβ pathology but also vascular Aβ pathology in an age-dependent manner (Okabayashi et al. 2015).

In aged monkey brains, Aβ level is significantly increased and correlates with age-dependent SP depositions (Leibson et al. 1997). In T2DM-affected adult monkey brains, Aβ level was slightly but apparently increased as compared to normal adult monkey brains (Okabayashi et al. 2015). Since the number of SPs was very small in T2DM-affected adult monkey brains, it may be reasonable that Aβ level showed just slight increase in T2DM-affected adult monkey brains as compared to age-matched control group (Okabayashi et al. 2015). However, this finding strongly supports the previous finding that Aβ level correlates with SP depositions (Kimura et al. 2005)

7.4 T2DM Exacerbates Age-Related Endocytic Dysfunction

Although it remains unclear why Aβ markedly accumulates in AD brains, endocytic pathology, such as intraneuronal accumulation of abnormally enlarged endosomes, is frequently observed in the early stages of AD (Cataldo and Nixon 1990; Cataldo et al. 1997, 2004; Nixon 2005, 2007). Several studies showed that both APP and BACE1 are transported intracellularly via endocytosis (Grbovic et al. 2003; Koh et al., 2005; Lefort et al. 2012) and that endocytic disturbance induces the accumulation of Aβ, APP, and BACE1 in abnormally enlarged endosomes (Cataldo et al. 2004; Nixon 2005; Okada et al. 2010; Kimura et al. 2009). Moreover, recent genome-wide association studies (GWAS) identified AD-associated variants in endocytosis-associated genes (Harold et al. 2009; Seshadri et al. 2010; Vardarajan et al. 2012; Talwar et al. 2014; Chouraki and Seshadri 2014). Therefore, the alteration in endocytosis is considered to be involved in Aβ pathology.

Evidently, endosomes were apparently enlarged in the brains of T2DM-affected adult monkeys, and the immunoreactivity of APP was significantly stronger than the brains of normal adult monkeys (Fig. 7.3) (Okabayashi et al. 2015). Endosome trafficking is regulated by small Rab GTPases such as Rab5 (early endosome-associated GTPase), Rab7 (late endosome-associated GTPase), and Rab11 (recycling endosome-associated GTPase) (Jordens et al. 2005). Our previous studies showed that an increase in Rab GTPases is a good indicator for alterations in intracellular endosome trafficking associated with a particular Rab GTPase (Kimura et al. 2009, 2012). Indeed, increased Rab GTPase levels are strongly associated with endocytic disturbance (Kimura et al. 2009, 2012). In the brains of T2DM-affected adult

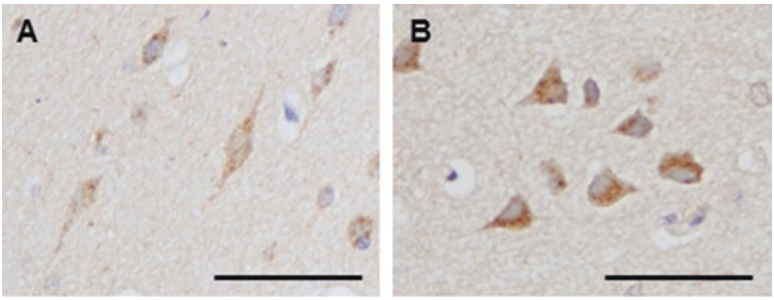

Fig. 7.3 Immunohistochemistry of APP in the brains of normal and DM-affected monkeys. Images of temporal lobe sections from a 20-year-old normal cynomolgus monkey (**a**) and a 20-year-old cynomolgus monkey with T2DM (**b**). Sections were immunostained with anti-APP antibody and then counterstained with hematoxylin. In the brains of normal adult monkeys, APP was observed as small granules in neurons (**a**). On the contrary, in the brains of DM-affected adult monkeys, APP clearly accumulated in enlarged endosomes, and its immunoreactivity was significantly more robust. (**b**) Scale bars, 100 μm

monkeys, Rab GTPases levels were apparently increased compared to the brains of normal adult monkeys (Fig. 7.4), being almost the same as in normal aged monkey brains (Okabayashi et al. 2015). This finding suggests that T2DM aggravates age-related endocytic dysfunction, leading to accelerate Aβ pathology. Moreover, the results of this study strongly support the idea that endocytic dysfunction is essentially involved in the development of Aβ pathology (Cataldo et al. 1997, 2000, 2004; Kimura et al. 2009).

It remains unclear how T2DM exacerbates age-related endocytic dysfunction. Endosome trafficking is mediated by axonal transport motor proteins (Schroer and Sheetz 1991), and a recent study showed that the experimental induction of type 1 DM alters axonal motor protein levels in rodent model (Baptista et al. 2013). However, we did not find any changes in axonal motor protein levels in the brains of T2DM-affected monkeys (Okabayashi et al. 2015). Previous findings showed that the breakdown in lysosomal degradation also induces endocytic disturbance, and the defective lysosomal-autophagosome clearance is associated with AD pathology (Nixon et al. 2000, 2005; Boland et al. 2008; Wolfe et al. 2013). In T2DM-affected adult monkey brains, the level of cathepsin D (CatD) heavy chain increased (Okabayashi et al. 2015). On the other hand, we observed the significant increase in autophagosome marker LC3-II level concomitantly with the selective autophagy substrate p62 in T2DM-affected adult monkey brains (Fig. 7.4) (Okabayashi et al. 2015). The increase of p62 level indicates that the autophagosome clearance was disrupted in T2DM-affected monkey brains (Fig. 7.4). Hence, the alteration in lysosomal-autophagosome clearance might be responsible for aggravated endocytic dysfunction in T2DM-affected adult monkey brains. Growing evidences suggest that membrane-bound phosphoinositides regulate endosome trafficking (Falkenburger et al. 2010; Zhang et al. 2012), and the metabolism of phosphoinosit-

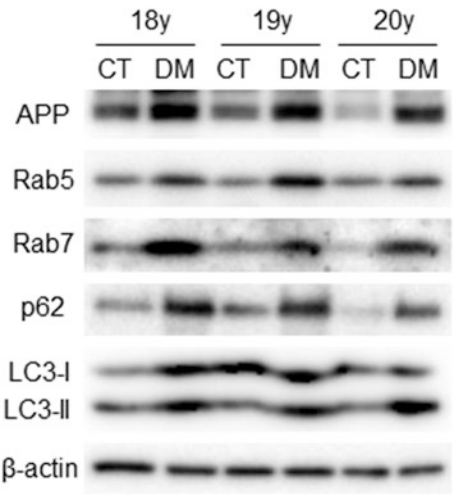

Fig. 7.4 Western blot analyses in the brains of normal and DM-affected monkeys. Western blots showing the amounts of APP, p62, LC3, Rab5, Rab7, and β-actin in the brains of normal monkeys and DM-affected monkeys of different ages. Western blot analyses showed that APP and Rab GTPases were significantly increased in both DM-affected adult and aged monkey brains. In the brains of T2DM-affected adult monkeys, APP, Rab GTPases, p62, and LC3-II levels were obviously increased compared to those of normal adult monkeys. Lanes contained microsome fractions derived from the brains of normal adult monkeys (age-matched control) and T2DM-affected adult monkeys. *18y* 18-year-old monkey, *19y* 19-year-old monkey, *20* 20-year-old monkey, *CT* normal adult monkeys, *DM* T2DM-affected adult monkeys

ides is affected by insulin signaling (Natarajan et al. 1981; Thakker et al. 1989; Kamada et al. 1992). Recent studies also showed that Rab activity is affected by insulin signaling and that PI3K inhibition causes upregulation of Rab5 (Huang et al. 2001; Runyan et al. 2012). Thus, although additional investigations are needed, impaired insulin signaling would exacerbate age-related endocytic disturbances via alteration in the metabolism of phosphoinositides and/or Rab GTPases.

7.5 Conclusion

In conclusion, T2DM accelerates age-dependent Aβ pathology in vivo in cynomolgus monkey brains. Since the amino acid sequence of cynomolgus monkey Aβ corresponds completely with that of human Aβ, it is reasonable that the enhanced Aβ pathology we observed in monkeys with T2DM should also occur in humans with T2DM. Moreover, our recent study showed that T2DM could exacerbate age-related endocytic dysfunction via alteration in lysosomal degradation (Fig. 7.5) (Okabayashi et al. 2015). Although additional studies are needed to determine more precisely the

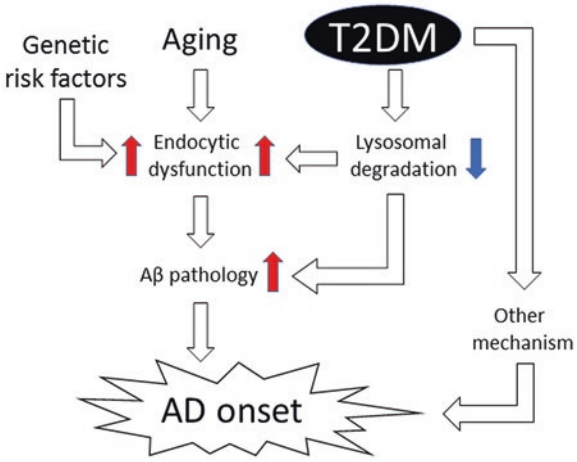

Fig. 7.5 Hypothetical schema of T2DM-induced Aβ pathology leading to AD onset. From the results of our study, we propose that T2DM exacerbates age-related endocytic dysfunction via alteration in lysosomal degradation, resulting in enhanced Aβ pathology in the brain. Recent GWAS identified AD-associated variants in endocytosis-associated genes, suggesting that several genetic risk factors may also aggravate age-related endocytic dysfunction. Although additional studies are needed to clarify the whole mechanisms underlying T2DM-associated pathology, we hypothesize that, at the very least, enhanced Aβ pathology accompanied by endocytic dysfunction might be involved in the development of AD

mechanisms how T2DM alters the endosomal-lysosomal system in the brain, endocytic dysfunction would be the key factor for Aβ pathology even in T2DM-affected brains (Fig. 7.5) (Cataldo and Nixon 1990; Cataldo et al. 1997, 2004; Nixon 2005, 2007; Grbovic et al. 2003; Koh et al. 2005; Lefort et al. 2012; Okada et al. 2010; Kimura et al. 2009; Okabayashi et al. 2015). Importantly, several studies showed that Aβ impairs insulin signaling itself (Zhao et al. 2008; De Felice et al. 2009; Bomfim et al. 2012), and then it may lead to aggravate the insulin resistance-related AD pathology (Salkovic-Petrisic et al. 2006; Baker et al. 2010; De Felice and Ferreira 2014). Thus enhanced Aβ pathology would contribute to DM-induced AD pathogenesis with other mechanism. Moreover, DM may also alter neuronal activity by exacerbating endocytic disturbance as we previously reported (Kimura et al. 2012). Hence, a reasonable therapeutic strategy to prevent the development of AD pathology is to treat or prevent DM.

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Chapter 8
Diabetes-Related Dementia

Haruo Hanyu

Abstract Type 2 diabetes mellitus (DM) has been shown to increase the risk for cognitive decline and dementia, such as in Alzheimer disease (AD) and vascular dementia (VaD). Additionally, there may be a dementia subgroup associated with specific DM-related metabolic abnormalities rather than with AD pathology or cerebrovascular diseases. This type of dementia, not showing hypoperfusion in the parietotemporal lobe on SPECT or cerebrovascular lesions on MRI, was characterized by old age, high hemoglobin A_{1c} level, long duration of diabetes, high frequency of insulin therapy, low frequency of apolipoprotein E4 carrier, less-severe medial temporal lobe atrophy, impaired attention and executive function, less-impaired word recall, and slow progression of cognitive impairment and might be referred to as "diabetes-related dementia" (DrD). ^{11}C-Pittsburgh compound-B PET shows often negative or equivocal amyloid accumulation in the brain, indicating different from AD pathology. In addition to insulin resistance, elevated inflammatory cytokines, oxidative stress, and advanced glycation end products were associated with cognitive impairment in this type of dementia. Glycemic controls can improve some domains of cognitive function, such as attention and executive functions, in subjects with DrD. Frequencies of frailty and sarcopenia/dynapenia are significantly higher in DrD than in AD, indicating that geriatric interventions are necessary to improve clinical outcomes for patients with DrD. DrD can be considered as a controllable or modifiable dementia. The identification of DrD, as distinct from other types of dementia, may be necessary for considering appropriate therapy and prevention in clinical practice.

Keywords Alzheimer disease · Vascular dementia · Diabetes-related dementia · Diabetes mellitus · Insulin resistance · Neuroimaging · Glycemic control · Frailty

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8.1 Introduction

Type 2 diabetes mellitus (DM) has been shown to increase the risk for cognitive decline and dementia, such as in Alzheimer disease (AD) and vascular dementia (VaD) (Biessels et al. 2006; Kopf and Frolich 2009). Several mechanistic studies have indicated that vascular disease, glucose toxicity, and changes in insulin and amyloid metabolism underlie the pathophysiology of dementia. The brains of elderly subjects with dementia and DM are likely to show a mixed pathology caused by a combination of the above factors. However, in some patients, cerebrovascular disease (CVD) may predominate, whereas in others AD pathology may predominate, leading to a clinical picture of dementia. In addition, there may be a dementia syndrome associated with DM-related neuronal injury (Fig. 8.1). We propose a new clinical entity of a dementia subgroup, referred to as "diabetes-related dementia" (DrD). Here the author reviews the concept, pathophysiology, diagnosis, treatment, and patient care concerning DrD.

8.2 Subgroups of Dementia Associated with DM Based on Brain Imaging

Neuroimaging studies, such as brain magnetic resonance imaging (MRI) and single photon emission computed tomography (SPECT), have been used for the diagnosis and elucidation of the pathophysiology of dementia. CVD can be easily depicted on

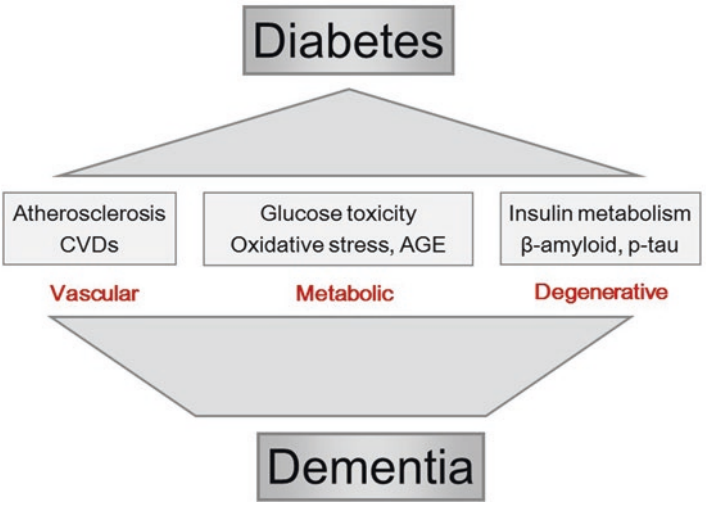

Fig. 8.1 The relationship between diabetes and dementia

MRI. Reduced perfusion in the parietotemporal and posterior cingulate regions on SPECT is recognized as a diagnostic pattern observed in AD. SPECT provides high specificity for AD against other types of dementia (Dougall et al. 2004; Bonte et al. 2006). Therefore, neuroimaging studies enable the demonstration of different patterns of cerebral damage in individuals with dementia.

We attempted to define possible subgroups of dementia associated with DM based on brain imaging (Fukasawa et al. 2013). We classified 175 patients with clinically diagnosed AD and type 2 DM into 4 subgroups on the basis of the presence or absence of cerebrovascular disease (CVD) on MRI (CVD or no CVD) and decreased regional cerebral blood flow (rCBF) in the posterior parietotemporal lobe on SPECT (AD pattern or no AD pattern). Differences in the clinical characteristics among the subgroups were examined. The subgroup showing neither a CVD pattern nor an AD pattern had significantly older age, higher hemoglobin A_{1c} (HbA_{1c}) level, longer duration of diabetes, higher frequency of insulin therapy, lower frequency of apolipoprotein E4 carriers, less-severe medial temporal lobe atrophy, more impaired attention and executive function, less-impaired word recall, and slower progression of cognitive impairment than the subgroup showing an AD pattern with or without CVD. This subgroup with characteristics predominantly associated with DM-related factors is clinically different from AD, VaD, and other types of dementia and is referred to as "diabetes-related dementia" (DrD) (Fig. 8.2). This subtype accounted for at least 10% of all patients with dementia associated with DM. The new term "diabetes-related dementia" is not suggestive of a particular underlying

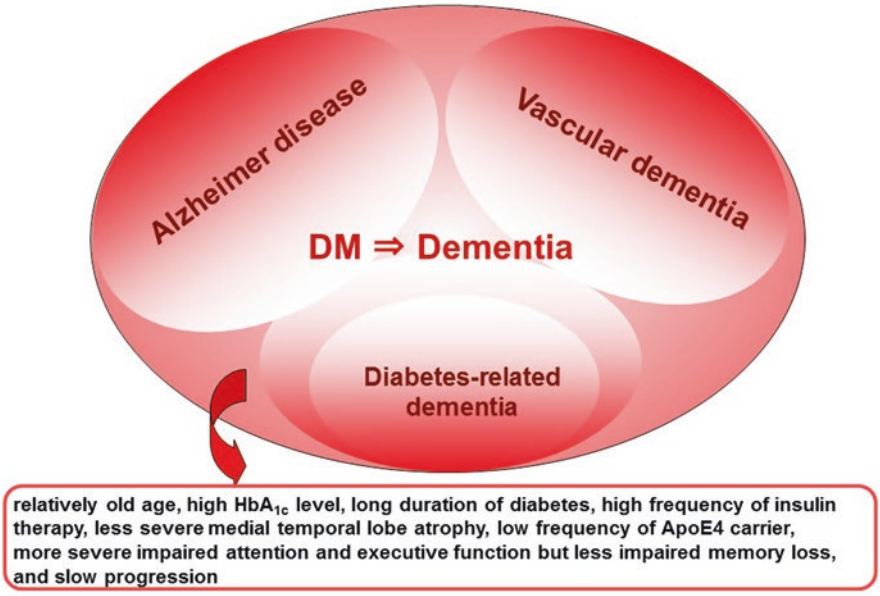

Fig. 8.2 Classification of dementia associated with diabetes

neuropathology but merely describes a dementia state predominantly associated with DM-related metabolic abnormalities rather than AD or vascular pathology.

8.3 Neuroimaging Studies in Diabetes-Related Dementia

We investigated longitudinal rCBF changes using SPECT in patients with diabetes-related dementia to determine the underlying pathophysiology. In addition, some patients underwent ^{11}C-Pittsburgh compound-B (PiB) positron-emission tomography (PET) to evaluate amyloid deposition (Fukasawa et al. 2015) and ^{11}C-pyridinyl-butadienyl-benzothiazole 3 (PBB3) PET (Maruyama et al. 2013) to assess tau pathology in the brain.

8.3.1 Longitudinal SPECT Study

We performed follow-up SPECT studies in 29 patients with probable AD and DM (AD[+DM] group) and 18 patients with DrD. Both groups showed no CVD, defined as either periventricular hyperintensity or deep white matter hyperintensity (grade 3) based on the scale of Fazekas et al. (1987) or by the presence of a varying degree of infarction.

Figure 8.3 (upper) shows three-dimensional views of decreased rCBF in the AD[+DM] group and DrD group, compared with 28 normal controls (12 men and 16 women, mean age of 75 ± 6 years) at the initial SPECT. The AD[+DM] group showed decreased rCBF in the parietotemporal lobe, posterior cingulate cortex, and frontal lobe, which is considered a characteristic feature of AD. On the other hand, the DrD group showed decreased rCBF predominantly in the lateral and medial frontal lobes. Figure 8.3 (lower) shows three-dimensional views of decreased rCBF in the AD[+DM] group and DrD group, compared with normal controls at the final SPECT (3 years after initial SPECT). The final SPECT showed more profound rCBF reduction in the parietotemporal lobe of the AD[+DM] group, reflecting progression of AD, whereas it showed rCBF reduction in some areas of the frontal lobe of the DrD group (Fukasawa et al. 2015).

8.3.2 PET Study

All PiB PET images were rated as positive (+), questionable (+/−), or negative (−), if the uptake in the cerebral gray matter, including frontal, lateral temporal, parietal, posterior cingulate, and precuneal regions, was more prominent, equivocal, or less than that in the white matter, respectively. Then, standardized uptake value (SUV) images were calculated from time-integrated radioactivity images by normalizing

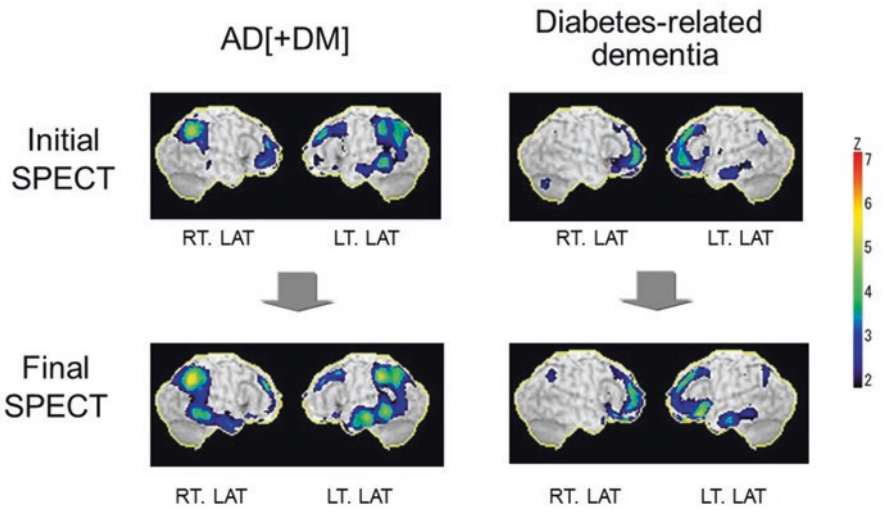

Fig. 8.3 Three-dimensional views of decreased rCBF at the initial and final SPECT in the AD[+DM] group and diabetes-related dementia group

tissue radioactivity concentration with injected dose per body weight. The ratios of regional SUV to cerebellar SUV (SUVR) were calculated as an index of PiB accumulation. We selected the cortical regions in the frontal, parietal, precuneal, posterior cingulate, and lateral temporal lobe regions and calculated the mean cortical SUVR (mcSUVR) in these regions. The mcSUVR values in normal controls rated as PiB negative (n = 13, mean age, 66 ± 5 years) and those in AD patients rated as PiB positive on visual inspection (n = 18, mean age, 74 ± 6 years) were 1.26 ± 0.15 and 2.11 ± 0.34, respectively.

Figure 8.4 shows representative PiB PET images and mcSUVR values of individual patients. Visual assessment on PiB PET images was in agreement with mcSUVR. Two patients with AD were rated as positive PiB, whereas three patients with DrD were rated as positive PiB, two as equivocal PiB, and four as negative PiB (Fukasawa et al. 2015). These findings indicate that underlying pathology in DrD differs from that in AD.

In our recent PBB3 PET study, most patients with DrD showed accumulation of PBB3 in the brain, including the medial temporal lobe and occasionally parietotemporal and frontal lobes, suggesting tau deposition in the brain. Although we have no autopsy data, DrD may be associated with tauopathy, including senile dementia of the neurofibrillary tangle type (Yamada 2003) or primary age-related tauopathy (PART) (Crary et al. 2014), in addition to non-specific neuronal damage due to glucose toxicity (Hanyu et al. 2016). Some studies showed that DM may promote neurodegeneration independent of an AD dementia diagnosis and its effect may be driven by tau phosphorylation (Roberts et al. 2014; Moran et al. 2015; Verdile et al. 2015). Recently, Li and Huang (2016) stated that tau-related neurofibrillary tangles

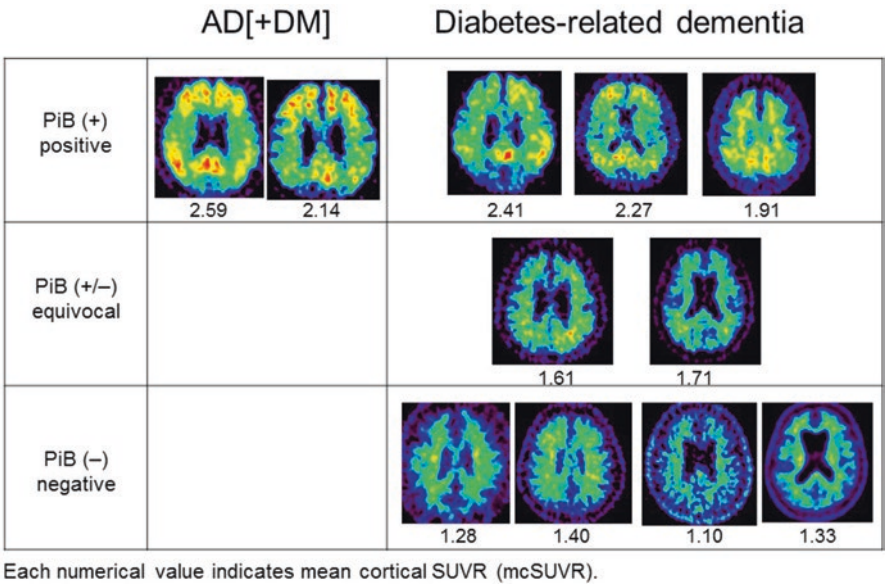

Fig. 8.4 PiB PET image and mcSUVR for each patient in the AD[+DM] group and diabetes-related dementia group

instead of amyloid-β plaques are more likely to be the pathological biomarkers for DM-related dementia. These studies are consistent with our findings showing negative amyloid and positive tau on PET in DrD.

Appropriate laboratory and neuroimaging studies would be necessary for the differentiation of DrD from other types of dementias, including AD and other neurodegenerative diseases.

8.4 Guidelines for the Clinical Diagnosis of Diabetes-Related Dementia

On the basis of the characteristic features of DrD, as described above, the following guidelines for its clinical diagnosis have been proposed (Hanyu et al. 2015):

1. Type 2 DM: long duration and less well-controlled glycemia
2. Dementia: impaired attention and executive function but less-impaired word recall and slow progression of cognitive impairment
3. CT/MRI: no evidence of vascular lesions and diffuse cortical atrophy but less-severe medial temporal lobe atrophy

4. SPECT/PET: no decreased hypoperfusion/hypometabolism in the posterior cerebral lobes and negative or equivocal amyloid accumulation but positive tau accumulation
5. Cerebrospinal analysis: normal or slightly increased p-tau and normal $A\beta_{42}$
6. ApoE4 carrier: low frequency
7. Exclusion of other causes of dementia (hypothyroidism, vitamins B_1 and B_{12} deficiency, head trauma, chronic alcoholism, cerebrovascular disease, other dementias)

The definition and guidelines for the clinical diagnosis of DrD proposed herein facilitate research into the pathophysiology and potential therapeutic interventions in the future.

8.5 Pathophysiology of Diabetes-Related Dementia

In addition to impaired insulin signaling and insulin resistance, inflammation, mitochondrial dysfunction and oxidative stress, and advanced glycation end products (AGEs) may also contribute to neuronal degeneration in individuals with DM (Verdile et al. 2015). We examined whether inflammation, oxidative stress, and AGEs are involved in the pathophysiology of DrD.

8.5.1 Inflammatory Markers

We compared peripheral levels of interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α), and high-sensitivity C-reactive protein (hs-CRP) between 49 patients with AD with DM (AD[+DM]) and 25 with DrD. The DrD group showed significantly higher levels of IL-6 ($p < 0.01$) and a *tendency* toward higher TNF-α ($p < 0.1$) and hs-CRP ($p < 0.1$) values, as compared with the AD[+DM] group (Fig. 8.5). In addition, a significant inverse correlation between IL-6 levels and MMSE scores was found in the DrD group, but not in the AD[+DM] group (Fukasawa et al. 2014). Although the mechanisms that link elevated inflammatory markers and cognitive decline remain unclear, amelioration of systemic inflammation may be considered to be a treatment strategy for preventing or delaying cognitive decline in DrD.

8.5.2 Oxidative Stress Markers

We measured endogenous plasma antioxidants, such as albumin, unconjugated bilirubin, and uric acid, and urinary 8-hydroxy-2′-deoxyguanosine (8-OHdG) and 8-epiPGF2α (8-isoprostane) in 31 patients with AD without DM (AD[–DM]), 58

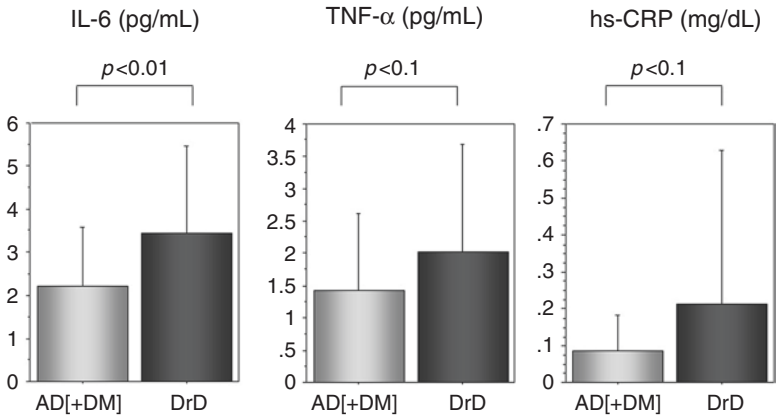

Fig. 8.5 Inflammatory cytokines. *AD[+DM]* AD with DM, *DrD* diabetes-related dementia

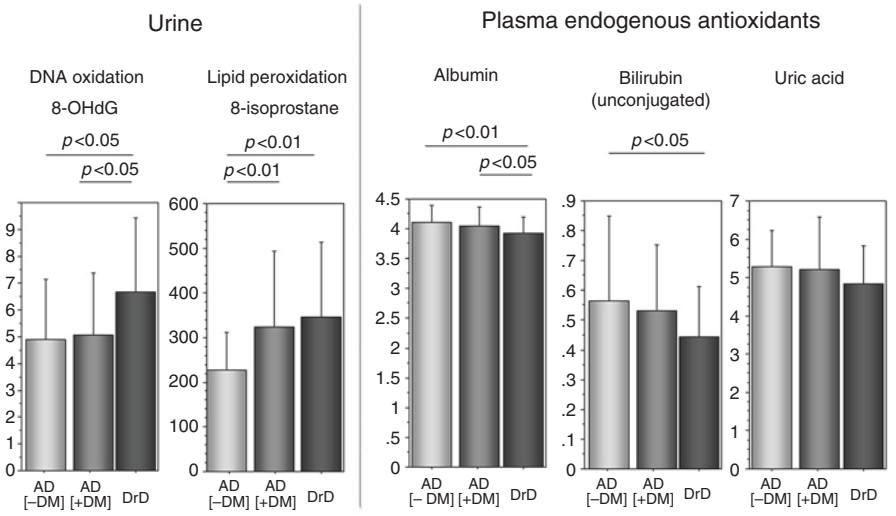

Fig. 8.6 Peripheral oxidative stress markers. *AD[–DM]* AD without DM, *AD[+DM]* AD with DM, *DrD* diabetes-related dementia

with AD with DM (AD[+DM]), and 35 with DrD. The DrD group showed a significant decrease in plasma levels of antioxidants, including albumin and unconjugated bilirubin, and a significant increase in urinary 8-OHdG and 8-isoprostane levels in contrast to the AD[−DM] and AD[+DM] groups (Fig. 8.6). Cognitive performance was negatively correlated with urinary 8-OHdG and 8-isoprostane levels in the DrD group (Hatanaka et al. 2016). These results strongly suggest that a decrease in

antioxidant levels and an increase in oxidative damage may be involved in the pathophysiology and cognitive decline associated with DrD.

8.5.3 *Advanced Glycation End Products (AGEs)*

We measured plasma levels of two AGE molecules, including N-ε-carboxymethyllysine (CML) and pentosidine, in 27 patients with AD without DM (AD[–DM]), 44 with AD with DM (AD[+DM]), and 20 with DrD. CML levels were significantly higher in both AD[+DM] and DrD groups than in the AD[–DM] group and, moreover, were significantly higher in the DrD group than in the AD[+DM] group. No significant differences in pentosidine levels were found among the groups (Fig. 8.7). There were no significant correlations between MMSE scores and AGE levels among the groups (Hirose et al. 2015). Since the DrD group showed high HbA_{1c} levels, AGE levels might be associated with diabetic complications. Further studies will be needed to determine the value of circulating AGE levels in the underlying pathophysiology of DrD.

These findings suggest that inflammation, oxidative stress, and AGEs are more associated with development of dementia and progression of cognitive decline in patients with DrD than in those with AD.

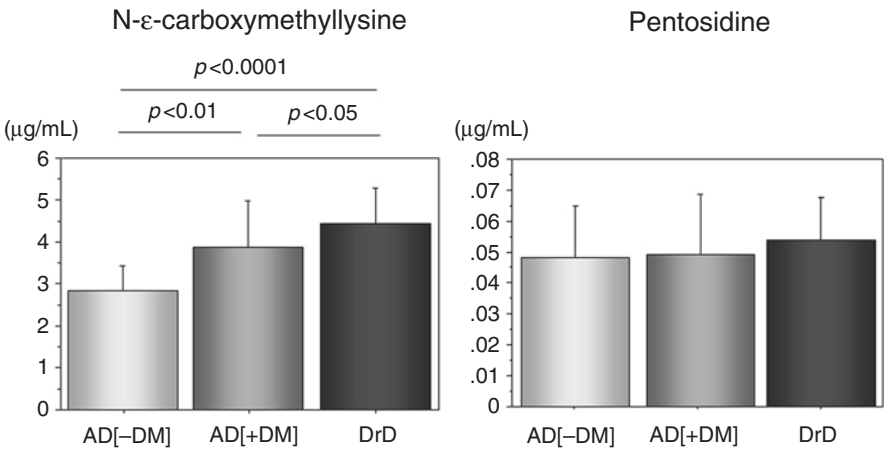

Fig. 8.7 Circulating advanced glycation end products. *AD[–DM]* AD without DM, *AD[+DM]* AD with DM, *DrD* diabetes-related dementia

8.6 Treatment of Diabetes-Related Dementia

Since hyperglycemia, hypoglycemia, and glycemic variability are all likely associated with cognitive impairment in patients with DrD, glycemic control is the most important treatment approach. These individuals have been often misdiagnosed as having AD and treated with cholinesterase inhibitors. However, indeed, some domains of cognitive profile, including attention, executive function, and speed of mental processing determined by the Trail Making Test Parts A and B and the Digit Symbol Substitution Test, can improve with control of blood glucose after treatment with oral antidiabetic medications or insulin. Therefore, DrD could be considered as a controllable or modifiable dementia.

Insulin resistance and peripheral hyperinsulinemia have been known to promote neurodegeneration. Therefore, correcting insulin dysregulation may offer a novel strategy for treatment. Some clinical trials of thiazolidinediones, such as rosiglitazone and pioglitazone, agonists of the nuclear receptor peroxisome proliferator-activated receptor-γ (PPAR-γ), showed some therapeutic relief for AD by lowering peripheral insulin and enhancing insulin sensitivity (Watson et al. 2005; Risner et al. 2006; Sato et al. 2011). In addition, PPAR-γ agonists have been shown to inhibit inflammatory gene expression, alter Aβ homeostasis, and exhibit neuroprotective effects. As shown in Fig. 8.8, we also found that PPAR-γ agonist pioglitazone treatment exhibited improvements in cognition and rCBF in patients with mild AD that had DM (Sato et al. 2011). These findings are consistent with a recent study showing that long-term use of pioglitazone is associated with a reduced dementia risk in a prospective cohort study of 145,928 individuals (Heneka et al. 2015). In addition, intranasal insulin therapy has been shown to improve cognition, function, and cerebral glucose metabolism for individuals with amnestic mild cog-

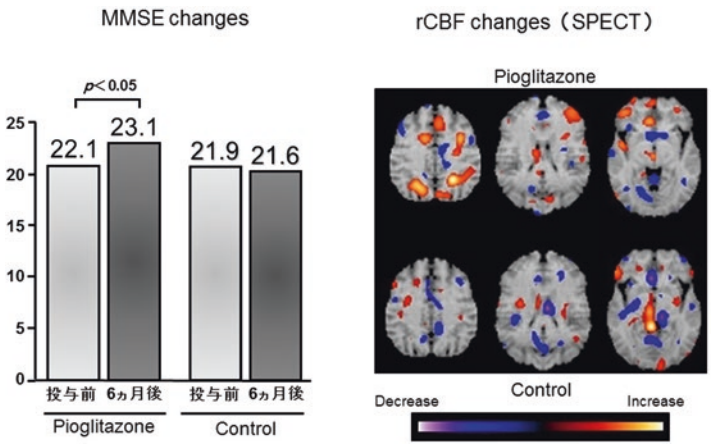

Fig. 8.8 Effects of pioglitazone on cognition and rCBF

nitive impairment or AD (Craft et al. 2012). These treatments might also be effective for patients with DrD.

As mentioned previously, inflammation, oxidative stress, and AGEs are involved in the pathophysiology of patients with DrD. Since these associations with cognitive decline are greater in DrD than in AD, intervention for inflammation, oxidative stress, and AGEs could be considered as appropriate therapy for, and prevention of, DrD.

8.7 Care of Diabetes-Related Dementia

Recent studies have shown that DM and insulin resistance appear to be associated with frailty, which is characterized by decreased reserve in multiple physiologic systems (Blaum et al. 2009; Kalyani et al. 2012). We investigated whether DrD is associated with greater prevalence of frailty status. According to the criteria from a report by Fried et al. (2001), the frequency of frailty was 14% in the AD[–DM] group (n = 56), 21% in the AD[+DM] group (n = 29), and 50% in the DrD group (n = 22) (Fig. 8.9). There was a significant difference in the frequency of frailty between the DrD group and the AD[–DM] group. Among the components of frailty, the frequency of low physical activity, weakness, and slowness was significantly higher in the DrD group than in the AD[–DM] group (Hirose et al. 2016). Frailty is associated with a greater risk for adverse health outcomes, including falls,

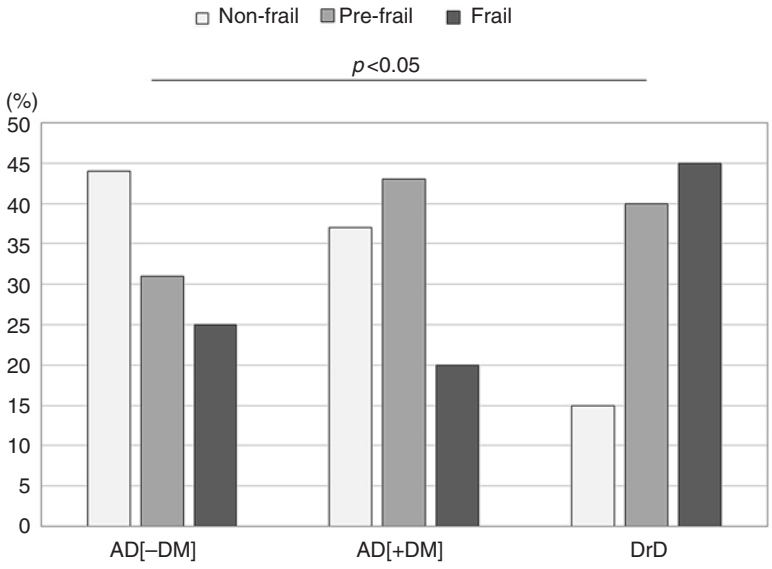

Fig. 8.9 Frequency of frailty, prefrailty, and non-frailty. *AD[–DM]* AD without DM, *AD[+DM]* AD with DM, *DrD* diabetes-related dementia

disability, institutionalization, and death. There is evidence for an association between frailty and cognitive impairment (Robertson et al. 2013). Cognition and frailty interact within a cycle of decline associated with DrD.

Some of the above components of frailty are associated with sarcopenia (age-related loss of muscle mass) or dynapenia (age-related loss of muscle strength) (Manini and Clark 2012). We evaluated whether DrD is associated with sarcopenia or dynapenia. We measured grip strength, gait speed, and skeletal muscle mass index (measured by electrical impedance analysis) in the AD[–DM] group (n = 79), AD[+DM] group (n = 41), and DrD group (n = 25). In women, the DrD group showed significantly lower grip strength and lower gait speed than the AD[–DM] and AD[+DM] groups. However, no significant differences in skeletal muscle mass index were found among the groups. Although no significant differences in the prevalence of sarcopenia, according to the consensus of the Asian Working Group for Sarcopenia criteria (Chen et al. 2014), were found among the groups, the prevalence of dynapenia defined as low handgrip strength (<26 kg for men and <18 kg for women) was significantly higher in the DrD group than in the AD[–DM] group (Hirose et al. 2017). Our results show that muscle strength and quality, but not muscle mass, decreased in female patients with DrD.

These characteristics may contribute to the development of physical disability in subjects with DrD. Muscle strength, but not muscle mass, is independently associated with poorer physical function (Visser et al. 2000). Therefore, geriatric interventions, including nutritional, hormonal, pharmacological, and exercise therapies, are necessary to improve clinical outcomes for frail or dynapenic patients with DrD.

8.8 Conclusion

Diabetes-related dementia (DrD) is apparently different from AD, VaD, and other types of dementia in terms of clinical features, clinical course, underlying pathophysiology, treatment, and care. DrD can be considered as a “controllable” or “modifiable” dementia. The identification of DrD, as distinct from other types of dementia, may be necessary for considering appropriate therapy and prevention in clinical practice.

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Chapter 9
Tortuous Paths of Insulin Signaling and Mitochondria in Alzheimer's Disease

Cristina Carvalho, Susana M. Cardoso, Sónia C. Correia, and Paula I. Moreira

Abstract Due to the exponential growth of aging population worldwide, neurodegenerative diseases became a major public health concern. Among them, Alzheimer's disease (AD) prevails as the most common in the elderly, rendering it a research priority. After several decades considering the brain as an insulin-insensitive organ, recent advances proved a central role for this hormone in learning and memory processes and showed that AD shares a high number of features with systemic conditions characterized by insulin resistance. Mitochondrial dysfunction has also been widely demonstrated to play a major role in AD development supporting the idea that this neurodegenerative disease is characterized by a pronounced metabolic dysregulation. This chapter is intended to discuss evidence demonstrating the key role of insulin signaling and mitochondrial anomalies in AD.

Keywords Alzheimer's disease · Brain · Insulin signaling · Mitochondria

9.1 Introduction

The improvement in public health and medical care is responsible for an increase in lifespan, which is accompanied by a parallel increase in age-related diseases, including neurodegenerative diseases (e.g., Alzheimer's disease, AD), particularly in developed countries (Niccoli and Partridge 2012; Jin et al. 2015). A panoply of events can underlie the development of neurodegenerative diseases; among them insulin

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signaling alterations and mitochondrial dysfunction are widely described as having pivotal roles in their development (Carvalho et al. 2012; Sebastiao et al. 2014).

For decades insulin was considered just a peripheral hormone responsible for the regulation of glucose. Initially, it was widely accepted that the brain was an insulin-insensitive organ and that insulin could not cross the blood-brain barrier (BBB) (Elgee et al. 1954; Haugaard et al. 1954). However, subsequent studies (Baura et al. 1993; Schwartz et al. 1991), using exogenous or radioactively labeled insulin, confirmed that insulin crosses the BBB by a saturable mechanism. Moreover, it was described that insulin is produced locally in the brain by insulin gene transcription (Devaskar et al. 1993; Deltouret al. 1993; Molnar et al. 2014). Afterward, the discovery of insulin and insulin-like growth factor receptors in the brain (Havrankova et al. 1979; Baskin et al. 1986; Unger et al. 1989) revolutionized the field, and nowadays several unique, non-metabolic functions are attributed to this hormone in the central nervous system (CNS). Indeed, besides the regulation of glucose transport to the brain through the glucose transporter 4 (Glut4), a key regulator of whole-body glucose homeostasis (Huang and Czech 2007), also a role for insulin was found in neuronal survival (Valenciano et al. 2006), synaptic and dendritic plasticity (Skeberdis et al. 2001; Chiu et al. 2008), learning and memory (Dou et al. 2005), and neuronal circuit formation (Chiu et al. 2008). Moreover, insulin regulates the exocytose of Glut4 from intracellular compartments, where it is retained under basal conditions, to neuronal plasma membrane (Grillo et al. 2009). This mechanism allows a rapid response to increases in neuronal activity and, consequently, increases in energy demand (e.g., learning processes), increasing glucose uptake and utilization (Thong et al. 2005). It is known that there are two main insulin-driven pathways in the brain, the phosphoinositide 3-kinase (PI3)/protein kinase B (Akt) and Ras/mitogen-activated kinase (MAPK) cascades (Niswender et al. 2003). These pathways are responsible for the activation of multiple parallel pathways, for example, PI3/AKT activates the mechanistic target of rapamycin complex 1 (mTORC1), glycogen synthase kinase 3 β (GSK3 β) pathways, and forkhead box (FoxO) family of transcription factors (Fernandez and Torres-Aleman 2012). Among other things, these downstream pathways mediate synaptic plasticity (Stoica et al. 2011), regulate autophagy (Son et al. 2012), and modulate neuronal functioning through regulation of neural progenitor cell proliferation, neuronal polarity, and neuroplasticity (Salcedo-Tello et al. 2011). A role for insulin in tau phosphorylation, energy homeostasis, and leptin sensitivity, as well as locomotor activity, has also been described (Ren et al. 2013; Kim et al. 2012). The activation of MAPK cascade has a pivotal role in cell proliferation, differentiation, gene expression, cytoskeletal reorganization, and normal function and survival of neuronal cells (Adams and Sweatt 2002). Insulin also has a central role in neuromodulatory actions through the regulation of N-methyl-D-aspartate (NMDA), alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), and type A gamma-aminobutyric acid (GABA) receptor transmission (Christie et al. 1999) and their membrane recruitment into excitatory synapses (Skeberdis et al. 2001) influencing the development of long-term potentiation in the hippocampus (van der Heide et al. 2005; Huang et al. 2004; Wang and

Linden 2000), memory consolidation and flexibility (Ge et al. 2010), and protein synthesis in synapses (Wan et al. 1997).

Moreover, since the brain is unable to store high amounts of energy due to the relatively small glycogen levels present in this organ (Obel et al. 2012), it is extremely dependent on constant energy supply to maintain its normal functioning. This energy can be provided by two different sources, oxidative phosphorylation or glycolysis, with mitochondria representing the main brain cells "powerhouses" and providing adenosine triphosphate (ATP) by oxidative phosphorylation (OXPHOS).

Mitochondria are extremely dynamic organelles and are associated with the normal functioning of several vital processes besides energy supply, such as the generation and detoxification of reactive oxygen species (ROS), regulation of cellular calcium homeostasis, substrate metabolism (e.g., glucose and fatty acids), and apoptosis (Koliaki and Roden 2016; Fillmore and Lopaschuk 2013). Although the literature reveals thousands of studies discussing mitochondrial function, its regulation seems complex and still not fully understood. The regulation of mitochondrial function involves rapid adaptations to alterations in metabolic conditions, which include dynamic shape changes through tightly regulated processes of fusion and fission, mitophagy, mitochondrial biogenesis, and active traffic between cell compartments (Montgomery and Turner 2015; Picard and McEwen 2014). The brain is highly vulnerable to mitochondrial defects with neurons being extremely sensitive to bioenergetics fluctuations (Picard and McEwen 2014), due to their high energy demand to maintain presynaptic vesicle recycling and recurrent generation of action potentials and postsynaptic potentials (Alle et al. 2009; Attwell and Laughlin 2001). Thus, brain aging is highly associated with mitochondrial alterations. According to the mitochondrial theory of aging, during normal aging the accumulation of mitochondrial DNA (mtDNA) mutations may lead to respiratory chain dysfunction, affecting particularly mitochondrial complexes I and IV, which may induce the activation of processes such as mitochondrial fusion, fission, and biogenesis. The activation of those processes is an attempt to increase the number of healthy mitochondria as a compensatory upregulation of mitochondrial mass, in order to counteract the decrease in respiratory chain function resulting from damaged mitochondria (Swerdlow 2011a). Also, the involvement of mitochondria in the process of neurogenesis starts to be explored, with evidence showing that changes in mitochondrial function are responsible for the age-associated decline in hippocampal neurogenesis, alterations that can be reversed with the pharmacological improvement of mitochondria (Beckervordersandforth et al. 2017). Consequently, the involvement of mitochondrial dysfunction in several neurodegenerative conditions is presently widely accepted.

So, it is expectable that alterations in both mitochondria and insulin underlie the development of neurodegenerative conditions, namely, AD. Indeed, AD is already described as the most prevalent form of metabolic neurodegenerative disease in old ages (Scheltens et al. 2016). Presently, there is a lack of effective diagnostic methods for early detection and preventive and/or therapeutic strategies to fight AD development due to the complexity of its pathophysiology. Neuroimaging studies reveal a state of hypometabolism in AD brains (Demetrius and Driver 2015;

Newington et al. 2013) and in cellular energy metabolism (Drachman 2006) as well as a decline in mitochondrial function compared with aged-matched controls in animal models of the disease (Carvalho et al. 2012, 2015). Additionally, the presence of alterations in cerebral glucose and insulin signaling was also described in AD (Chen and Zhong 2013), and most interesting, generally those changes begin decades before the clinical symptoms (Chen and Zhong 2013; Cunnane et al. 2011).

Thus, it is vital to understand the contribution of mitochondrial and insulin signaling anomalies in AD development to help design more effective strategies to fight this disease.

9.2 Mitochondrial Dysfunction in Alzheimer's Disease: When the Fuel Machine Fails in the Metabolic Highway

As previously referred, neurons are highly dependent on energy supply; thus, even slight changes in the process of ATP generation (through glycolytic and/or mitochondrial pathways) can interfere with their viability. Increased oxidative stress levels driven by mitochondrial dysfunction, associated with a drop in ATP production, will trigger neuronal degeneration and death (Facecchia et al. 2011). Since mitochondria are neurons' main power source, even slight alterations in their function can result in vital perturbations.

Data from the literature reveal that defects in mitochondrial respiratory chain complexes I, IV, and V, especially in the hippocampus and cortex (Liang et al. 2008; Manczak et al. 2004), are one of the most commonly described alterations in AD. Mastroeni et al. (2017) observed a downregulation of the mitochondrial complexes I–V in AD, particularly those encoded in the nucleus. More recently, Lunnon et al. (2017) also showed a decrease in the expression of nuclear-encoded mitochondrial genes in deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) samples from the whole blood of mild cognitive impairment (MCI) or AD patients relative to controls, with increased expression of some mitochondrial-encoded genes, a fact that was associated with a potential selective block in their translation. However, the authors did not observe any alterations in mitochondrial complex II, the only mitochondrial complex entirely driven by nuclear-encoded genes, in both MCI and AD blood samples (Lunnon et al. 2017). Moreover, alterations in gene expression of oxidative phosphorylation system (OXPHOS) are usually associated with an increased susceptibility of neurons to amyloid β (Aβ)-induced toxicity (Vlassenko and Raichle 2015). Indeed, studies performed in cells depleted of mtDNA, with subsequent dysfunctional mitochondrial respiratory chain complexes, showed insensitivity of those cells to Aβ toxic effects, a process that seems to be driven by a functional mitochondrial respiratory chain (Cardoso et al. 2001). Further studies revealed that the mechanism of Aβ toxicity relies on an Aβ-induced mitochondrial complex I defect with consequent increase in ROS production, which are responsible for an impairment in mitochondrial complex IV that is particularly vulnerable in

AD, possible through a process of membranes lipid peroxidation (Bobba et al. 2013; Atlante et al. 2017). Moreover, the literature extensively describes alterations in the activity of tricarboxylic acid (TCA) enzymes in AD brains (Fattoretti et al. 2010; Moreira et al. 2010a, b) that also contribute to the mitochondrial anomalies that characterize this disease. Alterations in pyruvate and alpha-ketoglutarate dehydrogenases were observed in postmortem samples of AD brains (Brooks et al. 2007; Casley et al. 2002; Liang et al. 2008). In fact, both enzymes are rate limiting in TCA cycle (Murray et al. 2011), with consequent alterations in the production of reducing equivalents, such as the reduced form of nicotinamide adenine dinucleotide (NADH), which enter mitochondrial electron transport chain helping in the production of ATP (Bubber et al. 2011). Furthermore, it was previously shown the existence of altered mitochondrial respiration and decreased mitochondrial membrane potential ($\Delta\Psi m$) (Carvalho et al. 2012) as well as an increased prevalence of swollen mitochondria with misshapen cristae (Hirai et al. 2001; Baloyannis et al. 2004) (Fig. 9.1).

More recently, it emerged the hypothesis of a "numbness" state for mitochondria in AD (Bobba et al. 2015). This "numbness" is described as a quiescent-active state of mitochondria as an unsuccessful effort of cells to avoid the imminent death, characterized by a reduction in various mitochondrial enzymes involved in cellular respiration, which has been observed in AD brains (Brooks et al. 2007; Liang et al.

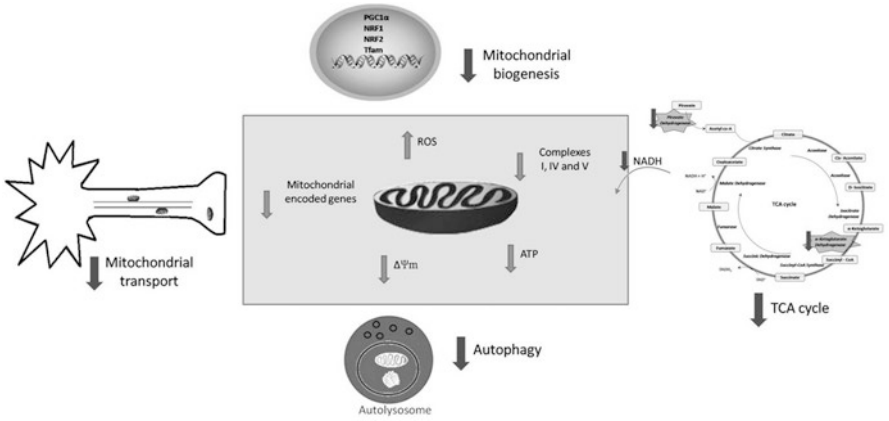

Fig. 9.1 *Mitochondrial anomalies in Alzheimer's disease*. A decrease in mitochondrial complexes I, IV, and V, ATP levels and $\Delta\Psi m$, and an increase in ROS production occur in AD. Furthermore, a decreased expression in mitochondrial-encoded genes has been reported. Alterations in TCA cycle enzymes, mainly in the two limiting enzymes pyruvate dehydrogenase and α-ketoglutarate dehydrogenase, can interfere with mitochondrial respiratory chain by the decrease in the levels of reducing equivalents, such as NADH, necessary for the correct activity of mitochondrial electron transport chain. Alterations in mitochondrial biogenesis, autophagy, and axonal transport have also been described in AD. *ATP* adenosine triphosphate, *NRF* nuclear respiratory factor, *PGC1-α* peroxisome proliferator-activated receptor gamma coactivator 1-α, *ROS* reactive oxygen species, *TCA* tricarboxylic acid cycle, *Tfam* mitochondrial transcription factor A, $\Delta\Psi m$ mitochondrial membrane potential

2008). This hypothesis postulates that the "awakening" of mitochondria can exacerbate their impairment and, ultimately, cell death (Atlante et al. 2017).

Moreover, alterations in the processes of autophagy and mitochondrial biogenesis seem to be involved in AD development (Carvalho et al. 2015). Indeed, in the last few years, alterations in mitochondrial dynamics, biogenesis, and autophagy have been the target of increased scrutiny in AD research field. Recent studies report significant modifications in the expression of roughly all mitochondrial fission and fusion proteins including dynamin-like protein 1 (DLP1), optic atrophy protein 1 (OPA1), mitofusins (Mfn) 1 and 2, and mitochondrial fission protein 1 (Fis1) in postmortem AD brains (Wang et al. 2009a, 2012; Manczak et al. 2011). It has been hypothesized that altered mitochondrial fission and fusion may negatively impact mitochondrial bioenergetics, calcium homeostasis, and mtDNA integrity (Su et al. 2010; Zhu et al. 2013). Since mitochondrial fission has a crucial role in the assembly of electron transport complexes, we can assume that fission changes will lead to increased ROS production (Wang et al. 2014). Moreover, uncontrolled fission also leads to a rapid accumulation of mtDNA mutations, since mitochondrial fusion allows the replacement of mitochondrial content including mtDNA (Chen et al. 2010; Hroudova et al. 2014). Highlighting the fact that when not properly removed, dysfunctional mitochondria become a major source of ROS (Lauri et al. 2014), and also unnecessary and unregulated autophagy can induce mitochondrial permeabilization, caspases activation, and apoptosis, through the leakage of certain enzymes from lysosomes/autolysosomes, such as cathepsins and other hydrolases (Kim et al. 2007). The removal of damaged mitochondria generally requires a compensation through mitochondrial biogenesis (Cherra and Chu 2008). However, a decrease in the protein levels of peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) and nuclear respiratory factor (NRF) 1 and NRF2, major regulators in mitochondrial biogenesis, was observed in hippocampal tissue from AD patients and amyloid precursor protein (APP) mice (Knott et al. 2008), M17 cells expressing the APP Swedish mutation (Sheng et al. 2012), and AD and MCI cybrid cell lines (Qin et al. 2009; Swerdlow 2012). The protein levels of mitochondrial transcription factor A (Tfam), another co-activator of PGC-1α, were found to be increased in AD and MCI cybrids, although no changes in its mRNA levels were observed (Silva et al. 2013).

Overall, an imbalance between mitochondrial biogenesis and mitophagy seems to occur in AD decreasing the healthy pool of mitochondria (Swerdlow 2011b). In AD, the hypothesis of impaired axonal transport has been widely accepted as having a major role in AD pathogenesis (Stokin and Goldstein 2006; Wang et al. 2009b). In vitro studies showed that hippocampal neurons treated with Aβ present impaired mitochondrial transport, a reduction of approximately 20% (Rui et al. 2006). Corroborating those results, studies performed in a mouse model of AD showed decreased mitochondrial anterograde and retrograde movements (Calkins et al. 2011; Trushina et al. 2012). Additionally, in fibroblasts from sporadic AD patients, an accumulation of elongated mitochondria in perinuclear areas was observed (Wang et al. 2008), suggesting a decrease in mitochondrial transport. Mitochondrial fission/fusion alterations are also responsible for a modification in mitochondrial

distribution since an increase in mitochondrial diameter affects mitochondrial movement (Chen and Chan 2009; Wang et al. 2009a). Alterations in mitochondrial distribution within neurons, as a result of defective axonal transport of mitochondria, are involved in synaptic dysfunction and loss observed in AD (Sheng and Cai 2012).

9.3 Brain Insulin Signaling Anomalies and Alzheimer's Disease

A close relationship among insulin resistance and AD pathology do exist (Sartorius et al. 2015; Correia et al. 2011). People suffering from peripheral insulin resistance, usually associated with type 2 diabetes (T2D), are more prone to develop AD (Rasgon et al. 2011; Sims-Robinson et al. 2010). It has been also demonstrated that brain insulin resistance develops independently of the periphery (Moloney et al. 2010; Talbot and Wang 2014). Nevertheless, the mechanisms underlying insulin signaling dysfunction in AD remain under intense debate.

During the last decade, evidence emerged from animal (Chua et al. 2012; Keeney et al. 2015) and clinical (Talbot et al. 2012) studies showing that dysfunctions in brain insulin signaling could be an early event in AD progression (Mullins et al. 2017). In fact, reduced insulin receptor expression; deficits in insulin-like growth factor 1 (IGF-1) signaling (Baglietto-Vargas et al. 2016; Talbot et al. 2012; Rivera et al. 2005); aberrant and sustained activation of PI3K/Akt/mTOR signaling with concomitant alterations in multiple pathways, including glucose metabolism and energy production; and altered protein synthesis/clearance have been observed in AD (Di Domenico et al. 2017; O'Neill 2013; Perluigi et al. 2015; Tramutola et al. 2015). Interestingly, brain insulin alterations seem to correlate with alterations in verbal memory found in patients with chronic hyperinsulinemia even in the absence of hyperglycemia, factors commonly associated with T2D (Fava et al. 2017; Peila et al. 2002).

Furthermore, it was observed an increase in phosphorylated insulin receptor substrate (ρIRS1) in brain areas associated with cognitive performance (Mullins et al. 2017), which are more prone to insulin resistance. For instance, an increase in IRS1 phosphorylation at serine 636/639 and 616 in the hippocampus and cortex of AD patients was observed (Talbot et al. 2012), resulting in a decrease in the activation of IRS1-dependent downstream pathways activation. Indeed, the conformational changes that IRS1 suffers are responsible for a decrease in its interaction with PI3K, resulting in a decreased AKT activation through phosphorylation that ultimately results in a blockage of glucose cellular uptake (Moloney et al. 2010).

Recently, the attribution of "AD biomarkers" title to two new phosphorylation sites of IRS1, by Kapogiannis and coworkers (2015), brought new insights to the field. In their study, it was found that pSer312-IRS1 and p-panTyr-IRS1 can effectively reflect the insulin resistance state present in AD brains, although with opposite ways of action. In fact, while the pSer312-IRS1 residue seems to stimulate the

disengagement of IRS1 inducing its degradation (Pederson et al. 2001), the p-panTyr-IRS1 residue seems to promote insulin-stimulated responses (Gual et al. 2005). Later, the authors confirmed the use of those residues as biomarkers, by showing differences in peripheral blood exosomes where pSer312-IRS1 levels were increased, while p-panTyr-IRS1 levels were decreased in AD patients, when compared with cognitively normal control subjects. Those changes seem to be correlated with brain atrophy supporting its protective and injurious role, respectively, in AD pathogenesis (Mullins et al. 2017).

As previously referred, alterations in insulin action in the brain can directly interfere with downstream insulin receptor (IR) and IGF1 receptor (IGF1R) pathways decreasing glucose proper usage by cells. However, other mechanisms can reinforce the connection between insulin signaling alterations and AD. Indeed, the decrease in PI3K pathway activation is responsible for alterations in GSK3β phosphorylation. In 1997, Hong and coworkers showed in human neuronal cultures that inhibition of GSK3β by insulin and IGF1 was responsible for a decrease in tau phosphorylation, a process that leads to its binding to microtubules (Hong and Lee 1997). Thus, a decrease in GSK3β results in an increase in phosphorylated tau levels, one AD pathological hallmark. As a matter of fact, the role of GSK3β in AD pathology reached such a high level of significance that, in 2008, it was proposed the "GSK3β hypothesis for AD" postulating that increased activation of GSK3β underlies memory impairment, tau hyperphosphorylation, increased Aβ production, and local plaque-associated microglial-mediated inflammatory responses (Hooper et al. 2008). This hypothesis was supported by the increased number of studies showing an increased expression and/or activation of GSK3β in the brain of AD patients (Blalock et al. 2004) and in circulating peripheral lymphocytes in both AD and MCI patients (Hye et al. 2005) (Fig. 9.2).

Insulin also participates in Aβ metabolism through a PI3K-dependent mechanism in which PI3K modulates the vesicular trafficking responsible either for the transport of APP into secretory compartments or trafficking of "secretase"-containing vesicles toward APP-containing membrane domains (Solano et al. 2000). For instance, an increase in insulin transport to the brain, through BBB, seems to occur in transgenic mice overexpressing APP (Poduslo et al. 2001), and brain insulin resistance seems to be increased in areas associated with cognitive performance, such as the hippocampus (Talbot et al. 2012). Additionally, an increase in APP processing seems to occur through increased expression of β-secretase 1 (BACE-1), leading to the overproduction, accumulation, and deposition of Aβ in AD models (Crespo et al. 2017; Jimenez-Palomares et al. 2012; Baglietto-Vargas et al. 2016). Additionally, alterations in Aβ degradation by insulin-degrading enzyme (IDE), the main soluble Aβ-degrading enzyme (Gasparini et al. 2001; Pandini et al. 2013; Baglietto-Vargas et al. 2016), also occur in AD probably as a result of the direct competition between insulin and Aβ for IDE (Qiu et al. 1998). Indeed, an increase in brain insulin levels leads to an increase in Aβ, as observed in cerebrospinal fluid (CSF) of normal older adults (Banks et al. 2012; Watson et al. 2003) and AD patients (Kandimalla et al. 2016). Moreover, defects in the clearance of Aβ may also be directly related with insulin role in the regulation of autophagic process through

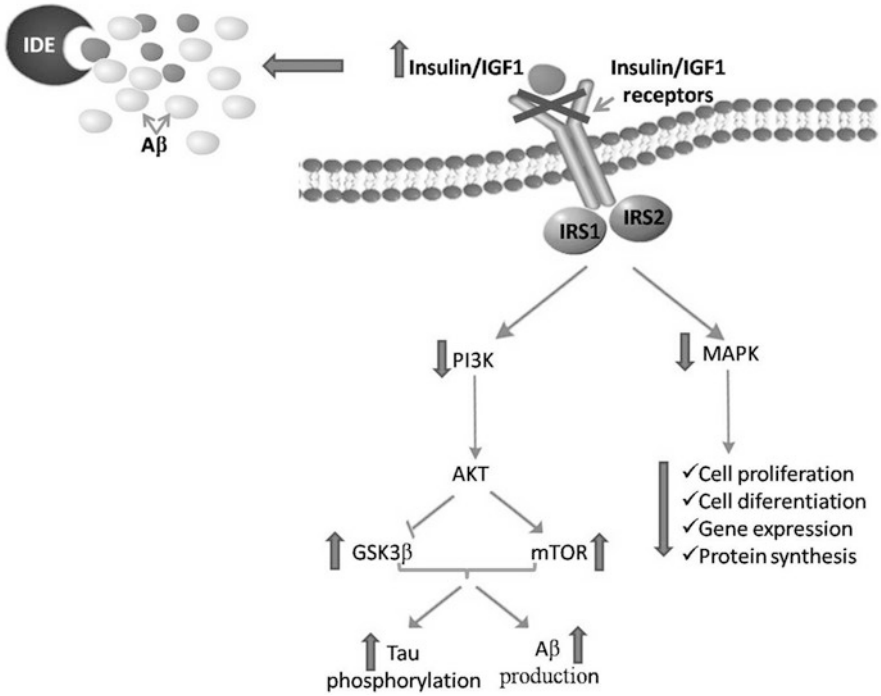

Fig. 9.2 *Insulin signaling alterations in Alzheimer's disease*. The existence of an insulin resistance state in AD is widely accepted. A decrease in PI3K/AKT/mTOR pathway activation and an increase in GSK3β activation resulting in increased levels of phosphorylated tau an Aβ production have been described. Furthermore, a decrease in MAPK cascade also occurs, decreasing cell proliferation, differentiation, cell survival, gene expression, and protein synthesis. Because insulin competes with Aβ peptide for IDE binding, a main enzyme responsible for Aβ degradation, increased insulin levels cause Aβ accumulation. *Aβ* amyloid β peptide, *AKT* protein kinase B, *GSK3β* glycogen synthase kinase 3β, *IDE* insulin-degrading enzyme, *IGF1* insulin growth factor, *IRS* insulin receptor substrate, *MAPK* mitogen-activated protein kinase, *mTOR* mechanistic target of rapamycin, *PI3K* phosphoinositide 3-kinase

mTOR (Di Domenico et al. 2017). Indeed, insulin is responsible for the activation of AKT through PI3K pathway. In insulin resistance conditions, a decrease in PI3K pathway activation occurs, being responsible for increases in mTOR phosphorylation levels and, consequently, a decrease in autophagy (Carvalho et al. 2015). Consistently, an overexpression of phosphorylated mTOR levels has been observed in AD brains (Oddo 2012), and its overexpression or suppression is responsible for an aggravation or relief, respectively, of AD-like pathology and behavioral deficits in experimental mouse models of AD (Caccamo et al. 2010, 2013; Norambuena et al. 2017). Besides its role in Aβ clearance, also a role for mTOR in tau phosphorylation is known. When mTOR is activated through Ser2481 phosphorylation, along with some of its downstream targets, an increase of tau protein translation occurs (Li et al. 2005) together with its hyperphosphorylation through the coordination of GSK3β and protein phosphatase 2A activities (Meske et al. 2008).

Presently, the use of intranasal insulin as a therapeutic strategy in AD is under phase II and III of clinical trials, showing promising results in decreasing AD-associated cognitive decline (Reger et al. 2006). Furthermore, alterations in Aβ levels in plasma seem to occur in MCI and AD subjects under intranasal insulin therapy together with an improvement in verbal memory in memory-impaired adults (Craft et al. 2012). However, it is relevant to consider new long-term studies in order to evaluate the possible side effects of this treatment since, until know, only a study by Bell and Fadool (2017) was able to show that recurrent intranasal insulin therapy in mice has no undesirable effects on olfactory threshold, discrimination, or odor-reversal learning.

9.4 Mitochondrial and Insulin Dysfunction in AD: What Comes First?

The existence of a close relation between mitochondrial dysfunction and insulin signaling alterations in the development of neurodegenerative diseases is generally accepted. However, it is not known if changes in mitochondrial function are a cause or consequence of insulin signaling alterations, with some genetic manipulations and interventional approaches being used in order to unveil this issue (Goodpaster 2013) (Fig. 9.3).

The idea that mitochondrial dysfunction can underlie the development of insulin resistance, including in AD, has a high number of followers. In fact, studies in both wild-type and triple transgenic mice for AD (3xTg-AD) support this theory (Barone et al. 2016) showing that increased levels of oxidative stress precede the molecular events in the basis of brain insulin resistance, with reduction of both insulin secretion, by pancreatic β-cells, and sensitivity (Gerbitz et al. 1996), during both normal aging and AD (Di Domenico et al. 2017; Barone et al. 2016). Studies carried out in both mice and human samples showed decreased expression of the genes encoding subunits constituting respiratory enzyme complexes (Mootha et al. 2003; Kelley et al. 2002), as well as genes involved in mitochondrial biogenesis (Patti et al. 2003; Pagel-Langenickel et al. 2008), mutations or deletions of mtDNA (Maassen et al. 2006; Liang et al. 1997), and a decline in mitochondrial bioenergetics capacity (Scheuermann-Freestone et al. 2003; Mogensen et al. 2007; Petersen et al. 2004). Peng and coworkers were able to show that neurons under high-glucose conditions develop mitochondrial dysfunction responsible for alterations in 5′ AMP-activated protein kinase (AMPK)/AKT activation causing an insulin resistance state (Peng et al. 2016). Resveratrol, an activator of metabolic sensors that ultimately lead to PGC-1α activation with proved efficacy in the recovery of mitochondrial function (Bitterman and Chung 2015; Burkewitz et al. 2014; Liu et al. 2016), stimulates AMPK/AKT signaling improving insulin sensitivity (Peng et al. 2016). Moreover, it was recently described, in the skeletal muscle and liver, that mitochondrial dysfunction and ROS overproduction were able to activate c-Jun N-terminal kinase (JNK) resulting in an increase of insulin resistance (Sebastian et al. 2012). A similar

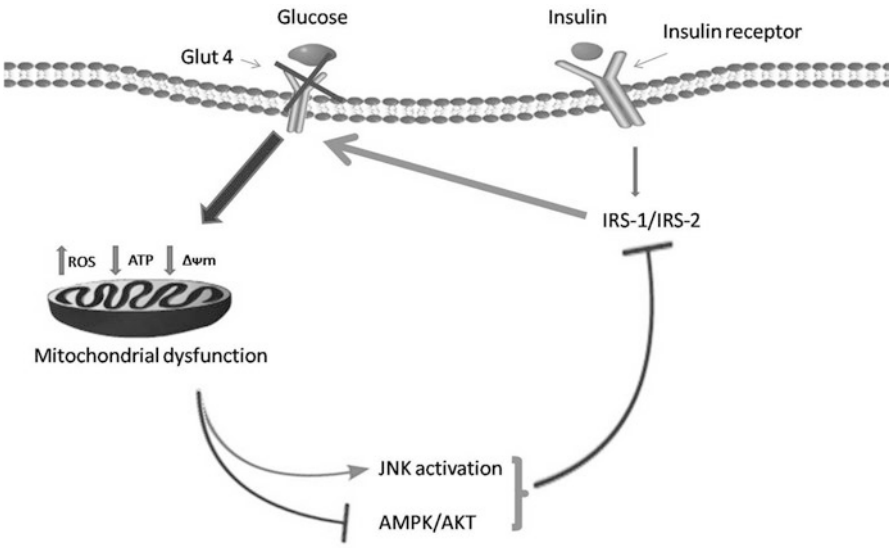

Fig. 9.3 *Mitochondria and insulin signaling interaction in Alzheimer's disease*. The most accepted theory involving mitochondria and insulin dysfunction hypothesizes that increased levels of oxidative stress precede the molecular events underlying brain insulin resistance, with mitochondrial dysfunction being responsible for alterations in AMPK/AKT activation. Moreover, a mitochondrial-driven activation of JNK seems to occur, resulting in an increase in insulin resistance (Sebastian et al. 2012). However, the close relationship between mitochondria and insulin signaling is a double-edged sword with insulin resistance leading to a decrease in mitochondrial function through a decrease in glucose uptake and energy production and an increase in ROS levels. *AMPK* 5′ adenosine monophosphate-activated protein kinase, *AKT* protein kinase B, *ATP* adenosine triphosphate, *Glut4* insulin-dependent glucose transporter 4, *IRS* insulin receptor substrate, *JNK* c-Jun N-terminal kinase, *ROS* reactive oxygen species, $\Delta\Psi m$ mitochondrial membrane potential

situation can occur in the brain since a close relationship between AD development and JNK activation has already been described (De Felice and Ferreira 2014; de la Monte 2012; Talbot et al. 2012; Bomfim et al. 2012).

However, insulin resistance can also be responsible for a decrease in mitochondrial function through a decrease in glucose uptake and consequent decrease in energy production and increase in ROS levels, crafting a vicious cycle (Di Domenico et al. 2017; de la Monte 2009; Neumann et al. 2008). Indeed, mitochondrial dysfunction occur in β-pancreatic cells from β-cell-specific insulin receptor knockout (βIRKO) mice, which is characterized by a decrease in ΔΨm and ATP levels (Liu et al. 2009b). Additionally, the deletion of insulin receptors in mice cardiomyocytes (CIRKO mice) induces mitochondrial respiratory deficits and reductions in TCA and fatty acid oxidation proteins in mitochondria, among them the catalytic subunits of pyruvate dehydrogenase impairing TCA flux (Boudina et al. 2009).

Furthermore, insulin levels and mitochondrial biogenesis seem to have opposite patterns. Indeed, it was described that prolonged exposure to insulin could induce changes in mtDNA, mitochondrial mass, and intracellular ATP content in hepato-

cytes through Akt activation (Liu et al. 2009a). Moreover long-term exposure to insulin seems responsible for the decrease in transcript levels of both NRF-1 and Tfam (Liu et al. 2009a). Furthermore, it has been previously showed that in vivo treatments with insulin in primary cultures of cardiomyocytes isolated from Sprague-Dawley rats and rat skeletal muscle L6 cell line were responsible for an increase in Opa-1 protein levels, promoted mitochondrial fusion, increased $\Delta\Psi m$, and elevated both intracellular ATP levels and oxygen consumption through the IRS-PI3K-Akt-mTOR signaling pathway (Parra et al. 2014). Insulin can also mediate mitochondrial biogenesis through mTOR-dependent regulation of PGC1-α, a master regulator of mitochondrial biogenesis responsible for the co-activation of several metabolically significant nuclear and nonnuclear receptor transcription factors such as NRF 1 and 2 (Finck and Kelly 2006; Hardie 2007; Schieke et al. 2006; Onyango et al. 2010). Likewise, studies showed that thiazolidinediones, clinically used to ameliorate insulin resistance in T2D, were responsible for the induction of mitochondrial biogenesis in human subcutaneous adipose tissue, human neuronal NT2 cells, and mouse brain (Ghosh et al. 2007; Strum et al. 2007; Bogacka et al. 2005) supporting the role of insulin in mitochondrial regulation.

Nevertheless, knowledge on how insulin affects mitochondrial function specifically in the brain is still scarce, and further studies are essential to unveil the cycle comprising mitochondrial function and insulin signaling in AD.

9.5 Conclusions

It is widely accepted that AD is an extremely complex metabolic disorder hindering the success of a cure. The literature shows that mitochondrial and insulin signaling anomalies play a major role in AD development. However, the answer for the "who comes first" remains under intensive debate. Although the bulk of the studies indicate mitochondrial dysfunction as a main causative agent, the existence of a feedback mechanism in which insulin can be responsible for mitochondrial anomalies makes it difficult to overcome obstacles in the quest for an effective treatment of the disease. Indeed, this could justify why clinical trials with promising mitochondrial and/or insulin directed drugs fail so often, due to the lack of knowledge about the interaction between different targets of this complex disease. Thus, it is of utmost importance to better understand how mitochondrial dysfunction and insulin resistance meet in AD, in order to identify new therapeutic strategies to counteract the development of this devastating disease.

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Chapter 10
Mammalian Target of Rapamycin at the Crossroad Between Alzheimer's Disease and Diabetes

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Abstract Accumulating evidence suggests that Alzheimer's disease may manifest as a metabolic disorder with pathology and/or dysfunction in numerous tissues. Adults with Alzheimer's disease suffer with significantly more comorbidities than demographically matched Medicare beneficiaries (Zhao et al, BMC Health Serv Res 8:108, 2008b). Reciprocally, comorbid health conditions increase the risk of developing Alzheimer's disease (Haaksma et al, PLoS One 12(5):e0177044, 2017). Type 2 diabetes mellitus is especially notable as the disease shares many overlapping pathologies observed in patients with Alzheimer's disease, including hyperglycemia, hyperinsulinemia, insulin resistance, glucose intolerance, dyslipidemia, inflammation, and cognitive dysfunction, as described in Chap. 8 of this book

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(Yoshitake et al, Neurology 45(6):1161–1168, 1995; Leibson et al, Am J Epidemiol 145(4):301–308, 1997; Ott et al, Neurology 53(9):1937–1942, 1999; Voisin et al, Rev Med Interne 24(Suppl 3):288s–291s, 2003; Janson et al. Diabetes 53(2):474–481, 2004; Ristow M, J Mol Med (Berl) 82(8):510–529, 2004; Whitmer et al, BMJ 330(7504):1360, 2005, Curr Alzheimer Res 4(2):103–109, 2007; Ohara et al, Neurology 77(12):1126–1134, 2011). Although nondiabetic older adults also experience age-related cognitive decline, diabetes is uniquely associated with a twofold increased risk of Alzheimer's disease, as described in Chap. 2 of this book (Yoshitake et al, Neurology 45(6):1161–1168, 1995; Leibson et al, Am J Epidemiol 145(4):301–308, 1997; Ott et al. Neurology 53(9):1937–1942, 1999; Ohara et al, Neurology 77(12):1126–1134, 2011). Good glycemic control has been shown to improve cognitive status (Cukierman-et al, Diabetes Care 32(2):221–226, 2009), and the use of insulin sensitizers is correlated with a lower rate of cognitive decline in older adults (Morris JK, Burns JM, Curr Neurol Neurosci Rep 12(5):520–527, 2012). At the molecular level, the mechanistic/mammalian target of rapamycin (mTOR) plays a key role in maintaining energy homeostasis. Nutrient availability and cellular stress information, both extracellular and intracellular, are integrated and transduced through mTOR signaling pathways. Aberrant regulation of mTOR occurs in the brains of patients with Alzheimer's disease and in numerous tissues of individuals with type 2 diabetes (Mannaa et al, J Mol Med (Berl) 91(10):1167–1175, 2013). Moreover, modulating mTOR activity with a pharmacological inhibitor, rapamycin, provides wide-ranging health benefits, including healthy life span extension in numerous model organisms (Vellai et al, Nature 426(6967):620, 2003; Jia et al, Development 131(16):3897–3906, 2004; Kapahi et al, Curr Biol 14(10):885–890, 2004; Kaeberlein et al, Science 310(5751):1193–1196, 2005; Powers et al, Genes Dev 20(2):174–184, 2006; Harrison et al, Nature 460(7253):392–395, 2009; Selman et al, Science 326(5949):140–144, 2009; Sharp ZD, Strong R, J Gerontol A Biol Sci Med Sci 65(6):580–589, 2010), which underscores its importance to overall organismal health and longevity. In this chapter, we discuss the physiological role of mTOR signaling and the consequences of mTOR dysregulation in the brain and peripheral tissues, with emphasis on its relevance to the development of Alzheimer's disease and link to type 2 diabetes.

10.1 Introduction to mTOR Signaling

mTOR is an evolutionarily conserved serine/threonine kinase, and member of the phosphoinositide-3-kinase (PI3K)-related kinases (PIKK) family; others include ATM, ATR, DNA-PK, and hSMG1. mTOR functions as the catalytic subunit of two independent multi-protein holoenzyme complexes, mTORC1 and mTORC2 (Fig. 10.1). Common to both core complexes are mTOR, mammalian lethal with Sec13 protein 8 (mLST8, also known as GβL), and both interact with DEP domain-containing mTOR-interacting protein (Deptor) and the Tel2/Tti1 complex. Furthermore, mLST8 is critical in promoting mTOR-mediated tumor progression

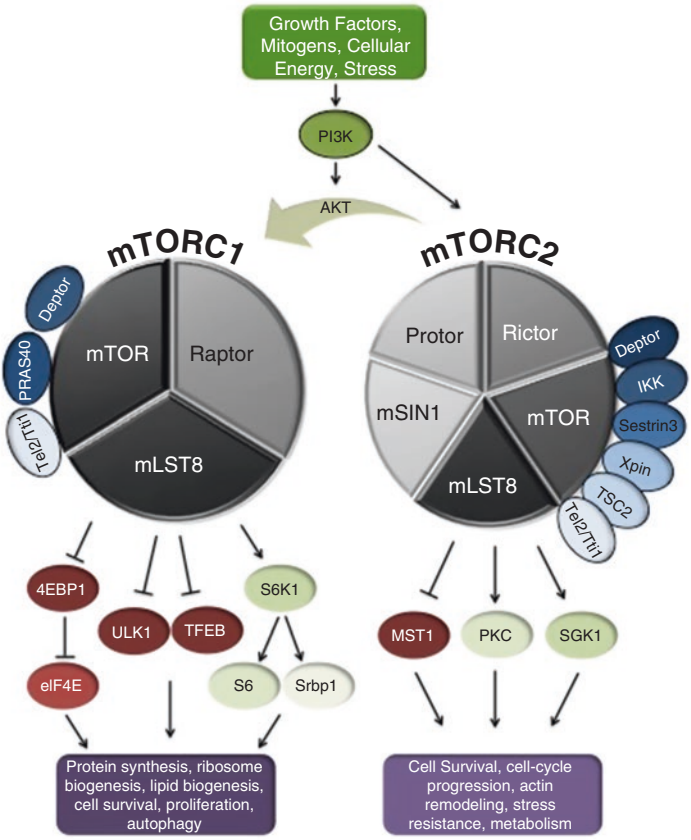

Fig. 10.1 mTOR complex proteins. Activation of both mTORC1 and mTORC2 occurs through growth factor and mitogen PI3K-dependent signaling. Active mTORC1 increases macromolecule biogenesis and suppress autophagy. Active mTORC2 promotes cell survival, proliferation, and cytoskeletal remodeling. AKT activates mTORC1 through PI3K signaling or downstream of mTORC2 activation and thus serves as a connecting node to these independent complexes. mTORC1 and mTORC2 share in common mTOR and mLST8 as core proteins and Tel2/Tti1 and Deptor as transient and/or nutrient-sensing regulatory proteins. Unique to mTORC1 is the scaffold protein Raptor and transient and/or nutrient-sensing proteins PRAS40. Rictor, Protor, and mSIN1 are unique to the mTORC2 core complex, as are the transient and/or nutrient-sensing proteins IKK, Sestrin3, Xpln, and TSC2

(Kakumoto et al. 2015), although it has no effect on physiological mTOR activity in vitro or in vivo (Guertin et al. 2006). Unique to the mTORC1 core complex is raptor and transient interactions with nutrient-sensitive proline-rich AKT substrate 40 kDa (PRAS40) (Wullschleger et al. 2006). Raptor has many functions that regulate mTORC1 assembly, substrate recruitment, subcellular localization, and amino acid sensing (Hara et al. 2002; Kim et al. 2002; Sancak et al. 2008). PRAS40 and Deptor are both substrates of mTORC1, whereby mTORC1-mediated phosphorylation weakens their association with the complex and promotes mTORC1

kinase activity (Oshiro et al. 2007; Sancak et al. 2007; Thedieck et al. 2007; Vander Haar et al. 2007; Wang et al. 2008; Peterson et al. 2009). Rictor, RPTOR-independent companion of mTOR, is the defining component of mTORC2. Rictor and raptor are mutually exclusive mTOR-binding partners and required for mTORC2 and mTORC1 activity, respectively (Jacinto et al. 2004; Sarbassov et al. 2004). The core protein complex of mTORC2 also consists of the mammalian stress-activated protein kinase-interacting protein (mSIN1); and protein observed with Rictor-1 (Protor-1, also known as PRR5). Proteins with nutrient-sensitive or transient interactions with the mTORC2 core are DEPTOR, IKK, Sestrin3, Xpln, and TSC2 (Fig. 10.1).

Elevated cellular energy, nutrient availability, and mitogens activate mTOR signaling. Excess cellular resource availability, as in diabetes and obesity, increases mTOR signaling through the convergence of numerous signals. For example, hormones such as insulin and IGF1 activate mTOR through phosphoinositide 3-kinase (PI3K). In the presence of insulin, the transmembrane tyrosine kinase insulin receptor (IR) becomes activated and autophosphorylates tyrosine residues located in the intracellular portion of the receptor. The signal is rapidly transduced by the phosphorylation of tyrosine residues on insulin receptor substrate 1 through 4 (IRS-1 through IRS-4) (Sun et al. 1991, 1995; Lavan et al. 1997a, b). Among the distinct pathways next affected, the most prominent is mTORC2/AKT. Activated mTORC2 promotes cell survival, cytoskeletal remodeling, cell growth, and cell proliferation by activating AKT, SGK1, and PKC while inhibiting MST1 (Sarbassov et al. 2005; Cybulski and Hall 2009; Laplante and Sabatini 2012; Manning and Toker 2017). AKT also is an upstream activator of mTORC1 and an indirect substrate of mTORC1 during times of hyperactive mTOR signaling; thus, AKT serves as a signaling node between mTORC1 and mTORC2. Specifically, AKT activates mTORC1 through inhibitory phosphorylation of TSC1/2, an mTORC1 inhibitor (Figs. 10.1 and 10.2).

mTORC1 also responds to cellular energy, i.e., ATP/ADP ratio through AMPK (Hardie and Ashford 2014). During low cellular energy, AMPK inhibits mTORC1 through both direct and indirect mechanisms: direct phosphorylation of raptor disrupts the mTORC1 complex, and phosphorylation of the mTOR inhibitor TSC2 dampens mTORC1 activity. Increasing cellular amino acid (Wang and Proud 2009) or glucose concentration activates mTORC1 through the Rag family of GTPases. In response, mTORC1 localizes to the lysosome and stimulates macromolecule biosynthesis. In contrast, during starvation or low nutrient availability, mTORC1 negatively regulates autophagy by inhibiting autophagy initiation and lysosomal biogenesis through phosphorylation of the ULK complex and TFEB, respectively (Roczniak-Ferguson et al. 2012; Settembre et al. 2012). During high cellular energy resources, mTORC1 also promotes ribosome biogenesis and mRNA translation through phosphorylation and activation of downstream substrates: ribosomal S6 kinases (S6Ks) and the inhibitory eIF4E-binding proteins (4E-BPs). mTORC1-activated S6K phosphorylates substrates to promote translation and elongation (i.e., 40S ribosomal subunit proteins, eiF4B and eEF2K), while mTORC1-phosphorylated 4E-BPs promote cap-dependent translation through their participation in the eIF4F

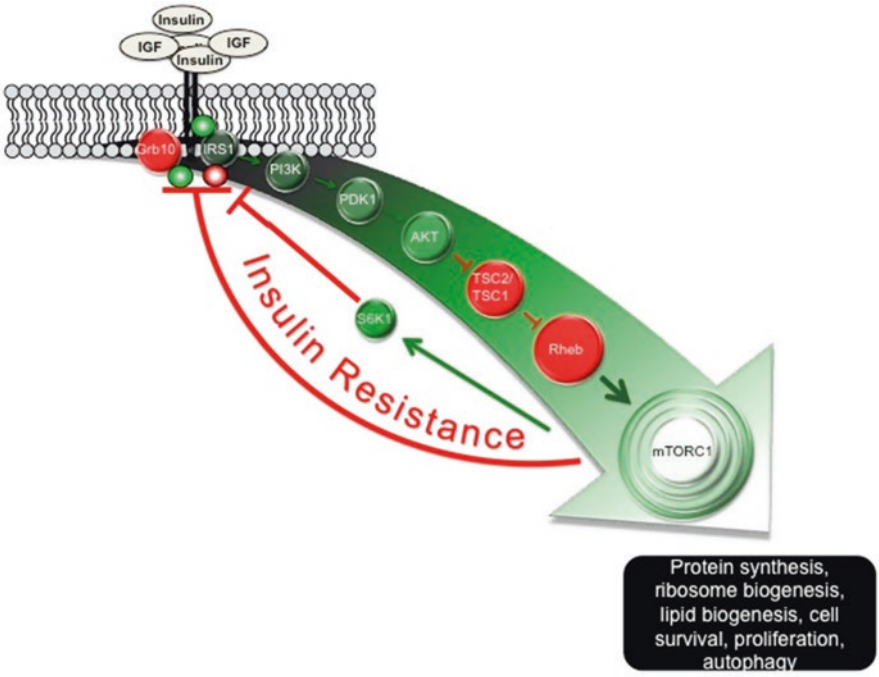

Fig. 10.2 Hyperactive mTORC1 signaling contributes to insulin resistance. Insulin signaling activates mTORC1 to promote macromolecule biogenesis and decrease autophagy. Activated mTORC1/S6K1 feeds back on the pathway to block insulin signaling through inhibitory phosphorylation of insulin receptor substrate 1 IRS1 (Ser307 and Ser636/639) and Grb10. Persistent nutrient availability induces insulin resistance through the sustained mTORC1/S6K1 inhibitory phosphorylation on IRS1 and Grb10 activation. Acute rapamycin releases the autoinhibitory signaling and prevents insulin resistance

complex (Laplante and Sabatini 2012; Saxton and Sabatini 2017a, b). Also, mTORC1 regulates lipid biosynthesis through activation of SREBP1, a major lipogenic transcription factor that controls genes involved in fatty acid and cholesterol synthesis, (Lamming and Sabatini 2013). In summary, mTOR is at the nexus of cellular metabolism, growth, and survival.

10.2 Physiological mTOR Signaling in the Brain

As in other cell types where mTOR regulates cell growth and proliferation, mTOR has an essential role in neuronal progenitor proliferation and in the temporal control of neuronal differentiation through insulin/IGF1-mediated PI3K/mTOR activation (Han et al. 2008; Fishwick et al. 2010; Malagelada et al. 2011). The principle growth factors that activate mTORC1 in neurons are brain-derived neurotrophic factor

(BDNF), insulin, insulin-like growth factor I (IGF-I), and vascular endothelial growth factor (VEGF) (Kim et al. 2008; Takei and Nawa 2014). The use of transgenic animal models and pharmacological approaches has provided strong evidence for the necessary role of mTOR signaling in the brain throughout life stages. Nestin-driven ablation of mTORC1 (raptor deletion) and mTORC2 (rictor deletion) activity was performed to determine the contribution of each complex on brain development (Cloetta et al. 2013; Thomanetz et al. 2013). Both studies found microcephaly, as well as reduced neuron cell number, size, morphology, and function indicating a necessary role of mTOR signaling during neuronal development. Interestingly, genetic upregulation of mTOR activity during forebrain development also resulted in microcephaly due to neural progenitor apoptosis in transgenic mice; in contrast upregulating mTOR in the adult brain resulted in cortical hypertrophy (Kassai et al. 2014). mTOR signaling is critical for axonal and dendritic sprouting, growth and regeneration during development (Inoki et al. 2006; Jossin and Goffinet 2007; Li et al. 2008; Nie et al. 2010), and in the mature nervous system. For example, in the adult central nervous system (CNS), neurons fail to regenerate; in contrast axonal sprouting and axonal growth can occur in response to injury in peripheral nervous system (PNS). This differential response to neuronal injury in the CNS and PNS is partially mediated through mTORC1 signaling. In the PNS, neuronal injury upregulates mTORC1; conversely, injury to CNS neurons causes mTORC1 downregulation (Park et al. 2008; Liu et al. 2010). In CNS neuron injury models, upregulation of mTORC1 by deleting negative regulators PTEN or TSC1 both enhanced axonal sprouting and regeneration retinal ganglion cells (Park et al. 2008); and PTEN deletion had the same benefits on corticospinal tract neuronal injury (Liu et al. 2010). Expression of constitutively active forms of mTOR pathway members, AKT and Rheb, also induce axonal regrowth. These studies indicate that mTORC1 activation is sufficient to promote axonal growth in both CNS and PNS neurons following injury and may have therapeutic importance to neurodegeneration and peripheral neuropathy in patients diagnosed with Alzheimer's disease and diabetes.

Proper mTOR regulation also is necessary for proper brain function. The use of rapamycin has elegantly demonstrated the requirement of mTORC1 activity for long-term potentiation (LTP) (Tang et al. 2002; Cammalleri et al. 2003; Banko et al. 2005; Ehninger et al. 2008; Stoica et al. 2011) and memory consolidation via mTORC1-mediated translational control (Stoica et al. 2011). mTORC1-dependent translational control also mediates changes in dendritic spine morphology that is required for memory storage and recall (Henry et al. 2017). Consolidation of memories also requires mTORC1 (Dash et al. 2006; Parsons et al. 2006; Schicknick et al. 2008; Stoica et al. 2011; Gafford et al. 2013) and mTORC2 activation for cytoskeletal remodeling (Costa-Mattioli and Monteggia 2013; Huang et al. 2013). While these studies collectively indicate the importance of mTOR in overall neuronal function, other experimental results contradict the necessity of mTOR in LTP (Antion et al. 2008), specifically in the dentate gyrus (Panja et al. 2009). Along these lines, mTORC1 hyperactivity induces seizures and epilepsy in rodent models (Sharma et al. 2010; Kassai et al. 2014; Rotschafer and Razak 2014; Russo et al. 2014), and genetic mutations resulting in hyperactive mTORC1 have been reported

in familial focal epilepsy (Dibbens et al. 2013). In models with hyperactive mTOR, such as aging and Alzheimer's disease, decreasing mTOR activity with rapamycin results in enhanced learning and memory (Zhou et al. 2009; Spilman et al. 2010; Majumder et al. 2011; Ehninger 2013; Neff et al. 2013; Ozcelik et al. 2013). Collectively these studies underscore that mTOR requires precise temporal regulation and level of activation for proper neuronal and brain function.

10.3 mTOR and Insulin Resistance in the Brain

In the late 1970s, the brain was deemed an insulin-insensitive organ; however, insulin now is well appreciated for its major physiological roles in the brain, as described in Chap. 1 of this book. While insulin is not a major regulator of glucose metabolism or transport of glucose in the brain (Marfaing et al. 1990; Hasselbalch et al. 1999; Seaquist et al. 2001), insulin and insulin-like growth factor type 1 (IGF-1) are important modulators of neurogenesis, neuronal growth, survival and differentiation, synaptic plasticity, lipid metabolism, and protein homeostasis (D'Ercole et al. 1996; Popken et al. 2004; Bedse et al. 2015). These processes are mediated through mTOR via the PI3K/mTOR axis of insulin signaling. Several studies report overactivation of the PI3K/mTOR pathway as an early feature of Alzheimer's disease (Pei et al. 2008; Caccamo et al. 2010; Tramutola et al. 2015) that can lead to aberrant glucose metabolism, energy production, and regulation of protein synthesis and degradation (Oddo 2012; O'Neill 2013; Tramutola et al. 2015). In Alzheimer's disease, neurons become increasingly resistant to insulin and IGF-1 (Moloney et al. 2010). Neuronal insulin resistance is maintained by overactivation of the PI3K/mTOR axis, which inhibits IRS1 activity via a negative feedback mechanism (Tramutola et al. 2015) (Fig. 10.2). In this way, insulin is both upstream and downstream of mTOR. The contribution of insulin-independent (e.g., oxidative stress, inflammation, protein accumulation, etc.,) chronic activation of mTORC1 signaling may be more responsible for the brain insulin resistance found in Alzheimer's disease and is discussed in the following sections.

10.4 mTOR in Alzheimer's Disease Pathogenesis

The human brain consumes ~20% of the body's glucose-derived energy to maintain its metabolic demands; compared to its modest 2% body weight, the brain's requirement is much higher than that of other tissues (Erbsloh et al. 1958). Neurons are the most energy-demanding cell type in the adult human brain and require continuous delivery of glucose from the blood (Howarth et al. 2012). Numerous clinical studies have shown that hypergylcemia causes cognitive impairment (Umegaki et al. 2008; Cukierman-Yaffe et al. 2009; Crane et al. 2013). Early stages of Alzheimer's disease are characterized by deficits in cerebral glucose utilization

(Caselli et al. 2008; Mosconi et al. 2008, 2009), brain insulin resistance, and insulin deficiency (Frolich et al. 1998) that continue to worsen as the disease progresses (Hoyer et al. 1991; Rivera et al. 2005). Furthermore, the impairment in insulin and IGF signaling is directly associated with neuropathological markers of Alzheimer's disease, including Aβ and phosphorylated tau (Orr et al. 2014). Aβ and tau pathologies are associated with mTOR hyperactivity in brains of patients with Alzheimer's disease and corresponding mouse models (An et al. 2003; Pei and Hugon 2008; Caccamo et al. 2010, 2011, 2013; Oddo 2012). Several groups have shown that Alzheimer's disease-associated pathology and cognitive deficits can be mitigated by using the mTOR inhibitor rapamycin to restore mTOR activity (Caccamo et al. 2010; Spilman et al. 2010; Majumder et al. 2011, 2012; Ozcelik et al. 2013), even in the presence of an insulin resistance-inducing diet (Orr et al. 2014). Since Alzheimer's disease is associated with increased mTOR activity, overactivation of both mTOR and insulin can contribute to brain insulin resistance in Alzheimer's disease through overlapping mechanisms.

Experimentally inducing insulin resistance in Alzheimer's disease models greatly exacerbates pathogenesis, cognitive decline, and insulin signaling (Cao et al. 2007; Ke et al. 2009; Jolivalt et al. 2010; Plaschke et al. 2010; Takeda et al. 2010; Bitel et al. 2012; Orr et al. 2014). Studies investigating the cellular mechanisms have found mTOR is a critical signaling molecule exacerbating cognitive deficits and pathogenic protein accumulation in diet (Ma et al. 2013; Orr et al. 2014) and pharmacological (i.e., use of a single streptozotocin injection to impair pancreatic β cells along with high-fat and/or high-carbohydrate diet) models of type 1/2 diabetes pathologies (Ma et al. 2015). Alzheimer's disease and type 2 diabetes rat models exhibit brain mTOR hyperactivity through oxidative stress, inflammation, protein accumulation, etc. (discussed below). When these diseases are combined, behavioral deficits are worsened coincident with increased mTOR and tau gene and protein expression levels (Ma et al. 2013, 2015). Administering 20% sucrose to drinking water of the 3xTgAD transgenic mouse model of Alzheimer's disease caused significant weight gain and insulin resistance (Orr et al. 2014). The peripheral phenotypes were accompanied by an increase in pathogenic Aβ, phosphorylated tau deposition, and mTORC1 pathway upregulation in the brain. The restoration of mTOR activity via rapamycin prevented the sucrose-induced exacerbation of Aβ and tau pathology, to strongly implicate disregulated mTORC1 as a nexus of peripheral insulin resistance and brain pathologies (Orr et al. 2014).

Neuronal autophagy is highly efficient and necessary for neuronal health. Loss of autophagy is neurotoxic even in the absence of disease and/or toxic protein accumulation (Hara et al. 2006; Komatsu et al. 2006). Disregulated autophagy (either hyper- or hypoautophagy) has been reported in neurodegenerative disease (Nixon 2013). In Alzheimer's disease mouse models with hyperactive mTOR, autophagic dysfunction is often cited as a contributing cellular mechanism responsible for the deleterious effects of protein accumulation (Caccamo et al. 2010, 2014; Majumder et al. 2011). Mechanistically, hyperactive mTOR decreases autophagy through ULK and TFEB inhibition (please refer to Fig. 10.1). In the rTg(tau_{P301L})4510 mouse model of Alzheimer's disease-associated tau accumulation

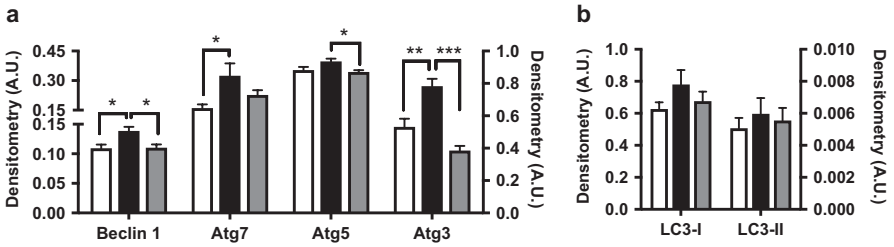

Fig. 10.3 Diet-induced insulin resistance caused autophagic impariment in the 3xTgAD Alzheimer's disease mouse model. (**a**) Protein expression analyses of brain tissue from 3xTgAD Alzheimer's disease mice indicate that dietary-induced insulin resistance increased autophagy-associated proteins. (**b**) The absence of concomitant LC3-II upregulation is indicative of autophagasome constipation. Treatment with rapamycin prevented the autophagasome accumulation and restored autophagic flux to control levels. (Open bar, control mice; solid bar, sucrose; gray bar, sucrose + rapamycin). $N = 8$ mice/group. One-way ANOVA Tukey's post hoc *, $p < 0.05$; **, $p < 0.005$; ***, $p < 0.0001$

(Santacruz et al. 2005), TFEB is significantly downregulated (Polito et al. 2014). Experimentally increasing TFEB resulted in decreased pathogenic neurofibrillary tangle formation and brain atrophy concomitant with improved synaptic function and cognitive behavior (Polito et al. 2014). Maintaining proper autophagy in the Alzheimer's disease brain is especially critical in a diabetes-like condition. Experimentally inducing insulin resistance in 3xTgAD mice caused an upregulation of autophagy-associated proteins in the brain (Fig. 10.3). The upregulation of Beclin 1, Atg7, Atg5, and Atg3 occurred in the absence of increased LC3 II/I ratio, which suggests an accumulation of autophagasomes. A decrease in autophagic flux occurs when either autophagasome formation or lysosomal clearance mechanisms are impaired; the resulting accumulation of defective autophagasomes and autolysosomes is capable of exacerbating Alzheimer's disease pathogenesis (Orr and Oddo 2013). Notably, treatment with rapamycin restored autophagic flux deficits in these 3xTgAD insulin-resistant mice indicating that restoring brain mTOR activity can overcome the negative effective effects of peripheral obesity and insulin resistance.

On a cellular level, the impaired energy metabolism maintained by mTOR-mediated inhibition of insulin and IGF-1 responses leads to oxidative stress and inflammation, which contributes to the pathogenesis of Alzheimer's disease, as described in Chap. 3 of this book (Craft and Watson 2004). Chronic overactivation of mTOR has been linked to systemic inflammation (Liu et al. 2016b; Paschoal et al. 2017), and there is evidence that mTOR also regulates neuroinflammation in several different disease models. For instance, high-fat diet-induced obesity is associated with increased neuroinflammation and overactivation of mTOR; and when neuroinflammation is reduced, mTOR activity also decreases (Dasuri et al. 2016).

However, much of the work showing mTOR-dependent regulation of neuroinflammation originates in models characterized by acute neuroinflammation. For instance, inhibiting mTOR after intracranial hemorrhage reduces neuronal death,

decreases expression of the proinflammatory cytokines TNF-α, IL1β, IL-6, and caspase-3, and reduces microglial activation (Li et al. 2016a; Wang and Zhang 2017). In fact, mTOR has been shown to specifically regulate cytokine-dependent microglial activation, such that pharmacological inhibition of mTOR reduces microglial, but not astrocytic, responses to inflammatory cytokine application (Dello Russo et al. 2009). Additionally, inhibition of mTOR with rapamycin also prevents proinflammatory M1 macrophage polarization and can shift macrophage polarization toward an anti-inflammatory M2 type (Xie et al. 2014b; Li et al. 2016b). In contrast, studies performed in cultured microglia indicate that rapamycin generally enhances proinflammatory activity (Xie et al. 2014b). This discrepancy suggests that mTOR regulates proinflammatory activity indirectly. Specifically, rapamycin likely acts on other cell types which then decrease proinflammatory markers in macrophages and microglia. Overall, these data indicate that mTOR regulates neuroinflammation through the activation of microglia and proinflammatory cytokines. However, since much of this work has been performed in disorders characterized by acute neuroinflammation, these results should be confirmed in disease states with chronic neuroinflammation, such as that found in neurodegenerative diseases.

Specific to Alzheimer's disease, neuronal insulin resistance is linked to neuroinflammation through activation of the TNF-α/JNK pathway, which inhibits IRS-1. Aβ oligomers (Bomfim et al. 2012; Lourenco et al. 2013) and misfolded tau (Kovac et al. 2011) activate TNF-α, which alters IRS-1/mTOR signaling. As insulin negatively regulates Aβ deposition and tau phosphorylation, dysregulation of insulin signaling increases these pathologies (de la Monte 2014). Additionally, Aβ oligomers inhibit the expression of neuronal surface insulin receptors (Zhao et al. 2008a) and IRS1 phosphorylation at Ser307 (Bomfim et al. 2012), which uncouples the interaction of IRS1 and IR (Harrington et al. 2004; Werner et al. 2004). Moreover, tau directly induces abnormal IRS-1 phosphorylation (Yarchoan et al. 2014), suggesting that Alzheimer's disease-associated pathologies can further contribute to aberrant insulin signaling in Alzheimer's disease. Therefore, Aβ and tau can influence abnormal insulin signaling both directly and indirectly through activation of the TNF-α/JNK pathway. Furthermore, dysregulation of brain insulin signaling in Alzheimer's disease is directly associated with increased Aβ accumulation, tau phosphorylation, and proinflammatory mediators (Di Domenico et al. 2017), as well as mTOR overactivation (Oddo 2012). Therefore, aberrant mTOR signaling is positioned at the crossroad of brain insulin resistance and neuroinflammation in Alzheimer's disease and acts as a vicious positive feed forward loop to accelerate disease progression.

Brain insulin resistance has been reported in nondiabetic Alzheimer's disease patients (Talbot et al. 2012), which is exacerbated by diabetes (Yoshitake et al. 1995; Leibson et al. 1997; Ott et al. 1999; Ohara et al. 2011). These reports indicate that brain insulin resistance in Alzheimer's disease can be a local disease process, as described in Chap. 3 of this book, but also is influenced by peripheral insulin resistance. For example, using rapamycin to reduce mTOR activity in Alzheimer's disease alleviates brain insulin resistance but simultaneously exacerbates peripheral

insulin resistance and obesity (Orr et al. 2014). Similarly, others have reported peripheral insulin resistance induced by rapamycin and rapalogs in wild-type mice, as well as an increased incidence of hyperglycemia and diabetes associated with pharmaceutical inhibition of the mTOR pathway in human clinical trials, indicating that physiological mTOR pathway activity levels are tissue specific (Johnston et al. 2008; Lamming et al. 2012; Geuna et al. 2015). Due to the promising therapeutic benefits of decreasing mTOR activity on various health conditions (Dazert and Hall 2011), recent work is now focused on intermittent dosing regimens to reduce the negative effects on peripheral insulin resistance and obesity while maintaining the benefits of decreasing mTOR activity in brain (Arriola Apelo et al. 2016a, b).

10.4.1 Peripheral Insulin Resistance

While the cause of elevated mTOR in Alzheimer's disease brain remains inconclusive, excess nutrient intake as seen in type 2 diabetes and obesity leads to the upregulation of mTORC1/S6K1 signaling in insulin-sensitive tissues (Um et al. 2004; Khamzina et al. 2005; Shigeyama et al. 2008). In response, the primary function of mTORC1 is to shift catabolism to growth-promoting anabolism through the synthesis of the major macromolecules (i.e., proteins, lipids, and nucleotides). In times of high nutrient availability, mTOR directly phosphorylates the insulin receptor leading to its internalization; this, in turn, results in a decrease of mTOR signaling (Wullschleger et al. 2006). However, chronic mTOR hyperactivity leads to pathogenic conditions including insulin resistance, a key feature of type 2 diabetes (Saha et al. 2011). Chronic mTORC1 activation by nutrient excess contributes to triacylglycerol or lipid deposition in white adipose tissue, liver, and muscle cells (Bentzinger et al. 2008; Cota et al. 2008; Polak et al. 2008; Sengupta et al. 2010). The induction of an S6K1-dependent negative feedback loop is one consequence from chronic mTORC1 hyper-activation and would lead to attenuation of AKT signaling in multiple tissues and insulin resistance (Harrington et al. 2004; Shah et al. 2004; Um et al. 2004; Khamzina et al. 2005). Therefore, it is conceivable that mTORC1 activation is required for an initial physiological adaptation of nutrient excess and obesity, but a negative feedback loop on IRS signaling caused by chronic and persistent hyper-activation could lead to development of insulin resistance.

10.4.1.1 Adipose Tissue

Obesity, defined as having a body mass index (BMI) of greater than 30 kg per m^2, greatly increases the risk of type 2 diabetes and has dichotomous effects on Alzheimer's disease risk depending on the individual's life stage. Specifically, obesity in midlife increases the risk of developing late-life Alzheimer's disease, whereas an increased BMI in older ages is protective (Whitmer et al. 2005, 2007; Emmerzaal et al. 2015; Rodriguez-Casado et al. 2017). As an exocrine organ,

adipose influences the activity and function of many tissues, including the brain. Through these neural connections, adipose tissue is well integrated in controlling whole-body glucose homeostasis in both normal and disease states. Mechanistically, mTOR signaling is hyperactive in numerous tissues derived from obese human and animal models due to the convergence of nutrients and growth factor stimuli (Um et al. 2004; Khamzina et al. 2005; Tremblay et al. 2007; Woods et al. 2008; Cota 2009; Kucejova et al. 2016; Tsai et al. 2016). Here we discuss the role of adipose tissue in type 2 diabetes and Alzheimer's disease, with particular focus on adipose-derived hormone signaling and how mTOR activity influences the interaction between obesity and cognition in Alzheimer's disease.

There are two main types of adipose tissue, white and brown. White adipose stores excess energy derived from food intake. In general, chronic nutrient stress signals resulting in uncontrolled white adipose tissue expansion promotes heart disease, diabetes, and metabolic syndrome. In contrast, brown adipose tissue is important for energy expenditure and non-shivering thermoregulation because it contains high mitochondrial content in the uncoupled state. This makes brown adipose tissue an attractive target for the treatment of obesity and type 2 diabetes. Interestingly, 3xTgAD Alzheimer's disease mice have impaired thermoregulation, which is exacerbated with age (Tournissac et al. 2017) and may suggest potential interactions between Alzheimer's associated protein aggregation and brown adipose tissue dysfunction. In line with this notion, cold exposure in these mice increases tau phosphorylation, full length APP, and soluble APP fragments; placing the animals in a thermoneutral environment reverses the effects on APP (Tournissac et al. 2017). In mice, white adipose tissue browning can alter whole-body energy expenditure, resulting in weight loss and increased insulin sensitivity. mTOR activity has a role in this cold stress-induced transition, resulting in an intermediate "beige" phenotype (Liu et al. 2016a). Furthermore, genetic activation of mTOR in white adipose tissue results in enhanced mitochondrial function and protection from high-fat diet-induced obesity and insulin resistance (Magdalon et al. 2016). In brown adipose tissue, genetically upregulating mTOR induces a transition to white adipose tissue, which can be reversed by pharmacologically decreasing mTOR with rapamycin treatment (Xiang et al. 2015). These dichotomous effects of mTOR in each adipose tissue type underscore its complexity.

Adipose tissue secretes numerous peptide hormones and cytokines (referred to as adipokines) including leptin, adiponectin, resistin, and lipoprotein lipase LPL allowing it to communicate with distant organs such as the brain (Ailhaud 2006). The effects of adipose-to-neuronal signaling have been demonstrated in vitro (Wan et al. 2015) and in vivo (Yamazaki et al. 2015). Human neuronal cells cultured with conditioned media from healthy female (males were not included in this study) adipocytes exhibit neuroprotection against toxic oxidative stress while increasing the activation of inflammatory proteins like JNK and ERK (Wan et al. 2015). In vivo, the systemic administration of adipocyte-conditioned media improved latency times in tail suspension and forced swim tasks in the 5xAD transgenic Alzheimer's disease mouse line (Yamazaki et al. 2015). In line with these findings, leptin treatment alone enhanced neural progenitor cell proliferation in transgenic APP/

PS1 mice, which is thought to confer some benefit to brain function in these mice (Perez-Gonzalez et al. 2011). Notably, leptin plasma concentration was positively associated with reduced incidence of Alzheimer's disease and whole brain and hippocampal weight in the Framingham Heart study, a large cohort study, to provide translational relevance of these in vitro and preclinical findings (Lieb et al. 2009; Paz-Filho et al. 2010).

The level of leptin in the CNS is dependent on the amount of body fat (Klein et al. 1996) and is correlated with BMI (Schwartz et al. 1996). Activation of mTOR is required for leptin biogenesis and is an important signaling event for healthy adipose tissue expansion (Roh et al. 2003). Like in the Alzheimer's disease brain, mTOR activity is elevated in adipose tissue from obese and insulin-resistant human subjects (Catalan et al. 2015). mTOR activation induces vascularization of white adipose tissue especially under nutrient replete conditions (Soumya et al. 2013). This process is critical for healthy adipose tissue expansion as evidenced by adipose tissue atrophy and insulin resistance in adipose-specific mTOR knockout mice (Shan et al. 2016). Though elevated mTOR is associated with obesity, it reduces adipose-derived inflammation, especially during high-fat diet feeding (Liu et al. 2016b; Paschoal et al. 2017).

Leptin receptors are highly expressed in several brain regions, highlighting the diversity and importance of leptin signaling in the brain. For example, leptin is involved in regulation of appetite and energy expenditure through its activity in the hypothalamus, satiety through signaling on neurons in the arcuate nucleus (Klein et al. 1996; Schwartz et al. 1996; Elmquist et al. 1998), and long-term potentiation, learning and memory in the hippocampus (Harvey et al. 2006). In Alzheimer's disease transgenic mice, leptin receptor expression is downregulated (Pedros et al. 2015), which lends support to the idea that patients with Alzheimer's disease have significant leptin resistance similar to obese and high-fat diet states. While leptin exerts many benefits to brain and neuronal health, a negative association between plasma leptin levels and brain region-specific volumes has been reported (Bentzinger et al. 2008). Obese individuals show greater brain atrophy in old age (Debette et al. 2010; Ho et al. 2010, 2011), which may result from alterations to leptin signaling (i.e., leptin resistance) as well as other adipose-derived molecules. For example, plasma and cerebral spinal fluid (CSF) levels of adipose-derived adiponectin are negatively correlated with cognitive acuity; specifically adiponectin levels increase in a stepwise fashion from control to mild cognitive impairment (MCI) and are even higher in patients with Alzheimer's disease (Une et al. 2011). However, like the inconsistent findings with leptin, other studies reported lower circulating adiponectin levels in patients with Alzheimer's disease than controls and concluded adiponectin levels provide no predictive value for disease progression (Teixeira et al. 2013). In vitro work further highlights the complexity of adiponectin signaling. For instance, globular adiponectin can increase the secretion of inflammatory cytokines in human astrocyte-like cells (Wan et al. 2014), but in cultured microglia, it can suppress Aβ-induced inflammatory signaling (Song et al. 2017). These studies have not been confirmed in vivo but underscore the diverse effects of adiponectin signaling dependent on cell type.

Adipose tissue also secretes non-peptide biologically active molecules such as activated lipids. One of the hallmarks of type 2 diabetes is elevated systemic free fatty acid (FFA) levels, which arises from resistance to insulin-induced suppression of lipolysis in adipose tissue (DeFronzo 2004). Furthermore, high levels of peripheral norepinephrine (NE) can also induce triacylglyceride (TAG) breakdown and release of FFA into circulation (Raclot and Groscolas 1993). In turn high levels of FFA can increase inflammation and induce insulin resistance (Liang et al. 2013) in a vicious cycle. Interestingly, one of the first brain regions to degenerate in Alzheimer's disease is the locus coeruleus, the primary producer of the NE to the brain (Grinberg et al. 2011). This decrease in central NE has been linked to elevated levels of NE in plasma and CSF of patients with Alzheimer's disease (Raskind et al. 1984). Increased peripheral NE may contribute to suppression of mTOR-mediated glucose uptake into fat cells and increased lipolysis (Mullins et al. 2014). Furthermore, NE mediates beta-adrenergic signaling-induced glucose uptake and mTOR activity in brown adipose tissue (Mullins et al. 2014). These findings suggest a potential link between Alzheimer's disease and increased susceptibility to insulin resistance. While elevated FFA levels have been shown to induce insulin resistance, FFAs have also been shown to accelerate the formation of Aβ and tau oligomers (Wilson and Binder 1997). Furthermore, Alzheimer's disease patients have increased CSF levels of the FFA shuttles (albumins) (Elovaara et al. 1985). CSF albuminuria is suggestive of blood-brain barrier leakage and elevated FFAs in the brain, which can facilitate toxic protein aggregation. Moreover, excess circulating FFAs cause accumulation of triglycerides and activated lipids in the form of long-chain fatty acyl-CoA esters in other tissues such as skeletal muscle, liver, and β-cells which disrupts the normal metabolic and secretory functions of these tissues. Thus, adipose tissue is the primary organ responsible for controlling systemic lipid levels, which greatly impacts the modulation of both glucose and lipid homeostasis and underscores the importance of maintaining proper BMI in preventing systemic metabolic dysfunction as in type 2 diabetes and Alzheimer's disease. It is generally accepted that two features are critical for obesity to elicit type 2 diabetes: skeletal muscle insulin resistance and the failure of pancreatic β cells to secrete the required levels of insulin needed to maintain euglycemia, which will be discussed below.

10.4.1.2 Skeletal Muscle

Skeletal muscle is the largest organ in the human body and comprises 30–50% of an individual's total body weight. It is classically known for its roles in the generation of power, locomotion, metabolism, and thermogenesis. Skeletal muscle is critically important in the regulation of metabolic homeostasis; it is the major site of glucose disposal (~80%), and muscle insulin resistance is considered one of the major hallmarks of type 2 diabetes (DeFronzo and Tripathy 2009). The risk for sarcopenia, the progressive decline in skeletal muscle mass resulting in decreased muscle strength and physical performance (Cruz-Jentoft et al. 2010), and physical disability increases in older patients with type 2 diabetes mellitus (Kalyani et al. 2010).

Sarcopenia negatively impacts cognition (Canon and Crimmins 2011), overall health and quality of life. Motor, sensory, and coordination deficits are not common early in Alzheimer's disease; however, abnormal weight and muscle loss are clinical features of Alzheimer's disease progression (McKhann et al. 1984; Burns et al. 2010; Takagi et al. 2017). Moreover, acquired resistance to insulin signaling and action in skeletal muscle is associated with obesity and promotes the development of type 2 diabetes mellitus. In this section, we will discuss the role of skeletal muscle in metabolic homeostasis, dysfunctions in type 2 diabetes and Alzheimer's disease, and the role of mTOR signaling in these processes.

Skeletal muscle is a major determinant of the basal metabolic rate (Zurlo et al. 1990, 1994; Janssen et al. 2000), which is the amount of energy that an individual requires for the body to maintain function while at rest. These basic processes include breathing, blood circulation, and controlling body temperature. The basal metabolic rate accounts for about 60–75% of the daily calorie expenditure by individuals and determines whether an individual maintains, gains, or loses weight. As in most tissues of the adult human body, mTOR signaling in skeletal muscle is critical for protein synthesis. Since muscle mass is regulated by the balance between protein synthesis and degradation, mTOR signaling in skeletal muscle is paramount for maintaining muscle mass. Furthermore, skeletal muscle mTOR activity is key to integrating nutrient, growth factor, and stress signaling, as well as promoting muscle mass accrual after exercise (Saxton and Sabatini 2017a, b). Both mTORC1 and mTORC2 are highly expressed in skeletal muscle. mTORC1 signaling is essential for maintaining muscle mass and has been associated with muscle hypertrophy (Bodine et al. 2001). Moreover, muscle-specific raptor knockout mice with diminished mTORC1 signaling exhibited severe muscle atrophy leading to early death (Bentzinger et al. 2008). Paradoxically, sustained activation of mTORC1 in muscle-specific TSC1 knockout mice also led to myopathy and reduced survival due to an inability of the body to remove damaged cells as a result of impaired autophagy (Castets et al. 2013). Similar to brain mTOR signaling, these data suggest that proper mTORC1 activity is important for maintaining optimal tissue health, and subsequently an individual's overall metabolic rate.

In contrast to mTORC1, the major function of mTORC2 in the muscle is the regulation of glucose uptake through PI3K/AKT signaling. Consistent with this notion, muscle-specific rictor knockout mice showed impaired insulin-stimulated glucose transport (Kumar et al. 2008). Injecting mice with the mTOR inhibitor, AZD8055, suppressed insulin-stimulated glucose disposal in the muscle (Kleinert et al. 2014). However, in muscle-specific Rictor knockout mice, AZD8055 did not cause further defects in glucose regulation, suggesting that AZD8055 impairs glucose metabolism in the muscle, in part by blocking mTORC2. These findings support the notion that mTORC2 signaling critically regulates glucose metabolism in muscle and subsequently whole-body metabolism.

Similar to brain and adipose tissue, muscle mTORC1 signaling is elevated in obesity and diabetes (Khamzina et al. 2005). It has been demonstrated that mTORC1 activation of S6K1 results in serine phosphorylation of IRS-1, leading to suppressed insulin signaling (Tzatsos and Kandror 2006) and subsequently insulin resistance

(Khamzina et al. 2005). Furthermore, rodent studies showed that mice with constitutive 4E-BP1 activity in the muscle, i.e., reduced downstream mTORC1 signaling, were resistant to age and diet-induced insulin resistance (Tsai et al. 2015). These studies suggest that downstream targets of mTORC1 signaling in the muscle play important roles in glucose metabolism.

In the brain during Alzheimer's disease pathogenesis, elevated mTOR activity is associated with dysregulation of insulin signaling and the accumulation of pathogenic proteins (Caccamo et al. 2014; Orr et al. 2014). Experimental evidence suggests that skeletal muscle of obese and/or Alzheimer's disease animal models may develop similar pathogenic protein accumulation and lead to disruptions in glucose regulation. Specifically, a high-cholesterol diet given to rabbits induced Aβ and phosphorylated tau deposition in skeletal muscle (Sparks et al. 1994). In transgenic Alzheimer's disease mice, mutant APP was found within skeletal muscle as well (Monteiro-Cardoso et al. 2015). These findings are also relevant to human patients: amyloid beta 42 (Aβ42) expression is detectable in skeletal muscle from cognitively normal older adults and is elevated in the skeletal muscle from patients with Alzheimer's disease as assessed during autopsy (Arai et al. 1991; Kuo et al. 2000). Collectively these findings suggest that hyperactive mTOR may be common to numerous tissues in patients with Alzheimer's disease and even produce similar protein accumulation pathologies, which could contribute to the muscular dysfunction that is present in Alzheimer's disease.

Skeletal mass and function have critical roles in the overall health of an organism. Gait speed, primarily governed by muscle function, is one of the closest predictors of mortality in older individuals (Studenski et al. 2011; Toots et al. 2013). Muscle atrophy and dysfunction in patients with Alzheimer's disease has been confirmed in several independent studies (McKhann et al. 1984; Burns et al. 2010; Takagi et al. 2017). Reduced motor function and grip strength have been associated with an increased risk of mild cognitive impairment (MCI), a diagnosis which often progresses to Alzheimer's disease (Boyle et al. 2009). Moreover, poor swallowing function in patients with Alzheimer's disease has been directly attributed to skeletal muscle dysfunction (Takagi et al. 2017). A loss of the homeostatic control of energy metabolism has been implicated as the common cause underling both brain and skeletal muscle dysfunctions detected in Alzheimer's disease subjects and is attributed to mitochondrial dysfunction (Hauptmann et al. 2009; Du et al. 2010; Boncompagni et al. 2012; Ding et al. 2013). Transgenic Alzheimer's disease mice recapitulate defects in skeletal muscle function similar to patients with Alzheimer's disease (Schuh et al. 2014). Specifically decreased skeletal muscle maximal respiratory capacity (Schuh et al. 2014), acetylcholinesterase and catalase activity, and altered skeletal muscle mitochondrial membrane composition (Monteiro-Cardoso et al. 2015) have all been reported in mouse models of Alzheimer's disease. Of note, acetylcholinesterase inhibitors are used as a standard treatment for Alzheimer's disease, although they provide little benefit (Kaduszkiewicz et al. 2005). Given that acetylcholinesterase activity in skeletal muscle is impaired in Alzheimer's disease (Monteiro-Cardoso et al. 2015), using acetylcholinesterase

inhibitors may also affect skeletal muscle function, which could impact systemic metabolism.

Muscle is increasingly recognized as an endocrine organ that communicates with other tissues, including the brain, through the secretion of myokines, soluble factors that regulate metabolism and other biological processes in a systemic manner (Henningsen et al. 2010; Pedersen and Hojman 2012; Schnyder and Handschin 2015). Myokines include cytokines, peptides, and other metabolites, which are released by muscle primarily in response to exercise (Schnyder and Handschin 2015). BDNF is predominantly expressed in the brain (Matthews et al. 2009) and is a recently identified myokine (Matthews et al. 2009). BDNF is a member of the neurotrophin family and is essential in regulating the survival, growth, and maintenance of neurons (Hofer and Barde 1988). BDNF plays a key role in learning and memory (Tyler et al. 2002) and in the regulation of body mass and energy homeostasis (Wisse and Schwartz 2003). Patients with Alzheimer's disease showed lower levels of BDNF in the brain and circulation (Connor et al. 1997; Laske et al. 2006). Interestingly, reduced plasma BDNF levels were also found in obesity and type 2 diabetes (Krabbe et al. 2007). Muscle contractions during exercise produce BDNF mRNA and protein in skeletal muscle, where it seems to play a role in enhancing glucose metabolism. Whether BDNF acts as a myokine that can improve Alzheimer's disease, however, is currently under debate. Muscle-derived BDNF does not appear to be released into the circulation suggesting that BDNF primarily acts locally in the muscle (Miura et al. 2012). Other neurotrophin family members such as neurotrophin 3 (NT-3) and NT-4/5 have also been found in the skeletal muscle (Omura et al. 2005). While the systemic effects of these aforementioned myokines is not yet understood, evidence for improved memory in Rhesus monkeys and humans due to the upregulation of muscle-derived cathepsin B has been elegantly demonstrated (Moon et al. 2016). Upregulated cathepsin B also improves learning and memory in Alzheimer's disease mouse models (Embury et al. 2017). Because skeletal muscle release of cathepsin B is increased with exercise, myokines may be directly contributing to the exercise-associated cognitive benefits reported in Alzheimer's disease (Brandt and Pedersen 2010).

Sarcopenia is associated with a proinflammatory state and lower cognitive function in older adults (Mazure and Swendsen 2016). Systemic inflammation was found to mediate the negative relationship between sarcopenia and cognitive function, especially in females (Mazure and Swendsen 2016). Interestingly, exercise training has been shown to lower all-cause mortality partially because it exerts an anti-inflammatory effect. Chronic "sterile" low-grade systemic inflammation has been implicated in the pathogenesis of a number of aging-related chronic illnesses including both Alzheimer's disease and type 2 diabetes. The etiology of sterile inflammation is still not clear and likely is a result of several factors, including physical inactivity, altered immune cell function, and somatic cell damage, among others, that can be largely abrogated by exercise. Exercise training reduces visceral fat mass, which is a major source of inflammation (please refer to the section on adipose). The production of anti-inflammatory cytokines, such as IL-1ra, IL-10, and sTNFR, increases after exercise training (Ostrowski et al. 1999). Also, contracting

muscle releases myokines that may create a systemic anti-inflammatory environment to improve the function of distant organs (Brandt and Pedersen 2010). Therefore, regular exercise offers protection against Alzheimer's disease and type 2 diabetes, as well as other chronic diseases, through decreasing adiposity, improving insulin sensitivity, and releasing myokines, many of which are regulated through the mTOR signaling axis.

10.4.1.3 Pancreas

Regulation of glucose homeostasis by insulin depends on pancreatic β cell growth and function. A primary characteristic of type 2 diabetes pathogenesis is the slowly progressive pancreatic β cell failure which results in impaired insulin secretion, decreased β cell mass, decreased insulin action on peripheral tissues, and ultimately β cell death. In general, the pancreas serves two main roles: an exocrine function that aids in digestion and an endocrine function that controls blood glucose level. The endocrine component of pancreatic regulation is controlled by the islet cells (islets of Langerhans), which create and release important metabolic hormones directly into the bloodstream. The two main pancreatic hormones are insulin, which is secreted from islet β cells to suppress catabolic processes and stimulate glucose uptake. Conversely, glucagon is secreted from islet α cells and stimulates hepatic gluconeogenesis. Each β cell contains over 10,000 secretory vesicles filled with insulin (Dean 1973; Olofsson et al. 2002), which are under close regulation to ensure tight control of blood glucose levels. During type 2 diabetes pathogenesis, individuals exhibit a progressive decline in β cell function, with gradual β cell degeneration and worsening of glycaemia over time (1995; Kahn et al. 2006); eventually pancreatic islets fail to compensate for insulin resistance in peripheral tissues. Great effort has focused on understanding mechanisms responsible for pancreatic dysfunction; mTOR signaling has emerged as a key molecular regulator of interest. In this section, we will highlight cellular processes that overlap between type 2 diabetes, β cell pathology, and brain pathogenesis in Alzheimer's disease with emphasis on hyperactive mTOR and protein accumulation.

Numerous studies highlight a positive role of mTORC1 activation in regulating β cell health in physiological conditions (Tremblay and Marette 2001; Khamzina et al. 2005; Teutonico et al. 2005; Ueno et al. 2005; Di Paolo et al. 2006; Sarbassov et al. 2006; Krebs et al. 2007; Fraenkel et al. 2008; Rachdi et al. 2008; Elghazi et al. 2010; Gu et al. 2011; Yang et al. 2011; Blandino-Rosano et al. 2012). Carbohydrate- and fat-rich Western diets provide chronic nutrient overload (Fig. 10.4). The Western diet results in chronic exposure of β cells to persistent glucose and FFAs resulting in obesity, β cell failure, and type 2 diabetes. This nutrient excess in type 2 diabetes and obesity drives elevated blood glucose, amino acids, proinflammatory cytokines, and insulin, all of which activate mTORC1 (Wellen and Thompson 2010; Zoncu et al. 2011; Efeyan et al. 2015; Kennedy and Lamming 2016). Indeed, pancreatic islets isolated from patients with type 2 diabetes and various type 2 diabetes mouse models (i.e., hyperglycemic obese high-fat diet-fed mice and leptin receptor-deficient

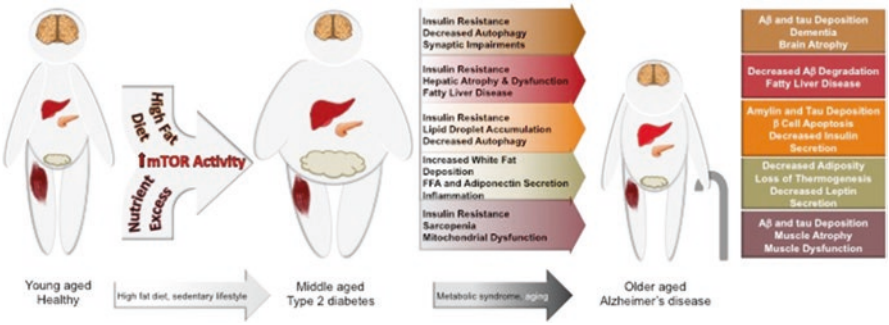

Fig. 10.4 Causes and consequences of mTOR hyperactivity in mid- and older ages. Carbohydrate- and fat-rich Western diets increase blood glucose and mTOR activity in several tissues, leading to obesity, insulin resistance, and type 2 diabetes in middle ages. With advanced age, the persistent mTOR hyperactivity contributes to tissue dysfunction and Alzheimer's disease. Brown, brain; red, liver; orange, pancreas; beige, adipose; purple, muscle

db/db mice) display elevated mTORC1 activity (Shigeyama et al. 2008; Bartolome et al. 2014; Hatanaka et al. 2014; Yuan et al. 2017) but reduced mTORC2/AKT signaling (Wang et al. 2010; Ardestani et al. 2014; Yuan et al. 2017). Genetically and pharmacologically modulating mTOR signaling have provided compelling evidence for a critical role of both mTORC1 and mTORC2 complexes in the regulation of glucose homeostasis by modulating β cell mass and function (Tremblay and Marette 2001; Khamzina et al. 2005; Teutonico et al. 2005; Ueno et al. 2005; Di Paolo et al. 2006; Sarbassov et al. 2006; Krebs et al. 2007; Fraenkel et al. 2008; Rachdi et al. 2008; Elghazi et al. 2010; Gu et al. 2011; Yang et al. 2011; Blandino-Rosano et al. 2012).

mTORC1 regulates several pancreatic islet functions including β cell size, growth, and proliferation, insulin secretion, and protein translation by modulating mRNA translation through phosphorylation of 4E-BPs and S6K1 (McDaniel et al. 2002; Briaud et al. 2003; Kwon et al. 2004; Zahr et al. 2007; Rachdi et al. 2008; Shigeyama et al. 2008; Mori et al. 2009; Barlow et al. 2013; Rhodes et al. 2013; Xie et al. 2014a; Stamateris et al. 2016). Whole-body mTOR loss-of-function/deletion was found to be lethal (Gangloff et al. 2004; Murakami et al. 2004; Guertin et al. 2006; Jacinto et al. 2006; Shiota et al. 2006; Yang et al. 2006); however, whole-body depletion of S6K1 caused hypoinsulinemia and reduced β cell size but improved insulin sensitivity (Pende et al. 2000; Ruvinsky et al. 2005). To further gain insight into pancreatic mTOR function, transgenic mice have been created with tissue-specific mTOR modulation. Overexpressing S6K1 in β cells increases insulin secretion without affecting β cell mass (Elghazi et al. 2010). Activation of mTORC1 by targeted deletion of mTORC1 repressors, tuberous sclerosis 1 (TSC1), or tuberous sclerosis 2 (TSC2) (Rachdi et al. 2008; Shigeyama et al. 2008; Mori et al. 2009; Blandino-Rosano et al. 2012) or overexpressing Rheb (Hamada et al. 2009) significantly increases islet β cell function (Saxton and Sabatini 2017a, b). In contrast, transgenic mice with decreased mTOR function exclusively in β cells

displayed reduced mTORC1 and mTORC2 signaling and developed β cell dysfunction and glucose intolerance (Alejandro et al. 2017; Blandino-Rosano et al. 2017; Chau et al. 2017; Elghazi et al. 2017; Ni et al. 2017; Sinagoga et al. 2017). While one model displayed normal β cell mass (Alejandro et al. 2017), others display reduction in β cell mass, smaller islets, and/or pancreas size (Blandino-Rosano et al. 2017; Chau et al. 2017; Elghazi et al. 2017; Ni et al. 2017; Sinagoga et al. 2017). Similarly, mTORC2 loss of function causes hyperglycemica, glucose intolerance, reduced β cell mass and proliferation, as well as reduced pancreatic insulin level and secretion (Gu et al. 2011). These studies underscore that proper regulation of mTOR signaling in β cells is critical for pancreatic function and whole-body glycemic control.

The chronic exposure of human and rodent β cells to persistent glucose and FFAs, as occurs in obesity and type 2 diabetes, causes β cell failure (Robertson et al. 2004; Prentki and Nolan 2006; Muoio and Newgard 2008; Leibowitz et al. 2010; Alejandro et al. 2015) and apoptosis through hyperactive mTORC1 signaling and mTORC1-dependent lipid drop accumulation (Bachar et al. 2009; Vernier et al. 2012; Mir et al. 2015; Yang et al. 2015; Varshney et al. 2017; Yuan et al. 2017). Additional mTORC1-mediated cytotoxicity occurs through inhibition of autophagy (Jung et al. 2008; Masini et al. 2009; Stienstra et al. 2014; Riahi et al. 2016) and compensatory downregulation of cytoprotective mTORC2 signaling (Gu et al. 2011; Blandino-Rosano et al. 2012; Ardestani et al. 2014; Ardestani and Maedler 2016). Rapamycin treatment significantly decreased triglyceride accumulation and β cell toxicity (Vernier et al. 2012), and mTORC1-S6K1 inhibition restored insulin secretion in human islets derived from type 2 diabetic patients providing further evidence that upregulated mTORC1 activity is responsible for these pathologies (Yuan et al. 2017).

Acute rapamycin treatment improves insulin sensitivity in humans and rodents through inhibition of mTORC1 (Tremblay and Marette 2001; Khamzina et al. 2005; Ueno et al. 2005; Krebs et al. 2007). In contrast, chronic rapamycin exposure exacerbates insulin resistance in wild type (Sarbassov et al. 2006) and Alzheimer's disease mouse models (Orr et al. 2014). The negative effects of long-term treatment occur, in part, through inhibition of mTORC2. While mTORC1 is sensitive to low-dose and short-term exposure to rapamycin, chronic rapamycin exposure also inhibits mTORC2; thus through the mTORC2/AKT signaling pathway, β cell proliferation and survival are negatively affected (Sarbassov et al. 2006). The relative contributions of long-term rapamycin-induced β cell dysfunction and insulin resistance from mTORC1 and mTORC2 signaling are not fully understood, but both complexes influence these phenotypes (Teutonico et al. 2005; Di Paolo et al. 2006). While rapamycin treatment has been proposed as a therapeutic strategy for metabolic diseases, more research is required to unravel the tissue-specific effects after acute versus chronic treatment in different metabolically active tissues. For example, negative effects of chronic mTOR inhibition have been reported in several studies using mTOR inhibitors; therefore, it is conceivable that rapamycin therapy could impair the adaptation of β cells to insulin resistance or have yet

unrecognized off-target effects, resulting in diabetes (Fraenkel et al. 2008; Yang et al. 2011).

In the brain, chronic mTOR activation contributes to Aβ and tau protein aggregation; evidence continues to suggest a role of protein accumulation contributing to pancreatic dysfunction in type 2 diabetes as well. Amylin, also known as islet amyloid polypeptide (IAPP), is a 37 amino acid peptide hormone that is derived by proteolytic cleavage of a precursor protein, called islet amyloid precursor protein, and is co-secreted with insulin from pancreatic β cells (Opie 1901; Westermark et al. 1986, 1987; Cooper et al. 1987a, b). Amylin plays a role in glycemic regulation by inhibiting insulin and glucagon secretion, slowing gastric emptying and promoting satiety. Amylin accumulates in pancreatic islets forming amyloid deposits that are present in ~95% of type 2 diabetes patients (Lopes et al. 2004). Aggregated amylin is cytotoxic and is positively correlated with the clinical severity of type 2 diabetes, β cell loss, and negatively correlated with insulin secretion and glucose metabolism (Cooper et al. 1987a, b; Hull et al. 2004) suggesting a causal role in the islet dysfunction. The proteolytic processing of amylin is akin to Aβ production by amyloid precursor protein in Alzheimer's disease brain tissue. Moreover, Aβ and amylin deregulate similar proteins in their respective tissues, of which about 25% are associated with mitochondrial dysfunction (Lim et al. 2010). Collectively, these studies suggest that pathophysiology of protein aggregation is similar between these diseases. Moreover, in 2010, autopsy performed on patients with Alzheimer's disease found hyperphosphorylated tau, as well as amyloid protein, in pancreatic tissue (Miklossy et al. 2010).

A common feature of Alzheimer's disease and type 2 diabetes is APP accumulation and tau hyperphosphorylation co-localizing with components of the JNK pathway in neurons and islet cells, respectively (Thedieck et al. 2007; Tramutola et al. 2015). Hyperphosphorylated tau accumulation, along with Aβ, is hallmark of Alzheimer's disease pathogenesis (Orr et al. 2017). Studies have since characterized the biochemistry of tau protein in β cell lines and revealed six unique tau isoforms with a balanced 1:1 ratio of 3R and 4R tau isoforms (Maj et al. 2016), but with higher molecular weight than that of cerebral cortex tau isoforms (Maj et al. 2010). Human insulinomas, pancreatic tumors comprised of β cells that overproduce insulin, display elevated tau expression with an imbalance in isoforms, specifically increased 3R isoforms (Maj et al. 2016), which is hallmark of many neurodegenerative tauopathies (Orr et al. 2017). Because tau protein stabilizes microtubules, elevated tau expression in pancreatic β cells would presumably decrease insulin secretion. Experimental evidence indeed supports this notion: exposing pancreatic cell lines to sera derived from diabetic patients modestly increased tau expression (Maj et al. 2010), and overexpressing tau in vitro significantly increases β cell proliferation and decreases insulin secretion (Maj et al. 2016). In neurons, tau is primarily expressed in axons where it stabilizes microtubules to allow for proper delivery of cargo throughout the cell. The microtubules are nucleated at the centrosome-based microtubule organizing center and extend to the cell periphery. However, in pancreatic β cells, microtubules form a dense meshwork with the Golgi acting as the microtubule organizing center. This microtubule configuration limits

granule density at the cell periphery and subsequently glucose-stimulated insulin secretion (Zhu et al. 2015). High glucose destabilizes microtubules and decreases microtubule density allowing for glucose-stimulated insulin secretion (Zhu et al. 2015). In diabetic mice, dysfunctional β cells display elevated microtubule density, which decreases insulin secretion. These data indicate that tau expression and microtubule regulation in β cells plays an important role in pancreatic dysfunction and type 2 diabetes pathogenesis.

10.5 Concluding Remarks

Dr. Alois Alzheimer initially described Alzheimer's disease as the histological accumulation of Aβ-containing plaques and tau-containing neurofibrillary tangles concomitant with neurodegeneration and dementia. Since this seminal report in 1906, basic scientists and physicians have primarily approached Alzheimer's disease as a brain-specific disease. However, Alzheimer's disease increasingly is being recognized as a complex systemic disorder involving numerous tissues that manifest extensive comorbid health conditions. The finding that type 2 diabetes doubles the risk for developing Alzheimer's disease is one such example that has prompted scientists to investigate pathological changes in peripheral tissues and systems. This slowly emerging change in dogma is accompanied by a new vision for therapeutic treatment. Instead of targeting a single aberrant gene or protein, biomedical researchers are beginning to witness benefits of modulating molecules that are highly integrated into numerous cellular pathways across tissues. Pathologically hyperactive mTOR activity is a common mechanism linking Alzheimer's disease and type 2 diabetes across multiple tissue types. Therefore, targeting mTOR epitomizes this new strategy: therapeutic modulation improves Alzheimer's disease pathogenesis (Caccamo et al. 2010, 2013) while simultaneously delivering numerous health benefits, most notably extended life span (Vellai et al. 2003; Jia et al. 2004; Kapahi et al. 2004; Kaeberlein et al. 2005; Powers et al. 2006; Harrison et al. 2009; Selman et al. 2009; Sharp and Strong 2010).

Embarking on this new treatment era does not come without challenges. Therapeutic approaches to precisely alter only pathological, but not physiological, mTOR signaling have not yet been developed. Since mTOR is a highly integrated signaling pathway that regulates cellular metabolism and physiology across multiple tissues, maintaining a physiological level of mTOR signaling will be critical to the success of mTOR inhibitors as a pharmacotherapeutic intervention in Alzheimer's disease. While rapamycin has celebrated numerous successes, a major obstacle is that chronic rapamycin treatment induces insulin resistance in animal models (Sarbassov et al. 2006; Orr et al. 2014) and human subjects (Teutonico et al. 2005; Blagosklonny 2013), likely through the inhibition of mTORC2 (Sarbassov et al. 2006). Nonetheless, investigators are continuing to devise strategies to overcome these pitfalls. For instance, since mTORC1 is more sensitive to low-dose and short-term rapamycin treatment, intermittent rapamycin dosing strategies are being

employed to circumvent the negative effects of mTORC2 inhibition, and this dosing strategy has had success in both animal models (Arriola Apelo et al. 2016a, b) and humans (Mannick et al. 2014).

While the need for research and therapeutics targeting brain-specific pathologies in Alzheimer's disease remains relevant, expanding the research focus to include common signaling pathways that are affected across organ systems offers a complementary approach to therapeutic discovery. Moreover, identifying and targeting the common molecular mechanisms linking Alzheimer's disease with common comorbidities, such as type 2 diabetes, may provide further insight into the role of mTOR and potentially uncover additional molecules for therapeutic intervention. This promising research approach offers hope to identify treatments that mitigate brain pathologies while simultaneously alleviating comorbid medical conditions that plague patients with Alzheimer's disease.

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Chapter 11
Therapeutic Strategies for Alzheimer's Disease in the View of Diabetes Mellitus

Yasumasa Ohyagi, Katsue Miyoshi, and Norimichi Nakamura

Abstract Recently, Alzheimer's disease (AD) is understood as "diabetes of the brain" or "type 3 diabetes." Recent clinical trials of anti-amyloid β-protein (Aβ) therapies have not proved to be successful. Thus, glucose-insulin metabolism in the brain is thought to be an alternative therapeutic target. Various types of antidiabetic drugs such as insulin, thiazolidinediones, dipeptidyl peptidase-4 (DPP4) inhibitors, glucagon-like peptide-1 (GLP-1) agonists, biguanides, and others have been reported to be effective on cognitive impairment in animal models and patients with DM or AD. Here, recent reports are reviewed. While we identified apomorphine (APO) as a novel drug that promoted intracellular Aβ degradation and improved memory function in an AD mouse model, more recently, we have revealed that APO treatment improves neuronal insulin resistance and activates insulin-degrading enzyme (IDE), a major Aβ-degrading enzyme. In this context, recovery of impaired insulin signaling in AD neurons may be a promising therapeutic strategy for AD dementia.

Keywords Alzheimer's disease · Diabetes mellitus · Insulin · Thiazolidinediones · DPP4 inhibitors · GLP-1 agonists · Apomorphine

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11.1 Introduction

Alzheimer's disease (AD) is the major cause of dementia in the elderly people, and the therapeutics for AD is the major topic in the world. At present, four drugs are approved to use for AD patients. Among them, three drugs (donepezil, galantamine, rivastigmine) are acetylcholinesterase (AChE) inhibitors, and one is a glutamate antagonist, memantine. All these drugs have effects to slow the progression of dementia but not to improve cognitive function persistently (symptom-modifying drugs). Thus, many pharmaceutical companies and researchers have been investigating to develop novel drugs that completely inhibit disease progression and improve cognitive function (disease-modifying drugs).

To date, one of the most widely known mechanisms of AD pathogenesis has been "amyloid cascade hypothesis." There are two major pathological hallmarks of AD, neurofibrillary tangles (NFTs) and senile plaques (SPs) (Serrano-Pozo et al. 2011). NFTs consist of hyper-phosphorylated tau protein (p-tau), and SPs consist of amyloid β-protein (Aβ). Remarkably, Aβ has long been thought to play a pivotal role in the pathogenesis of AD. Because, Aβ deposition is one of the earliest phenomena in brain, followed by p-tau formation and cognitive decline (Jack et al. 2010). As shown in Fig. 11.1, Aβ is produced from Aβ protein precursor (APP) by two enzymes, i.e., β-secretase and γ-secretase. Although approximately 90% of Aβ species secreted physiologically is Aβ40, only 10% Aβ species, Aβ42, is more aggregative and forms Aβ oligomers. Aβ oligomers are more neurotoxic than Aβ monomer.

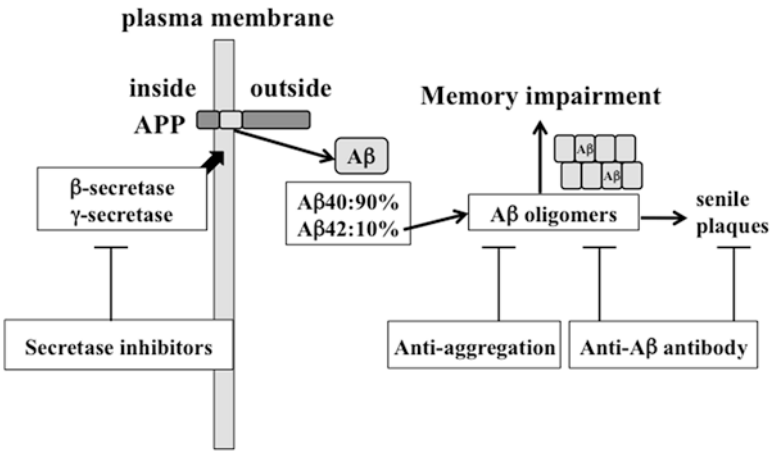

Fig. 11.1 "Amyloid cascade hypothesis" and therapeutic targets. Aβ is generated by β-secretase (β-amyloid clipping enzyme, BACE) and γ-secretase. Aβ42 takes only 10% in secreted Aβ but is highly aggregative and readily forms Aβ oligomers that are toxic for synapse and cause memory impairment. Aβ oligomers also promote hyperphosphorylation of tau protein. To attenuate this process, many inhibitors of β- or γ-secretase, anti-Aβ aggregation drugs, and immunotherapeutics such as anti-Aβ antibodies and Aβ vaccination have been developed. However, to date, almost all clinical trials of these drugs have been unsuccessful

Toxicity of Aβ may induce synaptic dysfunction leading to cognitive impairment (Ferreira et al. 2015) and may also accelerate p-tau formation (Hu et al. 2014). In addition, toxic turn Aβ42 form has recently been found (Murakami et al. 2010). Such a pathogenic cascade is named "amyloid cascade hypothesis." Based on this hypothesis, many therapeutic strategies targeting Aβ have been investigated. As shown in Fig. 11.1, β- and γ-secretase inhibitors that inhibit Aβ generation, anti-Aβ aggregation drugs, and immunological therapies using specific anti-Aβ antibodies or vaccination with Aβ peptides have been developed. Although many of these drugs were effective on AD mouse models, almost all phase III clinical trials for AD patients did not reach the primary end point. Some evidences of amyloid imaging and biomarkers in cerebrospinal fluids have been demonstrated, but cognitive impairment was not improved sufficiently (Doody et al. 2014; Salloway et al. 2014; Siemers et al. 2016). Possible causes for such unsuccessfulness are the following: (i) Aβ-targeting therapy may be effective only in preclinical and prodromal AD; (ii) sporadic AD cases in the elderly may be caused by some mechanisms different from those in AD mouse models produced by the gene engineering; and (iii) "amyloid cascade hypothesis" may not be the true mechanism in dementia of AD. As to the possibility (i), clinical trials of anti-Aβ therapy for the preclinical and prodromal AD patients are still pursued. As to possibilities (ii) and (iii), clinical trials of anti-Aβ therapy for the early-onset familial AD patients with the genes determined are now ongoing. The results of such investigation will provide us the validity of "amyloid cascade hypothesis." More recently, p-tau is focused on as a new therapeutic target other than Aβ (Boutajangout and Wisniewski 2014). However, it is unclear whether or not only the abnormal proteins accumulating in the brain are the powerful therapeutic targets to improve dementia. It is important to recover the neuronal network system improving generation of energy and metabolism in AD neurons. In this point of view, glucose-insulin metabolism may be an important therapeutic target.

11.2 Association Between Diabetes Mellitus (DM) and AD

Hypertension and DM have been widely known as the major risk factors for arteriosclerosis resulting in brain and cardiac infarction. Thus, DM has been thought to be one of the strong risk factors for vascular dementia. On the other hand, correlation between DM and AD has been investigated epidemiologically. Some reports found no correlation (Luchsinger et al. 2001; MacKnight et al. 2002; Hassing et al. 2002), but others found positive correlation between them (Leibson et al. 1997; Ott et al. 1999; Peila et al. 2002). Such discrepancies may be due to differences in determination of DM. DM was diagnosed by oral glucose tolerance tests (OGTT) in the reports that showed positive correlation but not in the negative reports. It suggests that subclinical diabetic status may contribute to AD risk. Recently, an epidemiological study in Japanese population (the Hisayama study) has clearly revealed that glucose intolerance may increase the risk of AD as well as VD in the future (Ohara

et al. 2011). In the same study, correlation between glucose intolerance and Aβ deposition (Matsuzaki et al. 2010) and DM-like gene expression patterns in the postmortem brain tissues (Hokama et al. 2014) were also demonstrated. In addition, Talbot et al. revealed an increased insulin resistance of neurons in the AD brain (Talbot et al. 2012). Taken together, increased peripheral insulin resistance, i.e., type 2 DM (T2DM), may be linked to increased neuronal insulin resistance in AD. Therefore, AD has recently been named "type 3 DM" or "brain DM" (De la Monte 2014) (Fig. 11.2). In addition, recurrent hypoglycemic attacks (Whitmer et al. 2009) and both increases and decreases in mean blood glucose levels (Crane et al. 2013) may increase the risk for dementia, indicating that marked alteration of blood glucose levels may strongly affect neuronal network function and cognitive function. Moreover, increased insulin resistance in neurons may decrease insulin-degrading enzyme (IDE), also a major Aβ-degrading enzyme (Miners et al. 2011), and may increase dephosphorylated GSK-3β, a major phosphokinase of tau protein (Avila et al. 2010), resulting in enhancing progression of the AD pathology. In this context, brain insulin resistance would be a new target in therapeutic approach for dementia in AD patients.

Recently increasing reports suggest that exercise may contribute to prevention of dementia (Barnes 2015). Also, the National Institutes of Health in the USA recommends control of T2DM, exercise habits, and healthy foods for prevention of dementia. Such recommendations may be similar to the prevention of DM. Such facts may imply a common basis of AD and DM.

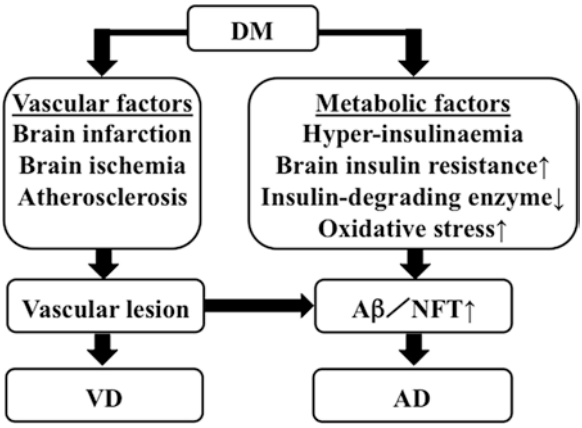

Fig. 11.2 AD pathogenesis associating with DM. DM is well known to accelerate arteriosclerosis and ischemic changes in the brain, leading to vascular dementia (VD) (left: vascular factors). While, DM may cause hyperinsulinemia, increase brain insulin resistance and oxidative stress, and decrease insulin-degrading enzyme (IDE), accelerating AD-related pathology (Aβ deposition and NFT formation). It is also known that vascular lesion due to ischemia may enhance the progression of AD pathology

11.3 Insulin Therapy

If insulin resistance is increased in neurons, insulin signaling may not work sufficiently. Insulin signaling may play a major role in signal transduction in cells, regulating cell cycle proteins (Yang and Guan 2007). Thus, first simple therapeutic strategy may be supply of insulin in AD brain. Recent reports demonstrating efficacy of insulin administration on cognitive function in rodents and human are listed in Table 11.1. In an AD model, 3xTg-AD mice ($APP_{KM670/671NL}/PS1_{M146V}/Tau_{P301L}$), high-fat diet (HFD), which increases peripheral insulin resistance, may accelerate Aβ deposition in brain and memory impairment; such phenomena may be improved by insulin injection (Vandal et al. 2014). Moreover, in these HFD-treated 3xTg-AD mice, Aβ deposition is observed in the pancreas, indicating a pathogenic self-amplifying loop between AD and T2DM (Vandal et al. 2015). More recently, many reports have demonstrated that nasal administration of insulin improved memory function, reduced Aβ deposition, increased brain-derived neurotrophic factor (BDNF) and its receptor protein tropomyosin receptor kinase B (TrkB), improved

Table 11.1 Efficacy of insulin administration

Reports of rodents	**Path**	**Subjects**	**Efficacy**
Vandal et al. (2014)	Injection	3xTg-AD	Improvement of memory function that is further impaired by HFD
Mao et al. (2016)	Nasal	APP/PS1	Improvement of cognitive function and Aβ pathology
Zhang et al. (2016)	Nasal	Anesthesia	Prevention of memory deficit and p-tau
Farzampour et al. (2016)	Nasal	Aβ injection	Improvement of memory function
Haas et al. (2016)	Ventricle	Aged rat	Increases in BDNF and TrkB receptors
Maimaiti et al. (2016)	Nasal	Aged rat	Improvement of memory and hippocampal after hyperpolarization (AHP)
Brabazon et al. (2017)	Nasal	Brain trauma	Improvement of memory and in FDG-PET
Rajasekar et al. (2017)	Nasal	STZ	Improvement of memory function and increases in Nrf-2 and BDNF expression
Kamei et al. (2017)	Nasal	SAMP8	Slowing the progression of memory loss
Reports of human	**Path**	**Subjects**	**Efficacy**
Craft et al. (2012)	Nasal	MCI/AD	Improvement of memory function
CLaxton et al. (2013)	Nasal	MCI/AD	Differential improvement of memory in male and female
Claxton et al. (2015)	Nasal	MC1/AD	Improvement of memory function especially in APOE-ε4 carriers

STZ streptozotocin, *SAMP8* senescence-accelerated mouse, *BDNF* brain-derived neurotrophic factor, *TrkB* tropomyosin receptor kinase B

hippocampal afterhyperpolarization (AHP), etc., in APP/presenilin-1 (PS1) double transgenic mice, anesthetic mice, Aβ-injected rats, aged rats, rats with brain trauma, streptozotocin (STZ)-treated rats, and senescence-accelerated mice (SAMP8) (Mao et al. 2016; Zhang et al. 2016; Farzampour et al. 2016; Haas et al. 2016; Maimaiti et al. 2016; Brabazon et al. 2017; Rajasekar et al. 2017; Kamei et al. 2017) (see Table 11.1).

While, clinical trials of nasal insulin administration to human preceded the investigation using the animal models. Craft and colleagues have demonstrated that nasal administration of insulin improves memory function in MCI and mild AD patients (Craft et al. 2012) and that such effects may be different among sex (Claxton et al. 2013) and apolipoprotein E gene alleles (Claxton et al. 2015). Insulin administered via nasal pathway did not cause systemic hypoglycemia (Craft et al. 2012; Claxton et al. 2013, 2015) and may thus seem a promising method to develop new drugs to improve the hippocampal function.

11.4 Thiazolidinediones (Glitazones)

Thiazolidinediones (glitazones) are peroxisome proliferator-activated receptor γ (PPARγ) agonists, which reduce insulin resistance of the liver and muscle. There is a possibility that these drugs improve insulin resistance of neurons in the AD brain, since neuronal insulin resistance may be increased in AD (Talbot et al. 2012). Recent reports demonstrating efficacy of thiazolidinediones (glitazones) on cognitive function in rodents and human are listed in Table 11.2. At present, there are two major glitazones, rosiglitazone (Ros) and pioglitazone (Pio). Disease models consist of some different types. First, transgenic mice with mutant APP, mutant APP + presenilin-1 (PS1) double, and mutant APP+PS1+tau triple genes were used as an early-onset familial AD models. Second, HFD- and high-fructose-diet (HFuD)-fed rats are models of T2DM, because those diets are well known to induce peripheral insulin resistance. Third, STZ-injected mouse is a model of type 1 DM (T1DM), because STZ causes selective damages in pancreatic β cells resulting in peripheral insulin deficiency. At last, congenital DM rats or mice (db/db mice) were also used. All these DM-associated mice or rats were exactly not the models of AD. However, based on the concept that AD may be "brain diabetes," drugs that improve cognitive function in these DM-associated animal models may become promising candidates for AD.

As shown in Table 11.2, Ros treatment improved memory function in HFD rats (Pathan et al. 2008), APP-Tg mice (Escribano et al. 2010), 3xTg-AD mice (Yu et al. 2015), DM rats (Ma et al. 2015), and db/db mice (Wang et al. 2016). Remarkably, Ros treatment removed the amyloid plaques and decreased p-tau in the hippocampus of APP-Tg mice (Escribano et al. 2010). Also, Pio treatment improved memory function of HFuD rats (Yin et al. 2013), STZ mice (Liu et al. 2013), 3xTg-AD mice (Yu et al. 2015), APP/PS1 mice (Toba et al. 2016), and db/db mice (Wang et al. 2016). In addition, Pio treatment prevented the β-amyloidogenic process such as Aβ

Table 11.2 Efficacy of thiazolidinediones (glitazones)

Reports of rodents	**Drug**	**Subjects**	**Efficacy**
Pathan et al. (2008)	Ros	HFD rat	Improvement of memory function
Escribano et al. (2010)	Ros	APP	Removal of Aβ deposition
Luo et al. (2011)	Pio	HFuD rat	Inhibition of Aβ deposition process
Yin et al. (2013)	Pio	HFuD rat	Improvement of memory function
Liu et al. (2013)	Pio	STZ mice	Amelioration of memory deficit
Yu et al. (2015)	Ros, Pio	3xTg-AD	Improvement of learning and inhibition of tau phosphorylation and neuroinflammation
Ma et al. (2015)	Ros	DM rat	Improvement of memory function
Toba et al. (2016)	Pio	APP/PS1	Improvement in pre-Aβ stage in cerebellum
Wang et al. (2016)	Ros, Pio	db/db mice	Improvement of Aβ transport and enhancement of hippocampal LTP
Reports of human	**Drug**	**Subjects**	**Efficacy**
Watson et al. (2005)	Ros	MCI/AD	Preservation of cognitive impairment
Sato et al. (2011)	Pio	AD+T2DM	Improvement of cognitive function
Heneka et al. (2015)	Pio	T2DM	Decreases in risk of dementia
Chou et al. (2017)	Pio	DM	Protecting against dementia

Ros rosiglitazone, *Pio* pioglitazone, *HFD* high-fat diet, *HFuD* high-fructose diet, *STZ* streptozotocin, *T2DM* type 2 DM, *LTP* long-term potentiation

overproduction and decreased Aβ degradation induced by insulin resistance in HFuD rats (Luo et al. 2011), strengthened antioxidant defense system in HFuD rats (Yin et al. 2013), reduced brain β-amyloid clipping enzyme 1 (BACE1) in STZ mice (Liu et al. 2013). Both Ros and Pio treatments attenuated hyperphosphorylation of tau and neuroinflammation in 3xTg-AD mice (Yu et al. 2015) and promoted Aβ clearance across the blood-brain barrier (BBB) and enhanced hippocampal long-term potentiation (LTP) in db/db mice (Wang et al. 2016). In the human studies, there have been the reports indicating dementia protective efficacy of both Ros and Pio in patients with MCI/AD (Watson et al. 2005), with AD and T2DM (Sato et al. 2011), with T2DM (Heneka et al. 2015), and with DM (Chou et al. 2017), whereas some other reports indicated the negative data as to the efficacy of Ros and Pio (Miller et al. 2011; Harrington et al. 2011; Seaquist et al. 2013; Hildreth et al. 2015; Galimberti and Scarpini 2017). Further large-size clinical trials are necessary to determine their effects.

11.5 DPP4 Inhibitors

Dipeptidyl peptidase-4 (DPP4) degrades incretin hormones, which stimulate secretion of insulin from the pancreas and decrease blood glucose levels. Incretin hormones contain glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). Thus, DPP4 inhibitors enhance incretin hormone activity followed by increase in levels of plasma insulin. DPP4 inhibitors would therefore increase insulin stimulation in the AD brain. Recent reports demonstrating efficacy of DPP4 inhibitors (gliptins) on cognitive function in rodents and human are listed in Table 11.3. Currently, there are some well-known gliptins such as sitagliptin (Sita), saxagliptin (Saxa), vildagliptin (Vilda), alogliptin (Alo), and linagliptin (Lina). As well as PPAR-γ agonists, many reports indicate that these gliptins

Table 11.3 Efficacy of DPP4 inhibitors (gliptins)

Reports of rodents	**Drug**	**Subjects**	**Efficacy**
D'Amico et al. (2010)	Sita	APP/PS1	Inhibition of Aβ deposition
Kosaraju et al. (2013a)	Saxa	STZ rat	Improvement of memory function, p-tau, Aβ burden and inflammation increasing GLP-1 in hippocampus
Kosaraju et al. (2013b)	Vilda	STZ rat	Improvement of memory function, p-tau, Aβ burden and inflammation increasing GLP-1 in hippocampus
Sakr (2013)	Sita	T2DM rat	Improvement of memory function increasing Adipo R1 expression
Pipatpiboon et al. (2013)	Vilda	HFD rat	Improvement of mitochondrial function
Sripetchwandee et al. (2014)	Vilda	HFD rat	Increases in dendritic spines in CA1
El-Sahar et al. (2015)	Sita	DM rat+ischemia	Protection against oxidative stress, inflammation, and apoptosis
Gault et al. (2015)	Sita	HFD mice	Improvement of memory function
Tsai et al. (2015)	Sita	Ischemia	Protection against chronic inflammation
Pintata et al. (2016)	Vilda	HFD rat	Improvement of cognitive function with energy restriction
Qin et al.(2016)	Alo	DM rat	Inhibition of inflammation in hippocampus
Kosaraju et al. (2016)	Lina	3xTg-AD	Improvement of cognitive function
Reports of human	**Drug**	**Subjects**	**Efficacy**
Tasci et al.(2013)	Vilda	T2DM	Inhibition of progression of cognitive impairment with metformin therapy
Rizzo et al. (2014)	DPP4I	T2DM	Protection against cognitive impairment
Isik et al. (2017)	Sita	DM±AD	Improvement of cognitive function in DIM with or without AD

Sita sitagliptin, *Saxa* saxagliptin, *Vilda* vildagliptin, *Alo* alogliptin, *Lina* linagliptin, *DPP4I* DPP4 inhibitors, *HFD* high-fat diet, *STZ* streptozotocin, *T2DM* type 2 DM

may improve memory function and mitochondrial function and inhibit Aβ deposition, p-tau deposition, and neuroinflammation (D'Amico et al. 2010; Kosaraju et al. 2013a, b, 2016; Sakr 2013; Pipatpiboon et al. 2013; Sripetchwandee et al. 2014; El-Sahar et al. 2015; Gault et al. 2015; Tsai et al. 2015; Pintata et al. 2016; Qin et al. 2016) (Table 11.3). The fact that such drugs may be effective for AD mouse models as well as for cognitive deficit in mice with T1DM (STZ) and T2DM (HFD), indicates a common mechanism in cognitive impairment in AD and DM. In human studies, although there have not been clinical trials for MCI or AD patients, DPP4 inhibitors may be beneficial to protect against cognitive impairment in patients with T2DM (Tasci et al. 2013; Rizzo et al. 2014) and may also be effective on patients with AD (Isik et al. 2017). Thus, further clinical trials of DPP4 inhibitors for AD patients are necessary.

11.6 GLP-1 Agonists

As mentioned above, GLP-1 is one of incretin hormones that stimulate insulin secretion. As well as DPP4 inhibitors, GLP-1 agonists and GIP are included in the incretin-related drugs. Recent reports demonstrating efficacy of GLP-1 agonists (glutides) on cognitive function in rodents and human are listed in Table 11.4. To date, liraglutide (Lira), lixisenatide (Lixi), exenatide (Exen), and exendin-4 (Ex-4) have been investigated using animal models. As shown in Table 11.4, many reports demonstrated that these GLP-1 agonists improved memory function and hippocampal LTP, inhibited Aβ deposition and microglial activation, and decreased insulin resistance and tau phosphorylation in HFD mice, STZ mice, APP/PS1 mice, intraventricular Aβ-injected mice, and 3xTg-AD mice (Table 11.4). Interestingly, Ex-4 treatment recovered permeability of BBB and blood-CSF barrier (BCSFB) damaged by DM, indicating a novel efficacy of GLP-1 agonists other than stimulation of insulin secretion (Zanotto et al. 2017). Remarkably, there have been much evidence for the efficacy of Lira treatment, and Lira seems to be a promising drug in the AD therapeutics. However, only a few reports have shown negative results (Egefjord et al. 2012) and a limited effect in patients with mood disorder (Mansur et al. 2017). Currently, further clinical trials for AD patients are still under investigation.

11.7 Other Antidiabetic Drugs

Recent reports demonstrating efficacy of other antidiabetic drugs on cognitive function in rodents and human are listed in Table 11.5. Sulfonylureas, biguanides, α-glucosidase inhibitors (α-GIs), and sodium-glucose cotransporter-2 (SGLT-2) inhibitors are also known as antidiabetic drugs. Sulfonylureas stimulate insulin

Table 11.4 Efficacy of GLP-1 agonists (glutides)

Reports of rodents	**Drug**	**Subjects**	**Efficacy**
Gault et al. (2010)	Ex-4	HFD mice	Improvement of cognitive function and LTP
Porter et al. (2010)	Lira	HFD mice	Improvement of memory function
McClean et al. (2011)	Lira	APP/PS1	Inhibition of Aβ deposition
Porter et al. (2011)	GIF	HFD mice	Improvement of cognitive function and LTP
Bomfim et al. (2012)	Ex-4	APP/PS1	Recovery of insulin signaling
Ma et al. (2012)	GLP-1	APP/PS1	Improvement of memory function
Long-Smith et al. (2013)	Lira	APP/PS1	Decrease in insulin resistance and attenuation of Aβ deposition and microglial activation
Faivre and Hölscher (2013)	GIP	APP/PS1	Improvement of synaptic plasticity and reduction of numbers of Aβ plaques and activated microglias
Lennox et al. (2014a)	Lixi	HFD mice	Improvement of learning and memory and LTP in hippocampus
Lennox et al. (2014b)	GLP-1	HFD mice	Improvement of learning and memory and LTP in hippocampus
McClean and Hölscher (2014)	Lira	APP/PS1	Prevention of Aβ deposition, microglial activation, and memory impairment
Gumuslu et al. (2016)	Ex-4	STZ mice	Improvement of cognitive function and upregulation of CREB and BDNF gene expression levels
Qi et al. (2016)	Lira	Aβ mice	Attenuation of tau phosphorylation via inhibiting GSK-3β
Hansen et al. (2016)	Lira	TauP301L	Reduction of tau phosphorylation and improvement of motor function
Chen et al. (2017)	Lira	3xTg-AD	Improvement of memory and reduction of tau phosphorylation
Palleria et al. (2017)	Lira	STZ rat	Inhibition of anxiolytic and pro-depressant actions as well as memory function activating AKT pathway
Zanotto et al. (2017)	Ex-4	DM rat	Recovery of permeability of BBB and BCSFB damaged by DM
Reports of human	**Drug**	**Subjects**	**Efficacy**
Egefjord et al. (2012)	Lira	AD	A protocol of clinical trial of liraglutide with PET; no effects on Aβ deposition
Mansur et al. (2017)	Lira	Mood disorder	Improvement of cognitive function

Ex-4 exendin-4, *Lira* liraglutide, *Lixi* lixisenatide, *Exen* exenatide, *GIP* glucose-dependent insulinotropic polypeptide/gastric inhibitory peptide, *HFD* high-fat diet, *STZ* streptozotocin, *LTP* long-term potentiation, *CREB* cAMP response element-binding protein, *BDNF* brain-derived neurotrophic factor, *BBB* blood-brain barrier, *BCSFB* blood-CSF barrier

Table 11.5 Efficacy of other antidiabetic drugs

Reports of rodents	**Drug**	**Subjects**	**Efficacy**
Baraka and ElGhotny (2010)	Gliben	Aβ-injected rat	Improvement of memory function
Patel et al. (2010)	Gliben	TBI rat	Improvement of memory function
Tosun et al. (2013)	Gliben	SAH rat	Reduction of neuroinflammation and cognitive impairment
Li et al. (2012)	Met	db/db mice	Attenuation of AD-like neuropathology
Asadbegi et al. (2016)	Met	HFD rat	Protection against Aβ-mediated inhibition of hippocampal LTP
Allard et al. (2016)	Met	HFD mice	Prevention of memory impairment
Tong et al. (2015)	Acarbose	SAMP8	Effect on behavioral impairment
Yin et al. (2013)	Acarbose	SAMP8	Alleviation of memory impairment
Lin et al. (2014)	Empa	db/db mice	Amelioration of cognitive dysfunction
Reports of human	**Drug**	**Subjects**	**Efficacy**
Imfeld et al. (2012)	SU	AD	No association between SU and AD risk
Cheng et al. (2014)	SU	T2DM	Reduction of risk for dementia
Ng et al. (2014)	Met	DM	Reduction of the risk for cognitive decline
Herath et al. (2016)	Met	DM	Reduction of the risk for cognitive decline
Ye et al. (2016)	Met	DM	Reduction of the incidence rate of dementia (A meta-analysis)

Gliben glibenclamide, *Met* metformin, *Empa* empagliflozin, *SU* sulfonylurea, *TBI* traumatic brain injury, *SAH* subarachnoid hemorrhage, *HFD* high-fat diet, *HFuD* high-fructose diet, *T2DM* type 2 DM, *LTP* long-term potentiation

secretion from β-cells in the pancreas. Glibenclamide, a sulfonylurea drug, improved memory function in the rats intracerebroventicularly injected with Aβ peptide (Baraka and ElGhotny 2010) and in the rats with traumatic brain injury (TBI) (Patel et al. 2010). Also, inhibition of the Sur1-Trpm4 channel by glibenclamide reduces neuroinflammation and ameliorates cognitive impairments in rat and human with subarachnoid hemorrhage (SAH) (Tosun et al. 2013). Although glibenclamide may have protective effects on cognitive function, there have been no studies using AD mouse models. In human studies, there is a report that indicates no association between sulfonylurea and risk of AD (Imfeld et al. 2012), while sulfonylurea would reduce the risk for dementia in T2DM patients (Cheng et al. 2014). Since hypoglycemic attacks may increase the risk for dementia (Whitmer et al. 2009), evaluation of the efficacy of sulfonylurea should be carefully investigated.

Biguanides inhibit glycogenesis in the liver and uptake of glucose from the intestine and improve insulin resistance. A well-known biguanide metformin was reported to attenuate tau phosphorylation in db/db mice (Li et al. 2012) and to have protective effects on cognitive function in combination in HFD mice (Asadbegi et al. 2016; Allard et al. 2016). In human, it is suggested that metformin treatment reduced the risk of cognitive decline in DM patients (Ng et al. 2014; Herath et al. 2016). Also, a meta-analysis suggests that metformin and thiazolidinediones may reduce the incidence rate of dementia with the relative risks, 0.79 and 0.75,

respectively (Ye et al. 2016). Efficacy of biguanides for AD patients should be evaluated in the future studies.

α-GIs inhibit postprandial hyperglycemia and would thus inhibit glucotoxicity in the brain. Although there have been no reports of investigation about efficacy on rodents or patients with AD, chronic acarbose treatment may have a protective effect on behavioral impairment (Tong et al. 2015) and alleviated memory impairment (Yan et al. 2015) in SAMP8 mice. The efficacy of α-GIs for the cognitive impairment in DM and AD remains to be elucidated.

SGLT-2 inhibitors are newcomers in antidiabetic drugs. These drugs inhibit reuptake of glucose in the kidney and lower the blood glucose level. Since the term of usage of SGLT-2 inhibitors is not long, there have been few reports studying about its efficacy on cognitive impairment. A recent report demonstrated that empagliflozin treatment ameliorates cardiovascular injury and cognitive dysfunction in db/db mice (Lin et al. 2014). At present, many SGLT-2 inhibitors are used for control of blood glucose levels. Thus, further investigation about its efficacy should be continued.

11.8 Apomorphine (APO)

Lastly, we describe about our recent finding of novel efficacy of apomorphine (APO) for AD. Although APO is well known to be a dopamine agonist for patients with Parkinson's disease (PD), we have recently found efficacy of APO for cognitive improvement in AD and have also found APO to be effective on brain diabetes.

In the beginning of this century, based on many studies using AD mouse models produced by mutant APP and PS1 genes, anti-Aβ therapies such as Aβ vaccination and anti-Aβ antibodies were thought to be a promising therapeutic strategy for AD. However, it is well known that many clinical trials targeting Aβ in AD patients have failed. While, our previous studies first revealed that oxidative stress-related apoptosis stimulation induced intracellular Aβ42 deposition in contrast to reduction of extracellular Aβ secretion in primary neuronal cultures (Ohyagi et al. 2000). Subsequently, we found intracellular accumulation of Aβ42 to promote the p53 mRNA expression resulting in neuronal apoptosis (Ohyagi et al. 2005). In addition, intracellular Aβ42 was reported to promote apoptosis via various pathways (Ohyagi 2008). Therefore, we did search for novel drugs that may promote intracellular Aβ42 degradation. Using SH-SY5Y cells, we established an assay system for intracellular Aβ degradation and found that treatment with APO, which has been suggested to protect neurons from oxidative stress in PD mouse models and from brain infarction in a gerbil stroke model (Mandel et al. 2004; Castri et al. 2006), accelerated Aβ42 degradation through activating insulin-degrading enzyme (IDE) and proteasome system (Himeno et al. 2011). Furthermore, APO therapy improved memory function and the AD pathology in 3xTg-AD mice (Himeno et al. 2011) (Fig. 11.3).

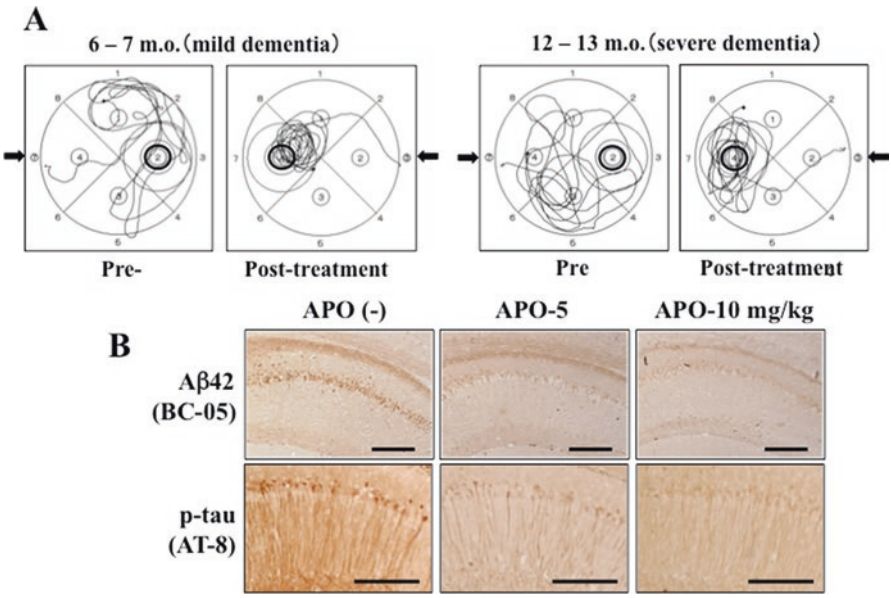

Fig. 11.3 Efficacy of APO on 3xTg-AD mice (Himeno et al. 2011; Nakamura et al. 2017). (**a**) Morris water maze (MWM) of the representative 3xTg-AD mice treated with APO. 6-month-old and 12-month-old mice were subcutaneously injected with 5 m/kg APO once a week for 1 month (total five times). After memorizing the platform location, track of 60 s free swimming was analyzed. Both 7- and 13-month-old mice exhibited improvement of spatial memory posttreatment compared to pretreatment. (**b**) Immunohistochemistry of hippocampus CA1 in 7-month-old mice. Both Aβ42 and p-tau levels were lower in APO-treated mice compared to untreated mice. Bars = 100 μm

Further investigation has revealed that APO treatment may enhance intracellular antioxidative stress system protecting cells from apoptosis (Ma et al. 2011). In addition, DNA microarray analysis has revealed that APO treatment may effect on regulation of cell cycle, which is a quite different characteristic from other kind of dopamine agonists, and upregulates molecules relating to insulin signaling (unpublished data). Taken together, we hypothesized that APO treatment may upregulate IDE through activating insulin signaling. In our recent report (Nakamura et al. 2017), western blotting and immunostaining revealed that IDE was upregulated and two types of serine-phosphorylated insulin receptor substrate-1 (pS^{616} and $pS^{636+639}$ IRS-1) were downregulated in APO-treated 3xTg-AD mice brain. Figure 11.4 shows immunostaining data of hippocampus (CA1) in 13-month-old mice in that report (Nakamura et al. 2017). IDE was increased in 3xTg-AD mice compared to non-Tg mice and was further increased by APO treatment, while Aβ was decreased by APO treatment (Fig. 11.4a). In the same 13-month-old mice, pS^{616} and $pS^{636+639}$ IRS-1 were increased in 3xTg-AD mice compared to non-Tg mice and were decreased by APO treatment (Fig. 11.4b). All the alterations were statistically significant (Fig. 11.4a, b, right panels), indicating that APO treatment may decrease

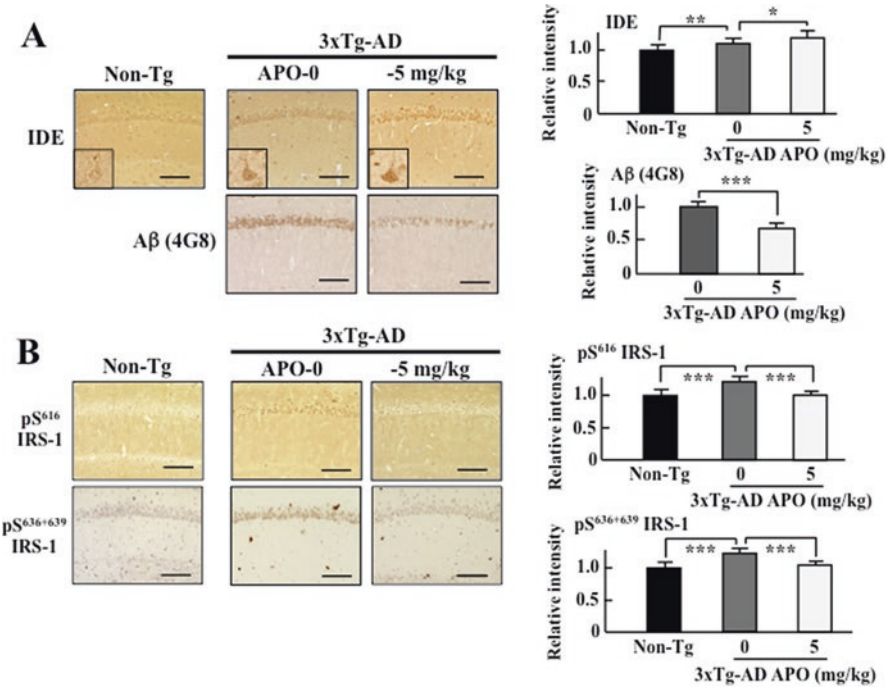

Fig. 11.4 Quantitative analysis of immunohistochemistry of hippocampus CA1 (Nakamura et al. 2017). (**a**) IDE and Aβ. IDE is increased in 3xTg-AD compared to non-Tg mice. APO treatment further increased IDE level. In contrast, Aβ is decreased by APO treatment. Inset shows a solitary neuron. (**b**) pS^{616} and $pS^{636+639}$ IRS-1. Both types of IRS-1 are increased in 3xTg-AD mice compared to non-Tg mice and are decreased by APO treatment. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$. Bars = 100 μm

insulin resistance of neurons (decreases in pS^{616} and $pS^{636+639}$ IRS-1) and may enhance insulin signaling associating with IDE upregulation.

Since APO is currently used as a subcutaneous injection drug for PD patients, we checked its effects on five AD patients without DM and have observed slight improvement of memory function (unpublished data). Also, APO treatment may reduce Aβ burden in the brains of PD patients (Yarnall et al. 2016). Thus, APO may be effective on "brain diabetes" as ~~well as~~ PPAR-γ agonists, DPP4 inhibitors, and GLP-1 agonists. In Fig. 11.5, our hypothesis of molecular pathogenesis in AD brain and therapeutic targets of APO therapy are presented. In AD neurons, increased insulin resistance decreases insulin signaling, leading to decreases in IDE levels and increases in GSK-3β, which may accelerate accumulation of both Aβ and p-tau, respectively. Increased Aβ oligomers may inhibit insulin signaling, which may result in a vicious cycle. APO may activate insulin signaling and IDE and may inhibit GSK-3β, thereby inhibiting AD pathology. In this context, APO may become a novel drug for AD targeting glucose-insulin metabolism in neurons. To evaluate

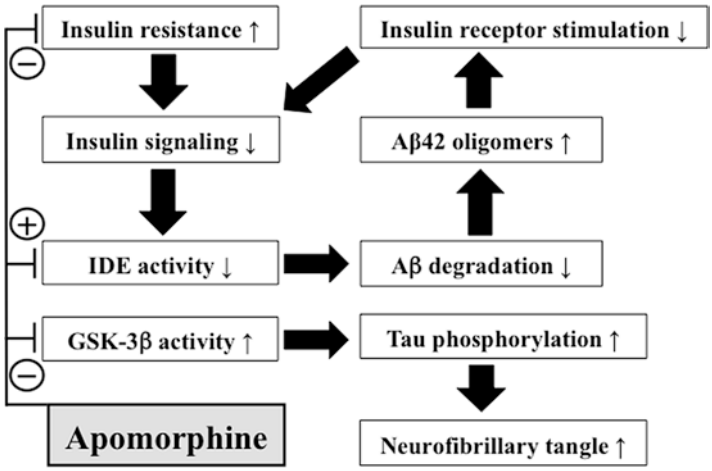

Fig. 11.5 Hypothetic scheme of pathogenesis related to insulin metabolism and therapeutic targets of APO in AD brain (Nakamura et al. 2017). Increased insulin resistance attenuates insulin signaling. Decreased insulin signaling downregulates IDE and upregulates GSK-3β, which increases Aβ oligomers and tau phosphorylation/neurofibrillary tangle, respectively. Increased Aβ42 oligomers attenuate insulin receptor stimulation, thereby fostering vicious cycle. APO treatment may improve insulin resistance, upregulate IDE, and attenuate GSK-3β activity

the significance of APO treatment, APO effects should be checked in comparison with other DM drugs in the future.

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