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Decoding Alzheimer's disease from perturbed cerebral glucose metabolism: Implications for diagnostic and therapeutic strategies

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ABSTRACT

Alzheimer's disease (AD) is an age-related devastating neurodegenerative disorder, which severely impacts on the global economic development and healthcare system. Though AD has been studied for more than 100 years since 1906, the exact cause(s) and pathogenic mechanism(s) remain to be clarified. Also, the efficient disease-modifying treatment and ideal diagnostic method for AD are unavailable.

Perturbed cerebral glucose metabolism, an invariant pathophysiological feature of AD, may be a critical contributor to the pathogenesis of this disease. In this review, we firstly discussed the features of cerebral glucose metabolism in physiological and pathological conditions. Then, we further reviewed the contribution of glucose transportation abnormality and intracellular glucose catabolism dysfunction in AD pathophysiology, and proposed a hypothesis that multiple pathogenic cascades induced by impaired cerebral glucose metabolism could result in neuronal degeneration and consequently cognitive deficits in AD patients. Among these pathogenic processes, altered functional status of thiamine metabolism and brain insulin resistance are highly emphasized and characterized as major pathogenic mechanisms. Finally, considering the fact that AD patients exhibit cerebral glucose hypometabolism possibly due to impairments of insulin signaling and altered thiamine metabolism, we also discuss some potential possibilities to uncover diagnostic biomarkers for AD from abnormal glucose metabolism and to develop drugs targeting at repairing insulin signaling impairment and correcting thiamine metabolism abnormality. We conclude that glucose metabolism abnormality plays a critical role in AD pathophysiological alterations through the induction of multiple pathogenic factors such as oxidative stress, mitochondrial dysfunction, and so forth. To clarify the causes, pathogeneses and consequences of cerebral hypometabolism in AD will help break the bottleneck of current AD study in finding ideal diagnostic biomarker and disease-modifying therapy.

Contents

Abbreviations: Aβ, β-amyloid; AD, Alzheimer's disease; ADNI, AD neuroimaging initiative; ADP, adenosine driphosphate; AGEs, advanced glycation end products; APOE, apolipoprotein E; APP, amyloid precursor protein; APP-CTFs, APP C-terminal fragments; ATP, adenosine triphosphate; BBB, blood brain barrier; CHEIs, cholinesterase inhibitors; CMRglu, cerebral metabolic rate of glucose; CNS, central nervous system; COX, cytochrome c oxidase; CSF, cerebrospinal fluid; FDG, ^{18}F-fluorodeoxyglucose; GLP-1, glucagon-like peptide-1; GLUT, glucose transporter; G6PDH, glucose-6-phosphate dehydrogenase; GSK-3, glycogen synthase kinase-3; IDE, insulin-degrading enzyme; IGF-1, insulin-like growth factor-1; IR, insulin receptor; IRS-1, IR substrate-1; KGDHC, α-ketoglutarate dehydrogenase complex; LTP, long term potentiation; MAPK, mitogen-activated protein kinase; MCI, mild cognitive impairment; MMSE, the Mini-Mental State Examination; MR, magnetic resonance; mTOR, the mammalian target of rapamycin; NFTs, neurofibrillary tangles; NMDAR, N-methyl-D-aspartic acid receptor; NSAID, non-steroidal anti-inflammatory drug; 8-OHG, 8-hydroxyguanosine; PDHC, pyruvate dehydrogenase complex; PET, positron emission tomography; PiB, ^{11}C-Pittsbergh compound; PI3K, phosphatidylinositide 3-kinases; PKM2, pyruvate kinase isozyme type M2; γ-PPAR, γ-peroxisome proliferator-actived receptor; PPP, pentose phosphate pathway; PS1, presenilin-1; RAGE, the receptor of AGEs; rCBF, regional cerebral blood flow; rCMRGlu, regional CMRGlu; ROS, reactive oxygen species; STZ, streptozotocin; TCA, tricarboxylic acid; TD, thiamine deficiency; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; TDP, thiamine diphosphate; TDPase, thiamine diphosphatase; TGF, transformation growth factor; TMP, thiamine monophosphate; TMPase, thiamine monophosphatase; TPK, thiamine pyrophosphokinase.

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1. Introduction

Alzheimer's disease (AD) is an age-related and progressive neurodegenerative disorder, characterized clinically by progressive cognitive impairment and pathologically by senile plaques and neurofibrillary tangles (NFTs). It has been more than 100 years since AD was described by German psychiatrist and neuropathologist Alois Alzheimer in 1906 (Berchtold and Cotman, 1998; Zilka and Novak, 2006). Currently, it becomes the most common type of dementia in the world. It is estimated to have more than 5.4 million AD patients in America (Alzheimer's Association, 2012), more than 6 million patients in China, and 35.6 million patients worldwide. Alzheimer's Disease International has predicted that people living with AD and other dementias worldwide will increase to 67.5 million by 2030 and 115.4 million by 2050 (Alzheimer's Disease International, 2010). Moreover, AD also exhibited a growing impact on global economic and social development. In USA, the costs for dementia patients will rise from $200 billion in 2012 to a projected $1.1 trillion (in today's dollars) by 2050 unless something is done (Alzheimer's Association, 2012). The total worldwide societal cost for dementia is estimated to be $604 billion in 2010, which is 1% of global gross domestic product (GDP), and is predicted to increase 85% of the costs in 2030 based on increase in the estimated number of people with dementia alone (Alzheimer's Disease International, 2010). However, ideal diagnostic biomarkers and efficient disease-modifying therapies for AD are still unavailable. Thus, developing easy-to-perform and low-cost diagnostic approaches and the disease-modifying therapies for AD has become a pressing issue in today's society.

There have been a huge number of studies on AD pathogeneses, including β-amyloid (Aβ) hypothesis (Hardy and Selkoe, 2002; Hardy and Higgins, 1992; Selkoe, 1991) and tau hyperphosphorylation hypothesis (Grundke-Iqbal et al., 1986; Ihara et al., 1986; Patrick et al., 1999). However, the precise etiologies and pathogeneses of AD still remain to be clarified, especially the molecular pathways by which the various pathological alterations selectively impair the cognitive domains related to learning and memory. Although Aβ hypothesis is evidenced by numerous experimental and clinical studies, Aβ vaccines that are significantly capable of reducing Aβ plaques were unable to prevent disease progression (Holmes et al., 2008). Unfortunately, to date, almost all the clinical trials targeting at eliminating Aβ deposit have done little to improve cognitive function (Gravitz, 2011; Holmes et al., 2008). Furthermore, effective therapy based on tau pathology is lack (Gozes, 2010; Medina, 2011; Pritchard et al., 2011). This frustrating situation has promoted us to reconsider current study strategies for AD diagnosis and therapy. In order to develop ideal diagnostic biomarker tests and efficient disease-modifying therapies for AD, greater emphasis should be paid on the initial events of the disease.

Accumulated evidence indicates that AD is an age-related metabolic neurodegenerative disease. The impairment in cerebral glucose metabolism is an invariant pathophysiological feature in AD and its occurrence precedes cognitive dysfunction and pathological alterations even for decades (Cunnane et al., 2011; Jack et al., 2010; Reiman et al., 1996; Small et al., 1995). Thus, clarification of the etiological factor(s) and consequences associated with abnormal cerebral glucose metabolism will likely provide valuable clues for treatment strategies as well as ideal diagnostic approaches in AD. This review will discuss the characteristic and central role of dysfunctional cerebral glucose metabolism in AD pathogeneses.

2. Feature of cerebral glucose metabolism

2.1. Feature of cerebral glucose metabolism

The brain is an organ with the most abundant energy metabolism in human body. On average, the adult brain accounts for only 2% of total body weight. However, it receives about 15% of the cardiac output and utilizes approximately 20% of total body oxygen consumption and 25% of total body glucose in the resting awake state (McKenna et al., 2006; Sokoloff, 1999). The fact that the respiratory quotient of brain is nearly 1 in the physiological state indicates carbohydrates as the predominant substrate for oxidative metabolism of the brain (Sokoloff, 1999). Now, it is unanimously recognized that glucose is an essential and predominant energy substrate for the adult brain under physiological condition (Bouzier-Sore et al., 2006). Even though other alternative substrates, like ketone bodies, glycogen and amino acids may also be used under certain circumstances, such as during the infant developmental period and extended fasting status in the adults, glucose is still the dominant energy substrate for the brain in most conditions. In addition, the limited pool size and compartmentation of these alternative substrates also restrict their capacity to satisfy cerebral energy requirements (Henderson et al., 2009). However, raising plasma ketones through dietary supplement under a mild and safe level of ketonemia has been demonstrated to enhance the proportional contribution of ketones to the brain's energy supply (Cunnane et al., 2011). Thus, ketones may be an

available fuel for improving deteriorated cerebral energy metabolism in AD.

Cerebral glucose metabolism includes two main processes: glucose transportation and intracellular oxidative catabolism. Normal physiological glucose transportation significantly depends on the function of astrocytes participating in the composition of blood brain barrier (BBB) (Molofsky et al., 2012) and various glucose transporters distributed in the brain (Duelli and Kuschinsky, 2001). Astrocytes play a vital role in adjusting glucose transportation and maintaining brain energy homeostasis, which readily take in glucose from blood through endothelial cells and convey energy metabolic substrates between blood and neurons (Erol, 2008; Simpson et al., 2007). Astrocytes also contain highly amounts of glycogen granules, and more granules accumulate in the region with more dense synapses (Phelps, 1972). It has been demonstrated that glycogen could be used to provide lactate for neuronal metabolism during hypoglycemia (Brown and Ransom, 2007; Pellerin et al., 2007), which may suggest astrocytes play critical roles in both normal glucose supply and hypoglycemic conditions. Different types of glucose transporters (GLUTs) also take part in the transportation of glucose from blood into neurons (Duelli and Kuschinsky, 2001). Among them, GLUT-1 and -3 are considered to play essential roles in the modulation of brain glucose transportation (Duelli and Kuschinsky, 2001; Simpson et al., 1994) and in the pathogenesis of AD (Liu et al., 2008).

Intracellular oxidative catabolism is composed of complicated pathways including glycolysis and pentose phosphate pathway (PPP) in cytoplasma, and Krebs cycle and oxidative phosphorylation in mitochondria (Kuzuya, 1990). Glycolysis and Krebs cycle provide reducing equivalents for oxidative phosphorylation and finally produce ATP from ADP through oxidative respiratory chain in mitochondria (Kuzuya, 1990), while PPP mainly plays an important role in fighting oxidative stress and synthesizing genetic substrates of the brain (Palmer, 1999; Russell et al., 1999). Either the abnormality of glucose transportation or intracellular oxidative catabolism dysfunction affects cerebral glucose metabolism, which likely contributes to the metabolic abnormalities in AD. Actually, glucose transportation abnormalities due to insulin resistance and intracellular metabolic alterations due to mitochondrial dysfunction have both been well demonstrated to occur in AD patients.

2.2. Glucose metabolism dysfunction increases the risk of cognitive impaired in the elderly

Notably, an improved understanding of physiological and pathological regulation of glucose homeostasis is impacting on our conception on chronic metabolic disorders of the brain including AD. The brain's high energy consumption dominantly deriving from glucose metabolism makes it vulnerable to impaired energy metabolism. In fact, both defects in hyperglycemia and hypoglycemia homeostasis heavily affect human brain health, especially cognitive function. The related observations have been documented by a huge amount of clinical and experimental studies (Biessels et al., 2006; Craft, 2005; Euser et al., 2010; Münch et al., 1998). Substantial evidence has also shown that in aging subjects, performance deficits on a series of cognitive tasks during training are due to insufficient cerebral glucose supply. Increasing glucose availability in selective brain areas can positively modulate subjects' performance in cognitive task, especially in aged animals. Microinjection of glucose into the medial septum, hippocampus, striatum and amygdala can enhance memory processing (Gold, 2005; McNay and Gold, 1998; Schroeder and Packard, 2003). These findings indicate that an aging individual is at a greater risk for exposure to glucose deprivation, especially during highly prolonged cognitive task or training. Now, there are a few studies to evaluate brain's susceptibility to varying levels of low glucose in aged, type 2 diabetes mellitus (T2DM) and AD subjects, particularly to confirm whether aged brain tissue will bear irreversible damage at shorter intervals compared to young brain tissue (Foster et al., 2008; Roberts and Chih, 1995). Our focus on the impairment of hypoglycemia, especially recurrent hypoglycemic episodes, on cognition is based on the evidence that a history of severe hypoglycemic episodes was associated with a greater risk of dementia among older patients with T2DM (Niswender, 2011; Whitmer et al., 2009). Analyzing the mechanism of physiological and pathological glucose metabolism in central nervous system (CNS) may help to establishing long-term preventative strategies, which thus could be used to improve metabolic buffering in the CNS related disorders including diabetes and AD (Shetty et al., 2011).

3. Cerebral glucose hypometabolism as an invariant biomarker in Alzheimer's disease

The advances in neuroimaging technology have allowed us to investigate the relationship in detail between brain energy metabolism and AD onset and progression. Positron emission tomography (PET) using the tracers such as ^{18}F-fluorodeoxyglucose (FDG) and ^{11}C-Pittsbergh compound (PiB) has become the most common and efficient in vivo approach in measuring brain energy metabolism (de Leon et al., 1983; Minoshima et al., 1997; Small et al., 1995), amyloid-related pathology (Jack et al., 2008; Klunk et al., 2004; Mathis et al., 2003), and the function of certain neural circuits (Kuhl et al., 1996; Nikolaus et al., 2009; Scheltens and Korf, 2000). In vivo ^{1}H-nuclear magnetic resonance (MR) spectroscopy may also be used to measure brain metabolism in humans but is rarely available in AD (Pan et al., 2001; Shulman et al., 2004). FDG is the suitable tracer for glucose metabolism in the brain with the advantage that it simulates both glucose transport and subsequent phosphorylation in glycolysis (Phelps et al., 1979). Besides, FDG is transported into brain at nearly the same rate as glucose. Furthermore, FDG also can be phosphorylated by hexokinase in the first step of glycolysis. However, it cannot be further catalyzed to fructose-6-phosphate by glucose-phosphate-isomerase. Hence, FDG is accumulated in the neurons as the form of FDG-6-phosphate but without further metabolism to produce CO_2 and H_2O (Cunnane et al., 2011). In AD PET studies, a reference brain region is used to minimize inter-individual variability in both absolute and relative measures of brain glucose uptake, which is usually the cerebellum because of its low involvement in AD pathology (Cunnane et al., 2011; Mosconi, 2005).

FDG-PET studies in AD have demonstrated consistent and progressive cerebral glucose metabolism reductions, of which the extent and topography correlate with symptom severity (Mosconi, 2005). Compared with age-matched controls, AD individuals show regional glucose metabolism impairment in parieto-temporal lobe, posterior cingulate cortex and the frontal areas during disease progression (Minoshima et al., 1997; Friedland et al., 1983;). In contrast, the primary motor and visual cortex, cerebellum, thalamic and basal ganglia nuclei are less severely affected (Mosconi, 2005). Previous study has shown that hypometabolism in AD firstly arises from memory-related brain regions, like hippocampus and entorhinal cortex, then to parietal, temporal and posterior cingulate cortex (Mosconi, 2005). It may indicate that the specific disease progression process occurs in AD patients. Moreover, the reduction of local cerebral metabolic rate of glucose estimated by FDG-PET also reflects the regional distribution of reduced synaptic activity and density in AD (Pappata et al., 2008; Rinne et al., 2003), which suggests that selectively regional hypometabolism correlates with specific cognition impairment in

AD patients. Although the mechanism of synaptic activity coupled to cerebral glucose metabolism has not been exactly identified, it does not preclude altered cerebral glucose metabolism determined by FDG-PET to be an effective biomarker for identifying the presence of cognitive dysfunction-associated progressive neurodegeneration (95% sensitivity and 79% specificity) and yielding higher diagnostic accuracy (89%) than clinical measures (77%) (Silverman et al., 2001). In addition, the studies also provide definitive evidence that FDG-PET has the capacity of high specificity in differentiating AD from other types of dementia (Albin et al., 1996; Silverman et al., 2001). Individuals with non-AD type dementia manifest different patterns of FDG-PET scan from those seen in AD patients (Silverman et al., 2003). Regional reduction of glucose metabolism in primary occipital cortex can efficiently discriminate dementia with Lewy bodies from AD (Albin et al., 1996; Hoffman et al., 2000).

Apolipoprotein E (APOE) ε4 allele is a risk factor for sporadic AD. The subjects with two copies of APOE ε4 allele have an especially high risk of AD. In late middle age, the cognitively normal subjects with homozygous APOE ε4 significantly showed reduced rates of glucose metabolism in the same posterior cingulate, parietal, temporal, and prefrontal regions as those are probably to develop AD (Reiman et al., 1996; Small et al., 1995). Small et al. (1995) found that in the 20 non-demented subjects carrying with APOE ε4 alleles, their memory performance did not show significant decline during following period, but cortical cerebral metabolic rate (CMRglu) significantly decreased. Mosconi and his colleagues found that the elderly subjects with homozygous APOE ε4 allele who manifest normal cognitive function can be predicted to convert to AD by evaluating their cerebral glucose metabolism using FDG-PET (Mosconi, 2005; Mosconi et al., 2004). Furthermore, researchers have also observed that the cerebral glucose metabolic reduction occurred on individuals with high risk of developing AD before their clinical symptoms appear for several years or even decades. For example, presenilin-1 (PS1) gene mutant carriers from families with early onset familial AD exhibited significant reduced cerebral glucose metabolism with an average of 13 years prior to the estimated age at the disease onset (Mosconi et al., 2008a,b, 2006). These data indicate that the combination of genetic risk with CMRglu decline would be beneficial for AD prediction and diagnosis.

As we described above, before the appearance of clinical manifestations in AD, some functional changes can be detected, like the hypometabolism in medial temporal lobe (Mosconi et al., 2008a, 2006). However, the insidious onset and progressive impairment of memory and other cognitive functions of AD make it difficult to distinguish from normal healthy aging (McKhann et al., 1984). Thus, finding an early asymptomatic event to mark those people who are cognitively normal seems to be important for AD prevention and early-intervention. Clinical and research interest has now focused on mild cognitive impairment (MCI) as a prodromal AD stage (DeCarli, 2003; Hatashita and Yamasaki, 2010; Petersen et al., 2001; Ringman et al., 2009). MCI is proposed as a transitional stage from healthy aging to dementia, during which individuals have the ability to perform regular activities of daily living but suffer isolated memory damage without or with other domain(s) of cognitive dysfunction which is often normal in healthy aging (DeCarli, 2003; Hatashita and Yamasaki, 2010; Petersen et al., 2001; Ringman et al., 2009). Several studies have demonstrated that MCI patients are at a higher risk to progress to AD, with an estimated conversion rate of 10–15% per year (Petersen et al., 2001). Magnetic resonance imaging findings have also provided strong evidence that in MCI, AD-associated volume losses could be repeatedly detected in the hippocampus, the entorhinal cortex and parahippocampal gyrus (Hatashita and Yamasaki, 2010; Henneman et al., 2009; Raji et al., 2009). Considering the fact that metabolism function alterations antedate structural change in AD brain, PET imaging may provide earlier diagnosis of this disease. With the combination of MRI, FDG-PET studies have shown that medial temporal lobe hypometabolism is a specific and sensitive marker for the identification of MCI (Mosconi, 2005).

Amnestic MCI is the most common form of MCI, with an incidence of 1–3% in the general community and a higher risk of developing AD (Petersen et al., 2001). The characteristic of the amnestic MCI symptoms is objective memory impairment, defined as scores <1.5 SD below the age-matched control mean on at least one of two delayed recall tests without other significant deficits on detailed neuropsychological examination (Petersen et al., 2001). Compared with amnestic MCI, other types of MCI may progress to non-AD dementia, like frontotemporal dementia, dementia with Lewy bodies, vascular dementia, primary progressive aphasia and Parkinson's disease, in which isolated memory damage does not exist (Mosconi, 2005).

There is an apparent decrease of glucose metabolism in hippocampal structures on FDG-PET scans in MCI (Mosconi et al., 2005), which is particularly prominent in amnestic MCI (Jauhiainen et al., 2008). According to previous evidence, the topographical progression of hypometabolism in MCI brain possibly arises from memory related regions, like hippocampus, entorhinal cortex, then to other higher cognition-associated neocortical regions like parietal, temporal, and finally frontal cortex (Jauhiainen et al., 2008; Mosconi, 2005), which may reflect different susceptibilities of brain regions to hypometabolism in MCI or AD brain.

In a European multicenter study in 1999, 52 patients with severe memory deficits and Mini-Mental State Examination (MMSE) score of 24 points or greater had been followed more than an average of 2 years (Herholz et al., 1999). The investigators found that impairment of temporoparietal cortex (angular gyrus and vicinity) predicted progression of cognitive impairments by 3 MMSE points or more, with 65% sensitivity and 86% specificity. These initial observations were followed by several studies indicating a high predictive power of FDG-PET, with a sensitivity of 70–93% and specificity of 47–89% for prediction of rapid progression to dementia (Herholz, 2010; Li et al., 2008). Posterior cingulate hypometabolism was a brain area to be recognized as an early sign of progression in a small study of eight patients with severe memory deficits (Berent et al., 1999; Minoshima et al., 1997; Mosconi et al., 2009). Combining with the results above, glucose hypometabolism of temporoparietal and posterior cingulate association cortex can serve as a reliable biomarker for the diagnosis of prodromal AD in MCI patients (Herholz, 2010). In a recent analysis of longitudinal AD Neuroimaging Initiative (ADNI) study data, Landau et al. (2010) proposed FDG-PET as a predictor in MCI for conversion to AD combining with memory testing. As MCI is a prodromal AD stage with a progression tendency to AD, establishing reasonable FDG-PET imaging criteria for MCI identification is very important for the initial prediction and diagnosis of AD.

However, it is still controversial whether the regional CMRGlu (rCMRGlu) measured by FDG-PET exists significant difference between MCI and normal control. The study has showed that cerebral glucose hypometabolism may be related to brain grey matter atrophy and is much less pronounced after correction of cerebrospinal fluid (CSF) partial volume effects (Chételat et al., 2008). Devanand et al. (2010) found that rCMRGlu was decreased in precuneus and parietal cortex in AD as compared with normal control and MCI, but without differences between MCI and normal control. The ratio of regional cerebral blood flow (rCBF) to rCMRGlu was found to have a similar behavior in all brain regions for young and old subjects as shown by a correlation coefficient of 88%, which

indicates a decline in rCBF and rCMRGlu values as a natural event of aging rather than a specific abnormal condition (Berti et al., 2010). A study in a small sample of people suggests that the diagnostic performance of rCMRGlu reduction in parietal and posterior cingulate cortex may be superior to those of ^{11}C-PiB in distinguishing MCI from normal control (Devanand et al., 2010; Driscoll et al., 2011). Berti et al. (2010) reported that MCI patients were identified by PiB-PET with 75% accuracy from controls. However, only 54% of the PiB-positive MCI patients also showed FDG reductions, reflecting a dissociation between fibrillar amyloid load and rCMRglu reductions, which indicates the hypometabolism of selective brain regions and Aβ deposition are induced by relatively independent pathways. Further researches need to be performed to confirm the sensitivity and specificity of cerebral glucose hypometabolism for MCI diagnosis, as well as the match-association of hypometabolism and Aβ plaques in MCI diagnosis.

In summary, glucose hypometabolism in the selective cortical regions is an invariant feature and a pre-clinical event both in familial and sporadic AD. The clarification of the mechanism in cerebral glucose hypometabolism will help not only to understand AD pathogenesis but also to find new diagnostic and therapeutic targets for AD.

4. Abnormal biochemical processes of glucose metabolism in Alzheimer's disease

As glucose metabolism is a multi-step process regulated by a lot of extracellular and intracellular factors (Kuzuya, 1990). Cellular glucose metabolism mainly includes two processes: glucose transportation and intracellular glucose metabolism. The function of insulin signaling pathway plays a key role in regulating glucose trans-membrane transportation (Apelt et al., 1999). T2DM is a metabolic syndrome characterized by insulin resistance, which is also a pathophysiological feature of AD. Thus, the links between T2DM and AD would be a window for us to understand the pathogenic mechanism of AD. Moreover, balanced cellular glucose transportation also depends on the normal function of astrocytes (Duelli and Kuschinsky, 2001) and various glucose transporters expressed in brain (Choeiri et al., 2002; Duelli and Kuschinsky, 2001). Intracellular glucose metabolism involves four pathways: Krebs cycle and oxidative phosphorylation that occur in mitochondria, and PPP and glycolysis that take place in cytoplasm (Kuzuya, 1990). Thus, the mechanisms involved in glucose transportation abnormalities, especially insulin resistance, and intracellular glucose metabolic disturbance possibly contribute to cerebral glucose hypometabolism in AD. The physiological processes of glucose metabolism are described in Fig. 1.

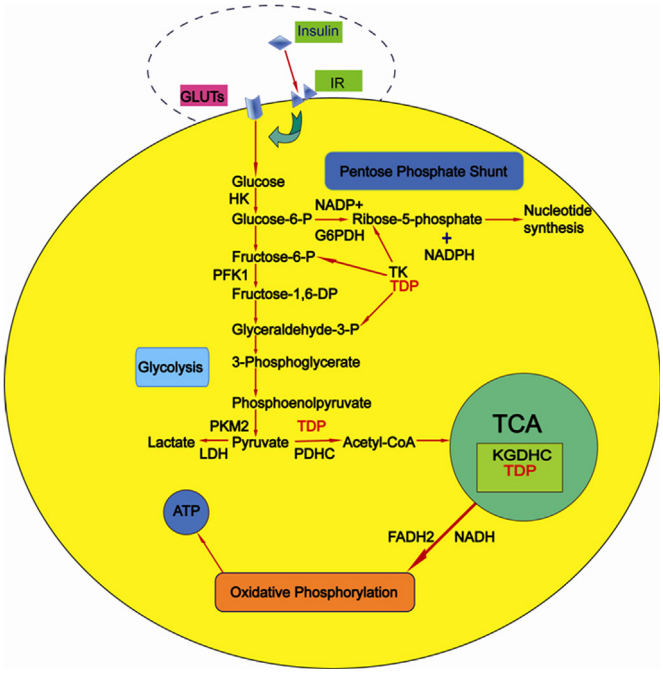

Fig. 1. The physiological process of glucose metabolism. Glucose is transported into cells through GLUTs, and further oxidized by different enzymes. Intracellular glucose metabolism involves four pathways: Krebs cycle and oxidative phosphorylation that occur in mitochondria, and pentose phosphate pathway and glycolysis that take place in cytoplasm. TPP is the co-enzyme of TK, PDHC, and KGDHC, which are all rate-limiting of enzymes in glucose metabolism. The most important factor to regulate glucose transport is insulin and its receptor, which is marked by dotted line.

4.1. Disrupted glucose transport

4.1.1. Brain insulin resistance: links between type 2 diabetes mellitus and Alzheimer's disease

Cognitive deficits have become a challenge for T2DM patients and vice versa, most of AD patients also show abnormal fasting glucose and insulin resistance. Some investigators even called AD as "Type 3 diabetes mellitus" or "brain insulin resistance"(de la Monte, 2012; Talbot et al., 2012; de la Monte and Wands, 2008; Steen et al., 2005). Based on our understanding, there are many similarities between AD and T2DM, including epidemiology, clinical manifestations, pathological alterations, and pathophysiological mechanism.

4.1.1.1. Epidemiologic, clinical, pathological links between type 2 diabetes mellitus and Alzheimer's disease. DM is a heterogeneous metabolic syndrome characterized by hyperglycemia that results from the impairment in insulin production and/or efficacy. In type 1 diabetes mellitus (T1DM), the autoimmune destruction of pancreatic β cells leads to the loss of insulin production, whereas T2DM is mainly characterized by an impaired insulin action—insulin resistance. Globally, estimates pointed to 250 million diabetic patients worldwide in 2010, with 90% of the patients being involved by T2DM (Correia et al., 2012; Roriz-Filho et al., 2009). Aging is a high risk factor of T2DM, and most of T2DM patients are elderly people. Currently, T2DM has become a common disease that seriously affects the life quality and span of the elderly people due to the long-term complications but not diabetes itself. These complications include cardiovascular disease, nephropathy, retinopathy, peripheral, autonomic neuropathy, and encephalopathy (Duarte et al., 2012; Sims-Robinson et al., 2010).

T2DM has been demonstrated to be correlated with AD. The individuals with T2DM have a two- to three-fold increased relative risk of AD, independent of the risk for vascular dementia (Arvanitakis et al., 2004; Leibson et al., 1997). A neuroimaging study using MRI showed that older patients with T2DM have a moderately increased risk for developing hippocampal atrophy and that the severity of lesions parallels the progression of T2DM. Moreover, T2DM has also been demonstrated to have a high risk of developing MCI. Furthermore, metabolic syndrome characterized by insulin resistance has also been demonstrated to have increased risk of AD (Ferreira et al., 2010; Garcia-Lara et al., 2010; Janson et al., 2004). Conversely, AD patients exhibit significantly increased prevalence of T2DM and impaired fasting glucose as compared to control subjects, which over 80% of AD patients comorbid T2DM and impaired fasting glucose (Janson et al., 2004; Li and Holscher, 2007). Using an ex vivo stimulation protocol with near physiological doses of insulin, Talbot K and his colleagues identified prominent brain insulin resistance of post-mortem AD patients even in the absence of diabetes (Talbot et al., 2012). Thus, these results suggest that T2DM is closely correlated with AD in their epidemiology.

Apart from the links in epidemiology, T2DM and AD also showed similar clinical symptoms and signs, including cognitive impairment, impaired fasting glucose, chronic hyperglycemia, hippocampal atrophy. As what we discussed above, T2DM has a high risk of cognitive impairment, possibly due to chronic hyperglycemia, repeated occurrences of severe hypoglycemia, microvascular complications, and insulin resistance during the process of disease. It indicates that T2DM has a significant impact in the patients' brain function (McNay and Recknagel, 2011; Moreira et al., 2009). In addition to above-mentioned dysfunction, many other conditions associated with T2DM may combine to facilitate its cognitive impairment, including stroke, hypertension, dyslipidemia, and obesity (McNay and Recknagel, 2011; Reijmer et al., 2010). The association between metabolic syndrome and cognitive deficit suggests that metabolic dysfunction may increase the risk of neurodegeneration (Reijmer et al., 2010; Roriz-Filho et al., 2009). Actually, patients with T1DM and T2DM have been previously shown to exhibit cognitive dysfunction and brain structure abnormalities (Correia et al., 2012; Kim and Feldman, 2012). Moreover, brain atrophy in T2DM patients is very prominent in cortical, subcortical, and hippocampal areas (Biessels et al., 2002; Correia et al., 2012), which has been demonstrated to be associated with cognitive impairment. In T1DM patients, cognitive deficit appears to be mainly attributed to its short-term complications, like acute hyperglycemia and/or hypoinsulinemia, which lead to lower performance on cognitive function tests (McNay and Recknagel, 2011; Roriz-Filho et al., 2009). However, in T2DM, the decline in cognitive function seems to be more related to elderly patients, which may be explained by insulin resistance that prevalently occurs in these patients (Duarte et al., 2012; McNay and Recknagel, 2011). Considering the effects T2DM on cognitive impairment, it is no doubt that T2DM patients should have higher risk to suffer from degenerative disease, including AD.

Aβ plaques and NFTs are two pathological markers of AD brain. Interestingly, a few of studies also showed that T2DM exhibited Aβ accumulation in similar regions from post-mortem brains (de la Monte and Wands, 2008; Steen et al., 2005). Impaired insulin signaling pathway increases Aβ accumulation in T2DM patients (Steen et al., 2005). Besides, in a model of T2DM produced by intracerebral injection of streptozotocin (STZ), de la Monte et al. found that brains with T2DM were atrophied and had evident neurodegeneration with neuron loss, gliosis, activated glycogen synthase kinase-3β (GSK-3β), hyperphosphorylated tau, and Aβ deposit, which are the features of AD brains (de la Monte and Wands, 2008; Lester-Coll et al., 2006). Moreover, the deficiency of insulin receptor (IR) substrate-2 has also been reported to reduce brain growth and enhance tau phosphorylation. Hence, these studies possibly indicate that T2DM shares some pathological alterations with AD.

4.1.1.2. Impaired insulin signaling in type 2 diabetes mellitus and Alzheimer's disease. Actually, there is a huge body of evidence supports impaired insulin signaling to be the fundamental correlation between T2DM and AD (Bomfim et al., 2012; Zhao et al., 2008a,b). Furthermore, the studies have showed that the dysfunction of cerebral insulin signaling pathway exacerbated neurodegeneration and synaptic loss, which are responsible for cognitive deficits (Bosco et al., 2011; de la Monte, 2012; Matsuzaki et al., 2010; Schrijvers et al., 2010).

Insulin and its receptor are the key factors for modulating glucose availability and energy homeostasis both for CNS and peripheral systems. IRs are widely expressed throughout CNS (Baskin et al., 1988; Havrankova et al., 1978; Zhao et al., 1999). The study have reported that AD exhibits the decrease in CSF insulin levels, the ratios of CSF insulin over plasma insulin, IR expression, and the increase in fasting plasma insulin levels (Moloney et al., 2010). Once the dysfunction of insulin signaling pathway emerges in brain, cerebral glucose availability and energy homeostasis will be disturbed. Most of the energy generated in brain is used for the transmission of synaptic signals. Intermediate metabolites of glucose such as acetyl coenzyme A and succinyl coenzyme A are the precursors of acetylcholine, a neurotransmitter closely linked to cognitive function. Thus, brain energetics contributes to neurotransmission associated with cognitive dysfunction (Kann and Kovacs, 2007). Impaired cerebral glucose availability rapidly causes the dysfunction of cognition-related synaptic transmission.

Based on the results from the previous studies, the reduction of expression of insulin, insulin-like growth factor type-1 and 2 (IGF-1 and IGF-2) as well as their receptors participates in the pathogenesis of AD. Steen et al. (2005) has demonstrated that the expression of insulin and IGF-1/2 receptors markedly reduce in AD brains, which is correlated with the pathological alterations, including increased GSK-3β activity and APP mRNA level. Moreover, the studies have demonstrated that endogenous deficiencies of genes encoding insulin, IGF-1, IGF-2 peptides and their receptors, can occur in AD brain without T2DM. These alterations are involved in the progression of AD according to Braak staging (Rivera et al., 2005). In addition, the disruption of insulin transportation may partially contribute to the decreased CSF insulin and IGF-1 levels in AD (Bosco et al., 2011; de la Monte, 2009), which is associated with decreased BBB function induced by continuous peripheral hyperinsulinemia (Bosco et al., 2011; Li and Holscher, 2007). However, neurons in brain also express and secrete the insulin (Kuwabara et al., 2011), and in AD brain, insulin mRNA expression was 4-fold lower in the hippocampus and 2-fold lower in the hypothalamus compared to control brains (Steen et al., 2005). Thus, both mechanisms of transportation disruption and local secretion dysfunction can induce the declined insulin level in AD brain. Beyond the above-mentioned mechanisms, impaired binding between insulin, IGF-1 and their receptors also was observed in AD, which is associated with changes in membrane cholesterol levels which affected the membrane dynamics upon aging and/or APOE4 genotype (de la Monte, 2009; Li and Holscher, 2007). Chua et al. (2012) has demonstrated that impaired insulin signaling precedes Aβ accumulation, which implies the importance of reduced insulin signaling among pathogenic factors of Alzheimer's neurodegeneration.

Insulin/IGF-1 signaling defects predominantly involve in phosphatidylinositide 3-kinases (PI3K)/Akt pathway through producing harmful cascades in glucose metabolism (Liu et al., 2011). It was recently proposed that decreased expression and function of PI3K/Akt-mediated GLUTs in AD brain could lead to brain glucose hypometabolism and the subsequent decline in mitochondrial ATP production (Bosco et al., 2011). By comparing the function of brain insulin-PI3K-Akt signaling pathway in the frontal cortices of AD, T2DM, T2DM with AD, and control subjects, Liu et al. (2011) found that the deficiency of insulin-PI3K-Akt signaling was more significant in subjects with both T2DM and AD. Furthermore, their studies also showed that the levels and the activation of the insulin-PI3K-Akt signaling components correlated negatively with the level of tau phosphorylation and positively with tau O-GlcNAcylation, suggesting that impaired insulin-PI3K-Akt signaling might contribute to neurodegeneration in AD through decreased O-GlcNAcylation and consequent tau hyperphosphorylation.

Recently, Bomfim et al. (2012) reported that Aβ oligomers could activate the tumor necrosis factor α/c-Jun N-terminal kinase pathway, induce IR substrate-1 (IRS-1) phosphorylation at multiple serine residues, and inhibit physiological phosphorylated IRS-1 (at Tyr896) in cultured hippocampal neurons. Moreover, the impairment of IRS-1 signaling was also observed in APP/PS1 transgenic mice as well as in cynomolgus monkeys intraventricularly injected

with Aβ oligomers (Bomfim et al., 2012). Similar pathophysiological alterations were also found in human AD brains by Talbot et al. (2012). These results showed that AD patients with T2DM may be closely associated with IRS-1 dysregulation and IGF-1 resistance.

However, the pathophysiological alterations associated with cerebral insulin signaling dysfunction in AD are much more complicated than we anticipated (Arab et al., 2011). It has also been reported that other factors involved in insulin resistance such as mitogen-activated protein kinase (MAPK) pathway, GSK-3, insulin degrading enzyme (IDE) and microvascular dysfunction are responsible for AD pathophysiological alterations (Arab et al., 2011; Carro and Torres-Aleman, 2004; Dorr et al., 2012; Farris et al., 2003; Yan et al., 1996). MAPK pathway also has been shown to be significantly activated in AD patients, which is correlated with increased neuroinflammation, tau hyperphosphorylation, and Aβ trafficking (Bosco et al., 2011). Actually, tau hyperphosphorylation is probably related to an excess activation of GSK-3β, MAPK, and cyclin-dependent kinase 5, which are major tau kinases responsible for tau phosphorylation (de la Monte, 2009; Moreira et al., 2009). Moreover, the decreased phosphorylation of GSK-3α and the increase in its activity may facilitate γ-secretase activity and APP processing, resulting in increased intracellular Aβ levels (Kim and Feldman, 2012; Moreira et al., 2009). Insulin has been also proposed to regulate extracellular Aβ degradation by modulating IDE activity (van der Heide et al., 2006). IDE is a zinc-metalloprotease that participates in the degradation of several extracellular substrates, like insulin and Aβ. Thus, low IDE activity in diabetes patients may contribute to increase Aβ levels in the brain. The study demonstrated that the reduced mRNA and protein levels as well as activity of IDE were negatively correlated with hippocampal $A\beta_{1\text{-}42}$ content in severe AD patients (Zhao et al., 2007).

To sum up, the dysfunction of insulin/IGF signaling and associated factors is a common pathophysiological mechanism to induce neurodegeneration in T2DM and AD. Therefore, some investigators have proposed the term, T3DM or brain insulin resistance, to reflect the dysfunction of insulin signaling pathway in AD (de la Monte and Wands, 2008; Steen et al., 2005). Insulin-sensitizing agents such as ligands for γ-peroxisome proliferator-actived receptor (γ-PPAR) and intranasal insulin have offered a potential therapeutic solution (Brodbeck et al., 2008; Reger et al., 2008a,b). The study by Zhao et al. (2008a,b) showed that neuronal insulin signal transduction was prone to be disrupted by soluble Aβ oligomers, which caused a rapid and substantial loss of dendritic IRs through redistribution of the receptors, suggesting that soluble Aβ oligomers are responsible for insulin resistance and synaptic dysfunction in AD brain. Some studies have proved that insulin treatment prevents the binding of Aβ oligomers with IR and synapse loss (De Felice et al., 2009; Gasparini et al., 2001), as well as improves cognitive dysfunction in AD.

Apart from insulin resistance, other pathophysiological alterations in T2DM also could occur and even play significant roles in AD, such as elevated advanced glycation end products (AGEs) and transformation growth factor (TGF). The term "AGEs" is currently used for a broad range of advanced products of the glycation process (also called the "Maillard reaction") (Martina and Gerald, 2010). The previous evidence has demonstrated that AGEs contribute to the pathological process of T2DM as well as AD (Gasser and Forbes, 2008; Li and Holscher, 2007; Martina and Gerald, 2010). AGEs formation is accelerated in T2DM and correlated with T2DM-associated vascular complications (Tan et al., 2006). On the other hand, AGEs also play an important role in AD pathogenesis (Martina and Gerald, 2010). Immunohistochemical studies have showed AGEs present in senile plaques (Kimura et al., 1995) as well as in NFTs (Castellani et al., 2001). Aβ, AGEs, and APOE were positively immunoreactive in most of the plaques in hippocampus of AD patient (Martina and Gerald, 2010; Sasaki et al., 2001). Besides, Aβ-, AGEs-, and the receptor of AGEs (RAGE)-positive granules were also found in hippocampus neurons (Martina and Gerald, 2010). In cell culture studies, the cytotoxic effect of AGEs was completely prevented by the addition of the anti-AGE-2-specific antibody, but not by other types of anti-AGE antibodies (Takeuchi et al., 2000), which may indicate that only specific type of AGEs could contribute to the pathology of AD. T2DM patients also have higher TGF-β1 levels in plasma and kidney than normal controls (Yener et al., 2007). Besides, hyperglycemia was demonstrated to trigger the elevations of TGF-β1 in patients with T2DM (Yener et al., 2007). Increase of TGF-β1 also has been demonstrated in STZ-induced T2DM rats (Shankland et al., 1994). Moreover, suppression of TGF-β signaling reduced mesangial expansion and interstitial fibrosis in experimental T2DM nephropathy (Ziyadeh et al., 2000), which indicates that TGF-β may participate in the inhibition of inflammatory factors induced by T2DM. Correspondently, TGF-β1 has been demonstrated to have an anti-inflammatory effect in brain. In AD, TGF-β1 was shown to reduce Aβ accumulation and increase Aβ clearance (Wyss-Coray et al., 2001). TGF-β1 was found within senile plaques, while TGF-β2 was found in NFTs in AD brains, suggesting that TGF-β1 plays a protective role in AD by clearing Aβ plaques and TGF-β2 seems to be a response against NFTs in neurons. Further investigation reveals that TGF-β1 may exert its protective role in AD by increasing B-cell lymphoma-2 (bcl-2) expression (Prehn et al., 1994), which is a well-known apoptotic inhibitory factor and balancing calcium dynamics in cultured neurons. Furthermore, suppression of TGF-β1 expression leads to elevations of Aβ levels and β-secretase-cleaved soluble amyloid precursor protein (APP) (Tesseur et al., 2006). The above-mentioned evidence suggests that TGF plays a significant role in both T2DM and AD pathology.

In all, T2DM and AD show many similarities in epidemiology, clinical manifestations, pathological alterations, and altered signal transduction pathways. Among these common features, insulin resistance is the most similar characteristic in T2DM and AD.

4.1.2. Abnormal glucose transporters

The abnormal transport of glucose from blood to astrocytes, and from astrocytes to neurons is associated with many CNS diseases (Harr et al., 1995; Kaushik Shah, 2012; Simpson et al., 1994), which may also be related to the function of many glucose transporters expressed in brain.GLUT1 mediates glucose transport from blood to astrocytes and includes two isoforms based on the difference of molecular weight: 55-kD GLUT1 expressed in endothelial cells of brain vessels and 45-KD GLUT1 mainly expressed in astrocytes (Duelli and Kuschinsky, 2001). GLUT3 is the mostly distributed in neurons and has a low Michaelis-Menten constant, which facilitates the continuous supply of glucose to the neurons even at low interstitial glucose concentrations (Duelli and Kuschinsky, 2001). Other types of glucose transporters, like GLUT4 and GLUT5 (Apelt et al., 1999; Duelli and Kuschinsky, 2001; Kaushik Shah, 2012), also distribute in brain. GLUT4 is insulin-responsive (Apelt et al., 1999) and only expresses in some specific type of neurons, like hippocampus neurons (Piroli et al., 2007).

The association of cerebral glucose transport dysfunction with AD pathology has been clinically investigated. AD patients show decreased GLUT1 and GLUT3 expressions, especially in the cerebral cortex (Simpson et al., 1994). The dentate gyrus of hippocampus also exhibits decreased GLUT3 expression (Harr et al., 1995). Significant decline in expression levels but without statistical changes in mRNA levels of GLUT1 in the human AD brain suggests a post-transcriptional regulation mechanism (Mooradian et al., 1997).

UDP-N-acetylglucosamine is a substrate for O-linked β-N-acetylglucosamine (O-GlcNAc) transferase, which is required for catalyzing O-GlcNAcylation of Ser/Thr protein residues (Liu et al., 2009). Its production needs 2–5% energy provided by glucose oxidative phosphorylation. Liu et al. (2008) reported the decreased O-GlcNAcylation paralleled GLUT1 and GLUT3 reductions, and it is shown to be negatively correlated between GLUT1 and GLUT3 reduction and tau phosphorylation levels. Thus, they proposed that diminished expression of glucose transporters could induce hypometabolism in the brain, which decrease the O-GlcNAcylation of tau and conversely increase its phosphorylation (Liu et al., 2008). Finally, the tau hyperphosphorylation-induced NFTs underlie the cognitive deficits of AD subjects.

The T2DM brain had a decreased level of neuronal GLUT3 expression as compared to AD brain. In addition, the decrease in O-GlcNAcylation and increase in tau phosphorylation were also observed, which is similar to the AD brain (Liu et al., 2009). It may suggest that the dysfunction of glucose transportersmay be the common feature of T2DM and AD pathology.

Based on the regulation mechanism of glucose transporter expression (Liu et al., 2008), it is more likely that reduction of GLUT1 and GLUT3 expression is the result of decreased energy demand of some brain regions in AD brain, but rather presented as an initiated force that causes brain hypometabolism in AD brain. Hence, Liu's study (Liu et al., 2009) can be alternatively explained that hypometabolism results in both reduced glucose transporters expression and decreased O-GlcNAcylation of tau. To date, no definitive links were established between the altered glucose transporter function and disease progression.

4.2. Intracellular glucose metabolic disturbance

By intracellular catabolism, glucose is eventually transformed into adenosine triphosphate (ATP) and the metabolites (e.g. acetyl coenzyme A and succinyl coenzyme A) to provide the energy for neural activities and the substrates for biosynthesis. The processes of intracellular glucose catabolism are mainly involved in four pathways: Krebs cycle and oxidative phosphorylation that mainly occur in mitochondria, and PPP and glycolysis that take place in cytoplasm. Mitochondrial dysfunction has been widely confirmed both in clinical and experimental studies of AD (Beal, 2005; Bubber et al., 2005; Lustbader et al., 2004; Schapira, 2012). Notably, as three key enzymes in Krebs cycle and PPP, the activities of pyruvate dehydrogenase complex (PDHC), α-ketoglutarate dehydrogenase complex (KGDHCC) and transketolase have been demonstrated to decrease in AD (Gibson et al., 1988; Mastrogiacoma et al., 1996a; Sheu et al., 1988; Sorbi et al., 1983). Their common coenzyme, thiamine diphosphate (TDP), also showed altered levels both in blood and brain of AD patients (Gold et al., 1998; Mastrogiacoma et al., 1996a). These results indicate the important roles of mitochondrial dysfunction and impaired thiamine-dependent processes in cerebral glucose hypometabolism of AD.

4.2.1. Altered functional status of thiamine metabolism

4.2.1.1. Decreased activities of thiamine-dependent enzymes. The decreased activities of mitochondrial thiamine-dependent enzymes are also the prominent manifestations in AD, which provides us an alternative clue to explore the culprit of mitochondrial dysfunction and cerebral glucose metabolic abnormality. The Krebs cycle and oxidative phosphorylation of glucose metabolism mainly occurring in mitochondria are essential for maintaining normal cerebral function and offer 95% of brain energy fuels (Bonda et al., 2010). The Krebs cycle and oxidative phosphorylation of glucose are significantly disrupted in AD brains possibly due to the alterations of relevant enzymes, especially two key enzymes: PDHC and KGDHC (Gibson et al., 1988). Bubber et al. (2005) tested impairments in the Krebs cycle enzymes of mitochondria in AD patients and found significantly decreased PDHC and KGDHC activities while the activities of the other four Krebs cycle enzymes were unchanged. In fact, many studies have verified this phenomenon that the activities of thiamine-dependent PDHC and KGDHC significantly decrease in peripheral and brain tissues of AD patients (Butterworth and Besnard, 1990; Gibson et al., 1988; Ko et al., 2001; Paoletti et al., 1990). In addition, transketolase, another thiamine-dependent key enzyme in non-oxidative branch of PPP is also significantly altered both in peripheral and cerebral tissues (Butterworth and Besnard, 1990; Gibson et al., 1988; Paoletti et al., 1990; Sheu et al., 1988). It catalyses the conversion of D-xylulose 5-phosphate and D-ribose 5-phosphate to D-glyceraldehyde 3-phosphate and D-sedoheptulose 7-phosphate, and needs TDP and divalent metal ions such as Mg^{2+} as cofactors (Schenk et al., 1998). Transketolase-catalyzing reactions play an important role in the exchange of glycolysis and oxidative branch of PPP (Butterworth and Besnard, 1990). To date, several sources of evidence have suggested transketolase was modified in AD. Transketolase activity has been shown to decrease first and to recover last following thiamine repletion in animals (Giguere and Butterworth, 1987), which may indicate that transketolase is much more sensitive to thiamine change than other thiamine-dependent enzymes. Reduced transketolase activity has been demonstrated in red blood cells, fibroblasts, and brain tissues from AD patients. The study on erythrocytes from AD shows reduced transketolase activity, which suggests structural abnormalities of transketolase rather than thiamine deficiency in AD (Butterworth et al., 1993; Sheu et al., 1988). Other data suggest abnormalities in proteinase actions contribute to the transketolase alterations. In cultured fibroblasts from AD patients, transketolase was shown to have an unusually high pI, which is characterized as a maker of Alzheimer's disease (Tombaccini et al., 1994). Further studies showed that it is attributed to the abnormal cysteine proteinases actions (Paoletti and Mocali, 1991; Paoletti et al., 1997). Brain cortical tissues from AD patients by biopsy also have been demonstrated to have low transketolase activity by 52% decrease (Butterworth and Besnard, 1990). Our previous study demonstrated that thiamine deficiency (TD) impaired hippocampal neurogenesis by inducing low transketolase activity (Zhao et al., 2008a,b, 2009). However, there is no definitive evidence to prove transketolase abnormality correlates with AD pathology, and the alteration of transketolase activity did not parallel AD progression (Schenk et al., 1998). Because TDP, active form of thiamine, is an essential coenzyme for mitochondrial PDHC and KGDHC as well as cytosolic transketolase in catalyzing the reactions of glucose metabolism, it suggested that altered thiamine metabolism is involved in abnormal glucose metabolism in AD.

4.2.1.2. Thiamine and glucose metabolism. As what we mentioned above, three thiamine-dependent enzymes (transketolase, PDHC and KGDHC) play the important roles in glucose metabolism (Schenk et al., 1998; Shoffner, 1997). Transketolase is the rate-limiting enzyme of non-oxidative branch in PPP (Butterworth and Besnard, 1990; Butterworth et al., 1993; Gibson and Blass, 2007), which is critical in the interchange of metabolites between glycolysis and the pentose shunt (Kauffman, 1972). PDHC is the entry point for carbon, as the form of acetyl CoA, where carbons were transported into the tricarboxylic acid (TCA) cycle to be oxidized (Kuzuya, 1990; Shoffner, 1997). KGDHC is the rate-controlling step of the TCA cycle under physiological conditions (Butterworth and Besnard, 1990). Thus, thiamine-dependent processes modulate essential aspects of brain glucose metabolism that are critical to normal brain function.

Furthermore, thiamine also takes part in the regulation of oxidative stress and carbonyl stress. Glycolysis is a crucial process for providing some reducing equivalents for respiration chain.

Glyceraldehyde-3-phosphate is a substrate of glucose during glycolysis (Gibson et al., 2012; Kuzuya, 1990), which is produced with two units of equivalents. It has been demonstrated that the increased level of glyceraldehyde-3-phosphate enhances carbonyl stress and leads to the increased formation of methyglyoxal and AGEs, which play an important role in the development of chronic disease, including T2DM and its complications. The response of thiamine to AGEs has been demonstrated in vivo. Thiamine seems to play an essential role in maintaining enough cellular defenses against the accumulation of AGEs (Shangari et al., 2007). Plasma AGEs was shown to increase even thiamine is marginally TD (Lonsdale, 2006; Shangari et al., 2003). In addition, increased oxidative stress by marginal TD in a dose dependent manner has been confirmed by increased AGEs concentration in plasma and tissues (Shangari et al., 2007).

Moreover, thiamine inhibits lipid peroxidation in liver microsomes, reduces free radical oxidation of oleic acid in vitro (Lukienko et al., 2000), and elevates glutathione reductase activity following cardiac hypoperfusion (Tolstykh and Khmelevskii Iu, 1991). In mice, TD elevates many markers of oxidative stress. These markers are also elevated in brains from AD patients (Calingasan and Gibson, 2000). Dietary TD and other sources of oxidative stress increase AGEs synergistically (Shangari et al., 2005). From all these observations, it can be easily concluded that TD not only contributes to the dysfunction of glucose metabolic process, but also leads to serious oxidative stress in cells, which may play essential roles in the pathogenesis of metabolic syndrome, as well as AD.

4.2.1.3. Increased risk of thiamine deficiency in elderly. Aging is a key risk factor for AD. Also, the studies have found that the elderly is a high-risk population suffering from TD. Under the condition of that average daily thiamine intake was above the recommended requirement (>0.4 mg/1000 Kcal), almost half of the elderly population (older than or equal to 65 years) had an effect of TDP on the transketolase activity above 14%, suggesting TD (Nichols and Basu, 1994). The study raised questions about the reliability of dietary intake in assessing metabolic availability of thiamine in the elderly. A cross-sectional and 3-year longitudinal survey suggested that lower TDP concentration in the elderly people appears to be related more to age itself than to co-existent illnesses (Wilkinson et al., 2000). Interestingly, the reported prevalence of biochemical TD ranges from 8% to 31% for elderly people living at home in United Kingdom of British and is significantly higher than those living in nursing homes (23–40%) and those admitted in acute geriatric ward (48%) (O'Keeffe, 2000).

4.2.1.4. Altered functional status of thiamine metabolism. The previous studies have reported that the activities of thiamine diphosphatase (TDPase) and thiamine monophosphatase (TMPase) were decreased in AD brains (Heroux et al., 1996). In frontal and temporal cortex, TDPase activities declined by 28% and 62% in AD patients, respectively, and reduced rate for TMPase in these two regions is 31% and 64%, respectively, in the same brain samples (Heroux et al., 1996). The activities of TMPase and TDPase occurred not only in pathological regions but also in normal regions (Gibson and Blass, 2007). It is different from brain glucose hypometabolism that happens selectively in some cerebral regions. Paradoxically, the levels of thiamine phosphorylated esters, TDP and thiamine monophosphate (TMP), were reported to decline significantly both in bloods and brains of AD patients by most of the studies (Glasø et al., 2004). Are decreased activities of TDPase and TMPase compensatory responses for reduced levels of TDP and TMP or caused by other factor(s)? It is still a puzzle. Contrasted to consistently decreased TDP levels in all AD studies, TMP and free thiamine levels were controversially altered in AD studies (Heroux et al., 1996). The study for autopsied brain tissues found that the level of TDP was significantly reduced by 18–21% whereas the levels of free thiamine and TMP were normal in all three cortical areas examined in the AD group as compared with control group (Mastrogiacoma et al., 1996a). Gold (2005) demonstrated the specificity of altered thiamine metabolism for AD, which significantly lower plasma thiamine level was found in AD but not in Parkinson's disease, another neurodegenerative disorder characterized by movement abnormality. Whatever, all these evidence may suggest that AD patients widely exhibit a disruption of thiamine phosphorylation–dephosphorylation processes.

The phosphorylated derivatives of thiamine have widely physiological effects in glucose metabolism, protein processing, gene expression and lipid metabolism (Gibson and Blass, 2007; Mastrogiacoma et al., 1996b; Tylicki and Siemieniuk, 2011). It is easy to suppose that the decreased activities of thiamine-dependent enzymes lead to glucose hypometabolism in cognitively normal people as well as in cognitively impaired patients. Besides, low glucose metabolism also causes oxidative stress and increases neuron's structural and functional impairments, including lipid peroxiation, apoptosis, electron chain uncoupling and so on (Gibson and Blass, 2007; Gibson et al., 2012).

It remains to be clarified the cause of altered thiamine metabolism in the elderly and AD subjects. There has been no study yet to demonstrate whether abnormal Aβ metabolism plays a role in altered thiamine metabolism. Thiamine uptake occurs in the human intestine via a specialized carrier-mediated mechanism and its functional conversion into TDP takes place in cytosolic compartment through the reaction catalyzed by thiamine pyrophosphate kinase (TPK). TDP is decomposed into TMP by TDPase and TMP is converted into thiamine by TMPase in cytoplasm. Thus, the balance of TPK and TDPase activities maintains the homeostasis of functional thiamine metabolism. Young people have a sufficient thiamine absorption in the intestine whereas the elderly manifests a declining trend following the age increase (Baum and Iber, 1984). The absorption of oral thiamine in older individuals was found to be poor as compared with that in young individuals (Tallaksen et al., 1993). It may be associated with the decreased activities of intestinal alkaline phosphatase in the elderly subjects (Detel et al., 2008; Rindi et al., 1995; Schaller and Holler, 1975). In addition, a case report also showed that thiamine couldn't be transported into the lumen of the gastrointestinal tract under the condition of alkaline phosphatase deficiency (Luong and Nguyen, 2005). However, there was no study to demonstrate the relationship between alkaline phosphatase and AD.

4.2.2. Mitochondrial dysfunction and oxidative stress

The feature of cerebral high energy consumption in maintaining normal neuronal and synaptic activities requires the appropriate mitochondrial function for ATP generation in brain. Two essential glucose metabolic pathways occur in mitochondria: Krebs cycle and oxidative phosphorylation. Abnormal Krebs cycle or/and oxidative phosphorylation cause(s) not only glucose hypometabolism but also multiple pathophysiological cascades such as apoptosis, oxidative stress, and so forth.

4.2.2.1. Perturbed Krebs cycle and oxidative phosphorylation. Krebs cycle, namely citrate acid or TCA cycle, is crucial for the production of reducing equivalents to oxidative phosphorylation for ATP synthesis in mitochondria. Glucose metabolism impairment can be attributed to the dysfunction of TCA cycle if basic components for its normal operation or key enzymes in this cycle present deficit(s), which reduce the supply of equivalents to oxidative phosphorylation.

TCA cycle is the main pathway for oxidation of glucose in brain. It starts with the acetyl CoA provided through the oxidative decarboxylation of pyruvate catalyzed by PDHC (Kuzuya, 1990). TCA cycle involves eight enzymes: citrate synthase, aconitase, isocitrate dehydrogenase, KGDHC, succinate thiokinase, succinate dehydrogenase, fumarase, and malate dehydrogenase (Bubber et al., 2005; Gibson et al., 2012). AD-related reduced activities of PDHC have been robustly documented by a lot of groups (Bubber et al., 2005; Butterworth and Besnard, 1990; Perry et al., 1980; Sorbi et al., 1983). Declined activity of KGDHC has been reported by four independent groups and appears to be highly associated with the occurrence of clinical dementia (Gibson et al., 2000). The decreased activities of these enzymes actually do not represent a wide mitochondrial dysfunction, considering that the activities of other mitochondrial enzymes, like glutamate dehydrogenase or fumarase, remain normal in AD brain. Bubber et al. (2005) found significantly decreased activities in PDHC (−41%), isocitrate dehydrogenase (−27%), KGDHC (−57%), and increased activities of succinate dehydrogenase and malate dehydrogenase. The activities of the other four TCA cycle enzymes were unchanged.

PDHC regulates TCA cycle by providing acetyl CoA through pyruvate metabolism; Reduced activities of PDHC (Perry et al., 1980; Sorbi et al., 1983) and KGDHC (Butterworth and Besnard, 1990; Gibson et al., 1988) are present both in normal and pathological areas of AD brain. Quantity analysis of PDHC by immunoblot in AD brain suggested that the reduced protein levels of this enzyme complex are consistent with the decreased enzymatic activities. In contrast to PDHC, the studies have suggested that the reduction of KGDHC activity is not involved in the expression level of enzyme protein (Mastrogiacoma et al., 1996b; Sheu et al., 1985). Although an inherited genetic defect in a KGDHC subunit was reported the association with AD (Sheu et al., 1994), no pathogenic mutations have been identified. It has been known that both PDHC and KGDHC present low activities in AD brain, which may lead to glucose hypometabolism, oxidative stress, as well as mitochondrial dysfunction of neurons.

As the final step of bioenergetics, oxidative phosphorylation plays an essential role in the production of ATP from ADP, which drives the neurons to exert variety of physiological functions, including neurotransmission, ion balance and so on. Cerebral glucose hypometabolism induced by dysfunction of oxidative phosphorylation is linked to AD pathophysiological alterations (Shoffner, 1997; Yao et al., 2009). Among the different levels of glucose metabolism, oxidative phosphorylation occurring in mitochondria may be thought as the process with a high risk of being impaired due to the following reasons: Firstly, oxidative phosphorylation is a multi-step metabolic process that comprises many enzyme complexes (from I to IV), coenzymes, as well as metals and cytochromes (Shoffner, 1997). Dysfunction of each element contributes to the disruption of oxidative phosphorylation and subsequent glucose hypometabolism. Secondly, oxidative phosphorylation is the final step of cell ATP production, any accidental breakdown of foregoing metabolic processes, like glycolysis or TCA cycle may affect the physiological function of oxidative phosphorylation. Finally, oxidative phosphorylation occurs in mitochondria, which is a susceptible organelle that tends to be influenced by different kinds of harmful factors, like external apoptosis signal, calcium overload and oxidative stress (Baloyannis, 2006; Bubber et al., 2005; Gibson et al., 2000).

Thus, the defects of oxidative phosphorylation might present among different aspects. Parker et al. (1994) found the activities of cytochrome c oxidase (COX) is more severely affected in the electron transport chain of AD brain. Further investigations of COX kinetics in AD brain revealed abnormalities in substrate binding kinetics (Parker and Parks, 1995). COX impairment is also found in the cingulate cortex and other cortical brain regions of AD patients (Hirai et al., 2001). However, some studies did not report significant COX defects. Cooper et al. (1993) reported normal COX activity in AD temporal lobe mitochondria. By mitochondrial DNA analyses, Reichmann et al. (1993) also demonstrated that no specific defects of respiratory chain were discovered although enzymes representing complex II, III and IV were reduced in activities. However, the biopsies of frontal neocortex from AD patients illustrated partial oxidative phosphorylation uncoupling in respiration chain (Sims et al., 1987). This study raises the hypothesis that Aβ accumulation in AD brain may participate in the deterioration of oxidative phosphorylation, as well as mitochondrial oxidative stress.

4.2.2.2. Mitochondrial dysfunction and oxidative stress. The vicious cycle initiated by AD specific pathophysiological alterations such as Aβ deposit, and comprised of AD specific pathophysiological alterations, oxidative phosphorylation dysfunction and oxidative stress could be the final force to cause AD onset. With increasing age as the primary risk factor for AD, mitochondrial respiratory function in ageing brain manifests a gradual decline and is difficult to constantly meet high energy consumption. It leads to the generation of redundant reactive oxygen species (ROS) and oxidative damage. Because mitochondria are also the main location suffering from ROS, oxidative stress further exacerbated mitochondrial dysfunction and the vicious circle starts gradually in ageing brain. Under genetic background and pathophysiological condition of AD, oxidative stress and this vicious circle are more prone to take place and have been demonstrated as an early event occurring before the appearance of senile plaques and onset of clinical manifestations (Bishop et al., 2010; Bonilla et al., 1999; Chong et al., 2005; Clark et al., 2010; Engelhart et al., 2002). Mitochondria are highly dynamic organelles that constantly fissure and fuse within the cell as the environment demands (Chan, 2006). Mitochondrial dysfunction in AD has been demonstrated the association with the imbalance of mitochondrial fission and fusion (Bonda et al., 2010; Wang et al., 2008). In addition, mitochondrial dysfunction in AD also includes enhanced mitochondrial permeability, reduced mitochondrial calcium modulating capacity and the release of pro-apoptogenic factors (Lloret et al., 2008).

As the most recognized pathophysiological hallmark of AD, Aβ deposition is also involved in mitochondrial dysfunction in AD. The definitive evidence has shown that Aβ accumulation in mitochondria of AD patients and mouse models occurs before extracellular amyloid deposition and increases with age (Devi et al., 2006; Du et al., 2008; Hirai et al., 2001; Manczak et al., 2006). Soluble Aβ oligomers harmfully impact on mitochondrial and neuronal properties/function through disrupting functions of respiratory chain (Cardoso et al., 2001) and other mitochondrial components such as cyclophilin D (Du et al., 2008), Aβ binding alcohol dehydrogenase (Lustbader et al., 2004) and TOMM40 (Devi et al., 2006). Besides, Aβ has been demonstrated to contribute to the defects of mitochondrial oxidative phosphorylation function. There are three major APP isoforms that can be produced by alternative splicing. By overexpressing one of these APP isoforms APP-751 in primary cultures of human muscle using an adenovirus vector, the study found APP-751 could cause decrease in COX activity and ultrastructural abnormality of mitochondria (Askanas et al., 1996). In rat hippocampal neurons, Aβ has a destructive effect on oxidative phosphorylation, which is related to the inhibition of complex II activity (Kaneko et al., 1995). These studies raise the hypothesis that Aβ accumulation in AD brain may participate in the deterioration of oxidative phosphorylation, as well as mitochondrial oxidative stress.

5. Multiple pathophysiological cascades induced by impaired glucose metabolism in Alzheimer's disease

Hitherto, the amyloid cascade hypothesis is undoubtedly the most convincing assumption for AD pathogenesis. The compelling genetic evidence from human and animal models strongly supports its objectivity. Recent study further strengthened the supporting evidence for amyloid hypothesis, which a coding mutation (A673T) in the APP gene delays cognitive decline and AD onset in the elderly (Jonsson et al., 2012). Down syndrome, also known as trisomy 21, manifests early-onset cognitive decline due to brain amyloid deposits induced by the increase of APP gene copy number (Webb and Murphy, 2012). APOE ε4 allele is the most recognized risk factor for sporadic AD and has been demonstrated to damage the capacity of cellular Aβ clearance (Swartz et al., 1999). In addition, Amyloidogenesis-related animal models through genetic manipulation further increase the persuasiveness of the amyloid cascade hypothesis. All these clinical and experimental studies provide a convincing pathophysiological link between abnormal amyloid metabolism and neurodegeneration.

However, there are still many sphinxes to be unveiled about the amyloid cascade hypothesis. As one of the prominent pathophysiological hallmarks of AD, brain amyloid deposit includes extracellular amyloid plaques and intracellular soluble amyloid enhancement. Extracellular amyloid plaques have been excessively emphasized but intracellular soluble amyloid received scant attention in AD studies. Many clinical trials against AD targeting extracellular amyloid plaques failed and acquired little beneficial effects on delaying or stopping neurodegeneration although extracellular amyloid plaques were eliminated (Gravitz, 2011; Holmes et al., 2008). This oppressive fact implies that extracellular amyloid plaques only are vestiges of neural death induced by intracellular excessive amyloid loading. This concept is also supported by the observation of that amyloid plaques contain many cytoskeletal components (Masters et al., 1985). Thus, intracellular amyloid deposit may be a real culprit of neurodegeneration.

In addition, APP and its metabolites as well as related metabolic enzymes such as β- and γ-secretases play the key roles in many physiological processes of neural cells (Bekris et al., 2011; De Strooper et al., 2012; Zhang et al., 2011b). It makes AD treatment of inhibiting Aβ production in a dilemma: How to inhibit the production of toxic Aβ in the case of avoiding side effects? Current studies have failed to provide methods that satisfy both sides. Furthermore, previous evidence has shown that occurrence of hypometabolism in AD brain did not parallel to the deposits of amyloid accumulation (Berti et al., 2010), which may indicate that glucose metabolism impairment and Aβ accumulation are two independent pathway that initiated AD pathology. Thus, the amyloid hypothesis is not complete and sufficient to interpret AD's phenotype, and needs to be complemented by the hypothesis of glucose metabolism impairment.

Both clinical and experimental studies have confirmed that impaired cerebral glucose metabolism is an invariant pathophysiological feature and precedes clinical symptoms and pathological alterations even for decades (Cunnane et al., 2011; Jack et al., 2010; Reiman et al., 1996; Small et al., 1995). Thus, we proposed a hypothesis that impaired cerebral glucose metabolism, especially altered thiamine metabolism and insulin resistance, could promote Aβ accumulation and tau hyperphosphorylation, as well as induce multiple pathogenic factors, which synergistically make for the pathological dysfunction of brain in AD. These pathophysiological cascades include mitochondrial dysfunction and oxidative stress (Gibson and Blass, 2007; Jhala and Hazell, 2011; Karuppagounder et al., 2009), inflammatory factors (Calingasan and Gibson, 2000; Karuppagounder et al., 2007; Watson and Craft, 2006), excitotoxicity (Hazell and Butterworth, 2009), AGEs (Vitek et al., 1994; Yan et al., 1996), apoptosis (Moley and Mueckler, 2000), hyper-activation of some protein kinases (Salminen et al., 2011; Zhao et al., 2011), and so forth (Fig. 2). All these pathogenic factors are involved in cognitive dysfunction and the formation of AD pathophysiological alterations.

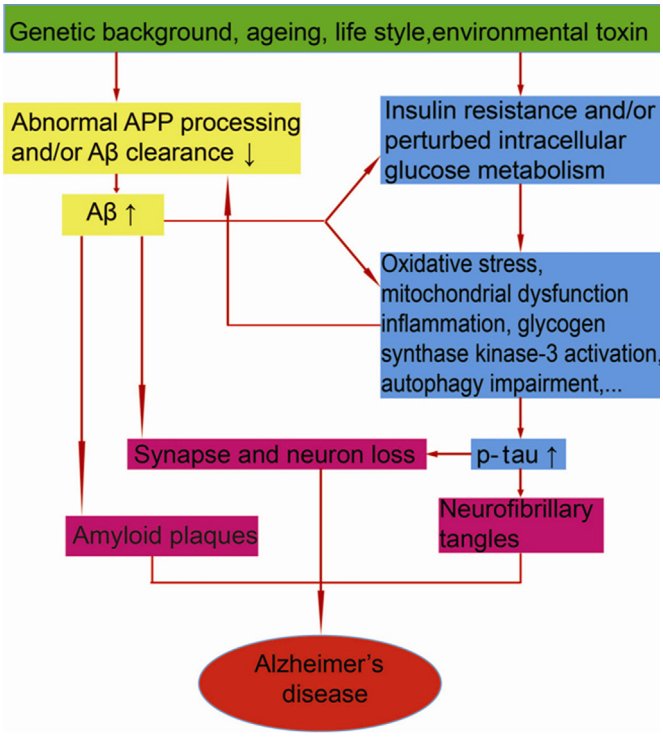

Fig. 2. The diagram of multiple pathogenic cascades in Alzheimer's disease. The multiple pathogenic mechanisms contribute to the pathological hallmarks of Alzheimer's disease consisted of synapse and neuronal loss, amyloid plaques, and neurofibrillary tangles. Perturbed cerebral energy metabolism plays a central role in multiple pathogenic cascades of Alzheimer's disease.

From previous studies, impaired energy metabolism was shown topromote Aβ accumulation. Insulin resistance leads to excess activation of GSK-3β, which may facilitate β-secretase activity and Aβ formation, resulting in increased intracellular Aβ levels (Kim and Feldman, 2012; Moreira et al., 2009). IDE participates in the degradation of several extracellular substrates, like insulin and Aβ. Insulin has also been proposed to regulate extracellular degradation of Aβ by modulating the IDE activity (Zhao et al., 2007). The negative correlation between IDE activity and hippocampal Aβ content has been demonstrated in severe AD patients (Salminen et al., 2011; Zhao et al., 2011). Moreover, energy production impairment induces Aβ accumulation. Reduced energy production in transgenic mice increased cerebral BACE1 levels compared with control (Velliquette et al., 2005). The authors also showed that TD may increase BACE1 levels and Aβ accumulation due to its induced hypometabolism. Similarly, disruption of electron transportation was also reported to cause the formation of amyloid fragments of APP. Furthermore, normal wild-type mice with TD was shown to promote the formation of neuritic clusters that could bind to several antibodies for amyloid precursor protein (APP) and amyloid precursor-like proteins, though plaques were not formed (Calingasan et al., 1995). By using pyrithiamine, an anti-thiamine compound, we have demonstrated that altered thiamine metabolism increases β-amyloid accumulation, Tau hyperphosphorylation, and glycogen synthase kinase-3 activity in transgenic mice brain (Zhao et al., 2011). However, to date, there is no report to confirm that TD can lead to Aβ aggregation in humans. On the

other hand, glucose metabolism dysfunction induces tau hyperphosphorylation. Glucose transporters abnormality increase tau hyperphosphorylation and NFTs formation (Liu et al., 2008). Insulin resistance promotes tau hyperphosphoyrlation through PI3K/Akt pathway (Correia et al., 2012). In the patients with Wernicke–Korsakoff syndrome characterized by severe TD, tangles have been found in their brains, especially in chronic alcoholics (Cullen et al., 1997). In all, glucose metabolism impairment could increase Aβ aggregation and tau hyperphosphorylation via different mechanisms. However, multiple pathogenic cascades induced by impaired glucose metabolism could be the fundamental impetus to form AD phenotype. These multiple pathogenic cascades include oxidative stress and mitochondria dysfunction, AGEs production, inflammatory factors, excitotoxicity, autophagy impairment, and GSK-3 activation and so on.

Although human brain only occupies 2% of the body by weight, brain metabolism requires about 20% of the oxygen supplied by the whole respiratory system (McKenna et al., 2006; Sokoloff, 1999). Thus, it is an organ with high energy production and consumption, which makes it more susceptible to mitochondria abnormality and oxidative stress than any other organs. Current research, in fact, suggests that both mitochondria dysfunction and oxidative stress play an important role in the AD pathogenesis. Oxidative stress is a result of misbalance of oxidative mechanism and antioxidant mechanism of the cells. Some investigators proposed a two-hit hypothesis to explain the role of oxidative stress in AD pathology (Wang et al., 2009a). Moreover, oxidative markers, generally like 8-hydroxyguanosine (8-OHG) appears to precede all the typical hallmarks of AD, such as NFTs and Aβ plaques. Specifically, studies showed that 8-OHG appears decades prior to Aβ aggregation. The Tg2576 transgenic mice exhibited oxidative damage prior to Aβ aggregation (Melov, 2004; Stowers et al., 2002; Wang et al., 2008). In AD, iron deposition has been demonstrated to show the association with oxidative stress, which causes increased protein and DNA oxidation, and inactivation of the human brain muscarinic cholinergic receptor required for memory (Jomova et al., 2010; Salvador et al., 2010; Fawcett et al., 2002). Moreover, iron chelators, such as intranasal desferrioxamine, also have been demonstrated to show beneficial effects in AD patients or AD transgenic models. Thus, iron deposition may play a significant role in the pathogenesis of AD (Crapper McLachlan et al., 1991; Hanson et al., 2012; Fine et al., 2012). In this case, oxidative stress is supposed to be an original contributor to AD pathogenesis. Glucose-6-phosphate dehydrogenase (G6PDH) is the rate-limiting enzyme of the phosphate pentose shunt (PPP) (McKenna et al., 2006; Sokoloff, 1999), which plays an essential role in the redox balance of cells. It participated in homeostatic redox control by providing reducing equivalents to glutathione. Russell et al. (1999) have found an up-regulation of G6PDH together with increased sulfhydryls in AD, which suggests that reductive compensation plays a crucial role in fighting oxidative stress in AD. Thus, by removing the ROS produced by neuronal oxidative stress, neurons may provide themselves a useful approach for self-protection in AD brain. Carbonyl stress marked by AGEs could also induce cell dysfunction, which contributes to AD pathology (Russell et al., 1999; Vitek et al., 1994). AGEs have been demonstrated to be a common pathological pathway resulting in CNS disease progression. Compared with young people and non-demented controls, AGEs have been found to increase in neurons of aging and AD, and even worse with the progression of AD (Martina and Gerald, 2010). Interestingly, intracellular AGEs accumulation has been observed in 75–95% of pyramidal neurons of patients with familial AD (PS1 mutations) (Munch et al., 2002), which indicates that AGEs may contribute to increased neuronal dysfunction and vulnerability.

Impaired glucose metabolism induces mitochondria dysfunction and oxidative stress, which may lead to the activation of apoptotic pathway mediated by mitochondria. Apoptosis, or programmed cell death, plays important roles in brain development, as well as neurodegenerative disease, including AD. Mitochondria have been characterized as a location where apoptosis can be induced by AD-related pathogeneses, such as oxidative stress, disruption of oxidative phosphorylation, mtDNA mutations and so on (Cottrell et al., 2002). The previous researches also reported that apoptosis participated in the neuron loss of AD, and mitochondria are the main organelles that mediate these apoptotic effects. Firstly, neurons with AD specific mutation (like PS1 mutant) have been demonstrated to exhibit increased sensitivity to mitochondria toxin-induced apoptosis (Chan et al., 2002), which is mediated by calcium overload and excess oxidative stress. Moreover, it has also been demonstrated that $A\beta_{1-42}$ could promote the release of cytochromose c from mitochondria of AD neurons, and initiate the process of neuronal apoptosis (Zhang et al., 2002), which can be inverted by antioxidate glutathione suggesting the involvement of oxidative stress in mitochondria dysfunction. Thus, blocking the mitochondria apoptosis signaling or related cascades could be a potential approach to prevent apoptosis and neuron loss in AD.

Though impaired glucose hypometabolism could induce inflammatory responses in AD brain and exacerbate AD's pathology, the inflammatory factors are generally regarded as products of other critical insults, such as Aβ, oxidative stress, and mitochondrial dysfunction. Former evidence has demonstrated that inflammatory factors participate in the pathogenesis of AD. IL-1, IL-6, TGF-β all have been found in AD brains by autopsy, and may play a destructive role in AD progression (Neuroinflammation Working Group, 2000; Lukiw and Bazan, 2010; Sardi et al., 2011). In addition, microglia and astrocytes have also been shown to be involved in the inflammation in AD. Microglia clusters located in Aβ deposits have be found in both the brains of AD patients and APP transgenic mice (McGeer et al., 1989). It has also been shown that cultured microglia can secrete Aβ and metabolize APP in a manner promoting Aβ deposition (Barnum et al., 1996). Moreover, microglia have also been demonstrated to aggregate much more around Aβ-containing neuritic plaques than fuse plaques in AD, in normal aging, as well as in APP transgenic mice. Furthermore, many different laboratories have shown that microglia, both *in vivo* and *in vitro*, phagocytose exogenous fibrillar Aβ (Frautschy et al., 1992, 1998; Oliver et al., 1997; Paresce et al., 1997). Finally, pathophysiologic relevance of inflammation to AD neurodegeneration has been established by multiple lines of converging tangential and direct evidence (in review Neuroinflammation Working Group, 2000).

Normal glucose metabolism is necessary to any cellular process, including autophagy, which responds to alterations of cell energy metabolism. Autophagy is a critical pathway involved in the elimination of proteins and organelles, and is highly conserved during evolution (Mizushima et al., 2008; Tung et al., 2012). The physiological function of autophagy is to help cells survive in nutrient starvation and stress. Loss of autophagy could result in CNS neurodegeneration (Komatsu et al., 2006). Suppression of basal autophagy in neural cells could lead to neurodegenerative disease in mice (Hara et al., 2006). It has been found that an important autophagy process initiating regulator, Beclin 1, is decreased in AD patients (Pickford et al., 2008). Knockout mice lacking Beclin-1 (Bcn1−/−) die during embryogenesis (Qu et al., 2003; Yue et al., 2003). In contrast, Bcn1+/− mice are viable. They have reduced autophagosome formation in skeletal muscle, bronchial epithelial cells and B lymphocytes (Qu et al., 2003), but the neuronal phenotype of these mice has not been characterized. Macroautophagic markers are proved to be related to senile plaques and tangles, including Atg5, Atg12, and LC3 in AD (Ma et al., 2010). Moreover, it has been demonstrated that

LC3-positive autophagosomes co-localized with APP and Aβ peptides in an APP-overexpressing cell line as well as in AD mouse models (Lunemann et al., 2007; Yu et al., 2004), which may indicate that autophagy participate in the process of Aβ degradation. Actually, by deletion of Beclin 1, cells exhibit increased Aβ peptides, full-length APP, as well as APP C-terminal fragments (APP-CTFs) (Jaeger et al., 2010). Consistent with this, in mouse model with Beclin 1 down-regulation also showed serious neurodegeneration marked by intracellular and extracellular Aβ accumulation (Lunemann et al., 2007; Yu et al., 2004). In contrast, gene therapy using locally injected lentivirus loading Beclin-1 reduced Aβ aggregates in APP transgenic mice (Pickford et al., 2008). Based on these results, autophagy is important in the degradation of Aβ deposits, and could play a critical role in the pathogenesis of AD.

The mammalian target of rapamycin (mTOR) pathway plays a major role in receiving autophagic stimuli with its ability to sense nutrient and metabolic hormonal signals to initiate autophagy (Cai et al., 2012). The mTOR-dependent signaling pathway seems to be involved in AD patients' brains as well as in AD models (Li et al., 2005; Pei and Hugon, 2008). Enhanced mTOR signaling activity increases Aβ deposits and NFTs formation in AD (Lafay-Chebassier et al., 2005). Inhibition of mTOR by rapamycin retards cognitive deficits and reduces Aβ pathology by increasing autophagy in AD models (Bove et al., 2011). Autophagy impairment also increases β- and γ-secretases activities, which results in Aβ overproduction and accumulation (Cai et al., 2012). In addition, autophagy impairment contributes to the tauopathy (Hamano et al., 2008; Murakami et al., 1998; Schaeffer et al., 2012; Wang et al., 2009b). Apart from the roles in Aβ production and tauopathy, autophagy impairment has been demonstrated to disrupt cell's physiological function by mitochondria dysfunction and oxidative stress, and it also exacerbates insulin resistance via reductions of insulin secretion in pancreas β cells (Wang et al., 2013). To sum up, autophagy is essentially responsible for the degradation of folded proteins in cells, and its dysfunction could lead to Aβ aggregation and tauopathy.

It has been reported that excitotoxicity is an early event in the onset of AD, which was demonstrated by neuropathological and neurochemical studies in AD brain (Cai et al., 2012; Hynd et al., 2004). Impaired glucose metabolism is an important contributor to excitotoxicity via disruption of astrocytes' normal uptake mechanism of glutamate. Clinical trials for AD therapy using N-methyl-D-aspartic acid receptor (NMDAR) antagonist memantine have been showed to improve AD patients' cognitive functions and display good tolerance (Frankiewicz and Parsons, 1999). Thus, excitotoxicity may play a critical role in AD pathogenesis. Some mechanisms have been proposed to explain NMDAR's excitotoxicity in AD pathology. They have showed that NMDAR is a receptor for Aβ oligomers and the interaction of NMDAR and Aβ could be neurotoxic (Tominaga-Yoshino et al., 2001). Furthermore, in post-mortem AD brains, co-localization of Aβ plaques, NFTs and excitatory pyramidal neurons also support the above-mentioned results (Braak et al., 1993). Thus, exictotoxicity could be a pathological mechanism involved in AD.

Glucose metabolism dysfunction could be influenced by GSK-3 activity, thus GSK-3 may be one of the mediators that participate in the AD pathophysiological process. For example, GSK-3 activation significantly increases production of Aβ and hyperphosphorylated tau through a dual pathway mechanism. Cumulative evidence has proved that GSK-3 increases tau phosphorylation, Aβ aggregation, memory impairment, as well as microglia activation-associated inflammatory reactions in AD (Hooper et al., 2008). An investigation showed that GSK-3 reduces acetylcholine synthesis, and acts as a mediator of apoptosis (Hoshi et al., 1996). AD brain tissues have been found to exhibit increase of expression or activity of GSK-3 (Blalock et al., 2004), and hence hyper-activation of GSK-3 could induce the apoptosis of cholinergic neurons (Hoshi et al., 1996), tau-hyperphosphoryaltion (Cho and Johnson, 2003; Lovestone et al., 1994), and subsequent NFTs formation (Lucas et al., 2001). Furthermore, the studies have demonstrated that GSK-3α has been demonstrated to modulate APP cleavage and induce Aβ production (Phiel et al., 2003; Sun et al., 2002), and that blockade of GSK-3β could prevent Aβ accumulation (Alvarez et al., 1999; Takashima et al., 1993). GSK-3 is also involved in the induction of long term potentiation (LTP) (Hooper et al., 2007), and overexpression of GSK-3 could prevent the induction of LTP by negatively regulating Wnt or PI3K signaling (Hooper et al., 2007). Thus, the preventive effects of GSK-3 on LTP could lead to memory impairment *in vivo* and hence plays a role in AD cognitive deficits.

In conclusion, AD is a complicated disease involved in multiple pathophysiological cascades induced by perturbed glucose metabolism. Combined with Aβ accumulation and NFTs formation, impaired glucose metabolism and its downstream pathophysiological alterations form a vicious cycle, which synergistically make for the pathological dysfunction of brain in AD. In this vicious cycle, impaired cerebral glucose metabolism plays a central role that can easily be modified. It is due to that correcting impaired cerebral glucose metabolism does not result in the dilemma situation like the treatment of reducing Aβ production. Secondly, brain glucose hypometabolism can independently cause AD pathological hallmarks, including Aβ plaques, tau hyperphosphorylation, synaptic and neuronal loss as well as other pathophysiological cascades in AD brain, which all contribute to AD pathogenesis (Fig. 2).

6. Implications for diagnostic and intervention strategies of Alzheimer's disease

The above-mentioned hypothesis provides a glimmer of sunlight for the current predicament of AD study. Indeed, it is time to change our strategies for AD diagnostic and intervention studies if we hope the long list of failed AD clinical trials no longer last in the future (Castellani and Perry, 2012).

6.1. New strategy for Alzheimer's disease diagnosis

The present clinical diagnosis of AD still relies primarily on clinical symptoms and neuropsychological tests. The existing AD biomarker tests can be divided into three categories: (1) CSF Aβ detection and cerebral PiB-PET examination reflecting abnormal amyloid metabolism in AD brains (Palmert et al., 1990; Price et al., 2005; Rosenmann, 2012), (2) CSF tau detection and structural MR imaging reflecting neurodegeneration (Rosenmann, 2012; Vigo-Pelfrey et al., 1995), and (3) FDG-PET reflecting the functional status of cerebral glucose metabolism (McKhann et al., 2011; The Ronald and Nancy Reagan Research Institute of the Alzheimer's Association and the National Institute on Aging Working Group, 1998). Although these existing biomarker tests can increase the certainty of AD diagnosis, they have not been recommended for routine diagnostic purposes in new AD diagnosis guideline due to several shortcomings as compared with ideal biomarker tests (McKhann et al., 2011). Ideal biomarker tests for AD diagnosis should not only reflect the fundamental pathophysiological features but also be reliable, non-invasive, simple-to-perform and inexpensive (Noel-Storr et al., 2012). However, the existing biomarker tests are either expensive (PiB-PET or FDG-PET) or invasive (CSF β-amyloid and tau), and all are difficult to perform. These shortcomings severely limit the application of the existing biomarker tests in clinical practice of AD diagnosis. In addition, AD dementia stage has been irreversible. It is too late to modify the disease when we diagnose patients as AD in this late stage. The existing biomarker tests are not suitable for screening the high risk

population at the pre-clinical stage of AD. Thus, to develop the ideal biomarker tests for AD diagnosis is still needed.

Brain glucose hypometabolism is an invariant biomarker, which precedes clinical manifestations of AD for years or even decades (Mosconi et al., 2008a, 2006). The pathophysiological alterations associated with cerebral glucose mal-metabolism may serve as ideal biomarkers for AD diagnosis. Among these alterations, altered thiamine metabolism is the most promising candidate. Both clinical and experimental studies have demonstrated that thiamine-dependent biological processes and thiamine metabolism are specifically involved in AD (Gold et al., 1998; Gold, 2005; Zhang et al., 2011a).

As the possible pathogenic factor of impaired glucose metabolism, altered thiamine metabolism should precede the alterations of brain glucose metabolism and subsequent cognitive deficits. Thus, altered thiamine metabolism is an early biomarker for AD diagnosis. Further clarification of abnormal thiamine-dependent processes as well as the cause and pathogenesis of altered thiamine metabolism may provide more biomarkers for AD diagnosis and prediction.

6.2. New strategies for the prevention and treatment of Alzheimer's disease

Though AD has been studied for more than 100 years (Berchtold and Cotman, 1998), there is no effective disease-modifying treatments. Since last century, the researchers have tried to develop reliable and effective therapeutics for AD treatment based on the amyloid hypothesis (Asai et al., 2006; Comery et al., 2005; Schenk et al., 1999) and tau hyperphosphorylation hypothesis (Noble et al., 2005). However, most of clinical trials targeting at Aβ are not demonstrated to show more significance efficacy than control placebo, though some of them effectively clear Aβ deposits in AD brain (Gravitz, 2011; Holmes et al., 2008; Gilman et al., 2005; Orgogozo et al., 2003). The researchers also dedicated to find effective antioxidants (Zandi et al., 2004), anti-inflammation (Aisen et al., 2006), and neuroprotective approaches (Tuszynski et al., 2005) for AD therapy. Unfortunately, the antioxidants (Zandi et al., 2004), anti-inflammatory agents (Aisen et al., 2000; Scharf et al., 1999) were also shown to be ineffective. Currently, there are five medications that are approved for treating AD in North America and most countries in Europe: memantine (an NMDAR antagonist) and four cholinesterase inhibitors: tacrine, donepezil, galantamine, and rivastigmine (Herrmann et al., 2011). However, all of them are only symptomatic therapies and can not halt and reverse AD pathology. Hence, developing effective disease-modifying therapies is the focus of future study for AD prevention and treatment.

AD is an insidious and progressive neurodegenerative disease. When the patients with overt symptoms of cognitive dysfunction are diagnosed as AD, the disease has gone through for many years or even for decades. Theoretically, AD includes four stages: Pre-disease stage (no detectable pathophysiological alterations), pre-clinical stage (with detectable pathophysiological alteration(s) but without cognitive impairments), pre-dementia stage (MCI stage), and dementia stage. Different strategies of AD prevention and treatment should be chosen for the different disease stages. To develop different preventive or therapeutic "formula" for each disease stage could be a priority for our future AD study. At the pre-disease and pre-clinical stages of AD, we should prevent the onset of the disease by controlling the initial pathogenic factor(s) of the disease, such as insulin resistance. At the pre-dementia stage, we could stop the disease progression by applying different combinations of preventive and curative drugs. At the dementia stage, we should develop "cocktail therapies" or drugs targeting multiple pathogenic mechanisms of AD. Hence, we proposed a new model for future AD therapy research based on our perspectives of AD pathophysiology (Fig. 3). In this model, we proposed a perspective of "personal therapy for AD" based on the different disease stages and correspondent biomarkers and pathogenic cascades. Different disease stages are labeled by different biomarkers and pathogenic cascades as disease progress, some of which have been proposed by Jack et al. (2013).

Thus, the failure of current clinical trials of drugs with only a single mechanism against AD at the dementia stage is not surprising. In our opinion, the following two approaches should be worth exploring to modify or halt the disease progress of AD: Firstly, to develop effective therapeutics against glucose metabolism dysfunction for AD prevention and early treatment. Secondly, to develop "cocktail therapies" or drugs targeting at multiple pathogenic cascades.

6.3. Drugs targeting altered thiamine metabolism and insulin resistance

The previous studies have showed that TD is a usual phenomenon in AD patients (O'Keeffe, 2000). Thus, the modification of altered thiamine metabolism could provide effective therapeutic approach to AD. However, the studies have exhibited the contradictory results of thiamine therapy in AD patients. A study in 11 AD patients by Blass and his colleagues reported significant improvement of cognitive function with thiamine therapy at 3 g/day orally in a 3-month crossover-design (Blass et al., 1988), whereas a follow-up study by the same group found no significant effects in a 12-month parallel group design in 10 AD patients (Nolan et al., 1991). Another study with thiamine therapy at 3–8 g/day orally for 12 months suggested that thiamine may have mild beneficial effects in AD at higher dosages (Meador et al., 1993). Combination of sulbutiamine and acetylcholinesterase inhibitors has been demonstrated to have a persistent improvement in early stage AD patients (Ollat et al., 2007). Fursultiamine (TTFD), a derivative of thiamine, has been shown to have a mild beneficial effect in AD patients, but only mildly impaired subjects showed cognitive improvement (Mimori et al., 1996). In our study, we have shown that benfotiamine, but not fursultiamine was beneficial for improving cognitive dysfunction and cerebral pathological alterations in APP/PS1 transgenic mice (Pan et al., 2010). Benfotiamine effectively reduced amyloid plaque numbers and phosphorylated tau levels in cortical regions of transgenic mice, and also enhanced spatial memory of transgenic mice in Morris water maze test, and this was demonstrated to be associated with elevated GSK-3 phosphorylation. Although these studies suggest that thiamine-related chemicals are potential candidates with low cost and toxicity for AD treatment, the extended double-blind, parallel-group design studies should be performed to completely settle this issue. In addition, the ultimate treatment always awaits a better understanding of the underlying mechanisms. Thus, it is important to further clarify the exact cause and mechanism of altered thiamine metabolism in AD.

Considering the common pathogeneses between T2DM and AD such as insulin resistance, it is possible that therapeutics for T2DM would be effective for AD (Zhong and Weisgraber, 2009). Thus, correcting insulin resistance and repairing insulin signaling dysfunction would be potential targets for AD therapy. One of the most popular targets is PPARs, which belongs to steroid hormone super family ligand-inducible transcription factors. It can enhance insulin sensitivity, improve mitochondrial function, modulate glucose metabolism, and reduce inflammatory responses (de la Monte, 2012). Rosiglitazone is a γ-PPAR agonist, which has been widely used in T2DM treatment. In a small-scale clinical trial, rosiglitazone was showed to preserve performance on delayed recall and attention tasks compared with placebo

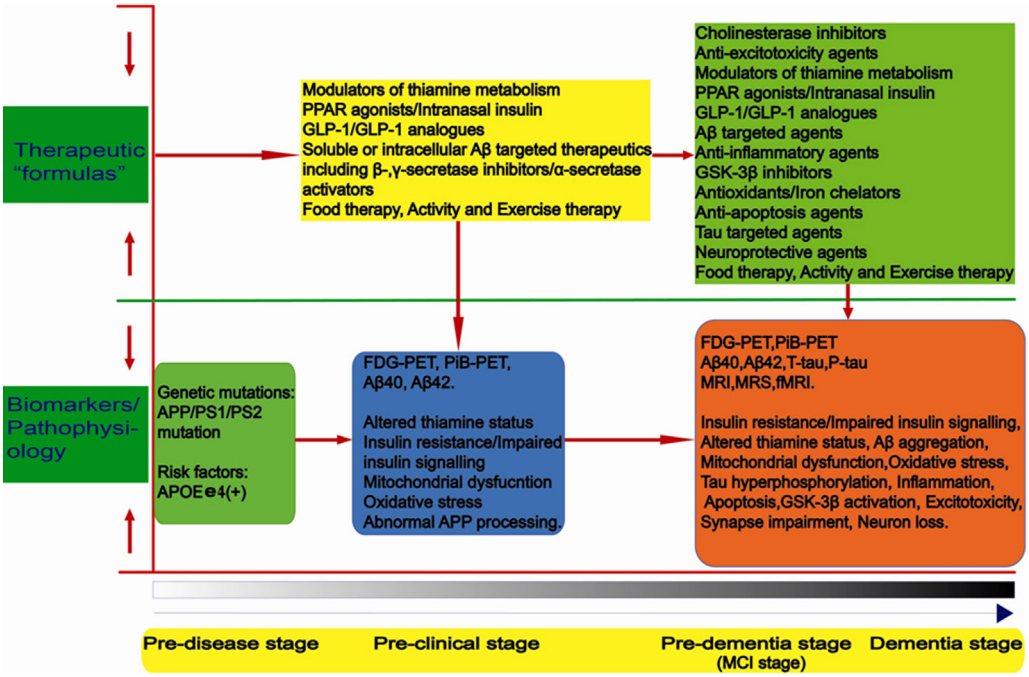

Fig. 3. The "personal therapy for AD" model. In this model, different clinical stages are labeled by different biomarkers and pathogenic cascades, some of which have been proposed by Jack et al. (2013). The lower column "Biomarkers/pathophysiology" lists the biomarker profiles and pathogenic alterations for every stage of AD. Correspondently, the upper column "Therapeutic 'formulas'" assumes some potential interventions for AD prevention and treatment based on our perspective of AD pathophysiology. We suggest that future AD treatment should focus on the prevention by early prediction and diagnosis in pre-disease stage and pre-clinical stage, and treatment by targeting multiple pathogenic cascades in pre-dementia stage and dementia stage.

group (Watson et al., 2005). Paradoxically, rosiglitazone seems to be effective only in APOE-4-negative subjects but not in APOE-4-positive subjects (Risner et al., 2006). However, recent phase three clinical trial has shown the negative effect of rosiglitazone on objective cognitive performance in AD patients (Gold et al., 2010). Another alternative therapy to correct insulin signaling for AD is intranasal administration of insulin. Intranasal insulin has been demonstrated to show improved memory in normal adults without obvious side effects (Benedict et al., 2008; Krug et al., 2010). Besides, intranasal insulin has shown to prevent cognitive decline, cerebral atrophy, Aβ accumulation and white matter lesions in T1DM encephalopathy model (Francis et al., 2008; Subramanian and John, 2012). In a rat model of T2DM, intranasal insulin has also been found to reduce tau hyperphosphorylation (Yang et al., 2013). Four phase two clinical trials of intranasal insulin for early AD or MCI have shown to improve memory and attention abilities without significant adverse effects as well as changes in blood levels of insulin or glucose (Benedict et al., 2008; Craft et al., 2012; Dhamoon et al., 2009; Djupesland, 2008; Reger et al., 2006, 2008a,b; Schioth et al., 2012; Shemesh et al., 2012). One of advantages of this therapeutic is non-invasive intranasal delivery method (Hanson and Frey, 2008). Many studies have shown that intranasal approach can directly deliver the drugs to brain (Dhuria et al., 2010; Hanson and Frey, 2008). It is not surprising that intranasal insulin treatment is a useful method for brain disorders, including AD. Further phase three or four clinical trials could be performed to testify its efficacy and safety. Glucagon-like peptide-1 (GLP-1), a member of the incretin family and which originates from preproglucagon and secreted by intestinal endocrine epithelial L-cells, may be a candidate drug for AD treatment (Mossello et al., 2011). It is the strongest stimulator for oral glucose-induced insulin secretion and exhibits the improvement in insulin resistance and cognitive deficits. Considering the linkage between AD and T2DM in insulin resistance, GLP-1 or its analogues could be effective for AD through intranasal delivery technology. Studies have showed that extendin-4, a GLP-1 analogue, prevents the neurotoxicity of cerebral $A\beta_{1\text{-}40}$ both in triple transgenic AD-mouse and STZ-induced T2DM mouse (Bertilsson et al., 2008; Hamilton et al., 2011). Another GLP-1 analogue, Val (8)-GLP-1(7-36), has been shown to invert cognitive impairment and long term potentiation (LTP) suppression induced by $A\beta_{1\text{-}40}$ (Wang et al., 2010). Consistent with this, other studies also showed the beneficial effect of Val (8)-GLP-1 on LTP in APP/PS1 mice (Gengler et al., 2012). Furthermore, the study also has shown that intranasal GLP-1 administration using the novel device improves the glycemic control in T2DM patients without any adverse effects (Nakazato, 2011). Thus, GLP-1 and GLP-1 analogues through intranasal administration could be potential therapeutics for AD. Further trials should be performed in the future.

6.3.1. "Cocktail therapies" or drugs targeting at multiple pathogenic cascades.

Based on our hypothesis of multiple pathogenic cascades induced by glucose metabolism dysfunction in AD (Fig. 2), it may be unavoidable to develop "cocktail therapies" or drugs targeting multiple pathogenic cascades for AD treatment, similar to cancer and AIDs therapies (Radhakrishnan and Tidor, 2008). Previous basic experiments and clinical trials actually have provided some examples for AD combination therapy (Masashi et al., 2010; Sobow, 2010). The combination of memantine and cholinesterase inhibitors (CHEIs) has been tried for AD treatment in the last decade, some of them showed additive or synergistic effects (Beier, 2004; Fox et al., 2006; Moreira et al., 2006). The short-term efficacy of complement of memantine to ChEIs treatment has been evaluated in some randomized controlled trials (Beier, 2004; Porsteinsson et al., 2008), one of them showed significant benefits of adding memantine verse placebo; but another trial failed. Masashi et al. (2010) reported additive effects on the reduction of

Aβ levels in cultured cells by combination of NSAID, statin, and β- and γ-secretase inhibitors. Other combinations have also been tried, like tacrine–melatonin (Spuch et al., 2010), selegiline and vitamin E (Sano et al., 1997), indomethacin and CHEIs (de Jong et al., 2008). In addition, the supplement of compound nutrients from natural dietary supplements may have some potential value for AD treatment. Parachikova et al. (2010) have demonstrated that medical food cocktail could improve cognitive function in AD models.

In our "personal therapy for AD" model, different therapeutic "formulas" are listed in Fig. 3. We propose that future AD treatment should focus on the prevention by early prediction and diagnosis in pre-disease stage and pre-clinical stage, and treatment by targeting at multiple pathogenic cascades in pre-dementia stage and dementia stage. Additionally, the interaction and compatibility of different drugs with different mechanism and pharmacological effects should be carefully considered before the combination therapies are applied. Combination of memantine and CHEIs has shown some side effects and low efficacy because of incompatibility and cumulative toxicity (Porsteinsson et al., 2008).

In all, our perspectives highlight that the early intervention of the disease and combinational therapies targeting multiple pathogenic cascades in different disease stages are the core of future AD research.

7. Conclusions

Though AD has been studied for over 100 years, there are still some key problems to be addressed in its diagnosis, prevention, and treatment. Recent researches have highlighted the role of impaired brain glucose metabolism in AD pathophysiological cascades. In this review, we proposed that AD is a complicated disease due to multiple pathogenic mechanisms caused by impaired cerebral glucose metabolism. Based on this hypothesis, we discussed the alternative strategies for AD diagnosis and intervention in the future. With the advances of AD studies, we believe that the further understanding for AD pathogenesis will help us to develop efficient diagnostic approaches and treatment methods.

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