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Original article

Molecular pathophysiology of impaired glucose metabolism, mitochondrial dysfunction, and oxidative DNA damage in Alzheimer's disease brain

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ABSTRACT

In normal brain, neurons in the cortex and hippocampus produce insulin, which modulates glucose metabolism and cognitive functions. It has been shown that insulin resistance impairs glucose metabolism and mitochondrial function, thus increasing production of reactive oxygen species. Recent progress in Alzheimer's disease (AD) research revealed that insulin production and signaling are severely impaired in AD brain, thereby resulting in mitochondrial dysfunction and increased oxidative stress. Among possible oxidative DNA lesions, 8-oxoguanine (8-oxoG) is highly accumulated in the brain of AD patients. Previously we have shown that incorporating 8-oxoG in nuclear and mitochondrial DNA promotes MUTYH (adenine DNA glycosylase) dependent neurodegeneration. Moreover, cortical neurons prepared from MTH1 (8-oxo-dGTPase)/OGG1 (8-oxoG DNA glycosylase)-double deficient adult mouse brains is shown to exhibit significantly poor neuritogenesis *in vitro* with increased 8-oxoG accumulation in mitochondrial DNA in the absence of antioxidants. Therefore, 8-oxoG can be considered involved in the neurodegenerative process in AD brain. In mild cognitive impairment, mitochondrial dysfunction and oxidative damage may induce synaptic dysfunction due to energy failures in neurons thus resulting in impaired cognitive function. If such abnormality lasts long, it can lead to vicious cycles of oxidative damage, which may then trigger the neurodegenerative process seen in Alzheimer type dementia.

1. Introduction

About 47.7 million people worldwide suffer from dementia, with 7.7 million new cases every year (World Health Organisation, 2015). Sporadic AD (also known as late-onset AD) is the most common dementia subtype, accounting for 60–80% of all dementia cases (Prince et al., 2013; Sosa-Ortiz et al., 2012). AD is characterized by the accumulation in the brain of both senile plaques containing aggregated amyloid β (Aβ) and neurofibrillary tangles (NFTs) consisting of aggregated highly phosphorylated TAU protein, and by neuronal loss mainly in the cortex and hippocampus (Gotz et al., 2012; Querfurth and LaFerla, 2010). About 1% of AD cases develop as a result of mutations to any of three specific genes for the amyloid precursor protein (APP), the presenilin 1 protein and the presenilin 2 protein, with the latter two regulating APP processing through their effects on γ secretase (an enzyme that cleaves APP). Individuals with mutations in any of these three dominantly inherited genes, tend to develop AD symptoms before the age of 65, sometimes as early as age 30, and it has been shown that Aβ plaques can be present for more than 20 years before the onset of dementia in patients with such inherited mutations (Bateman et al., 2012; Haass and Steiner, 2002; Kang et al., 1987; Sinha et al., 1999; Takasugi et al., 2003). The vast majority of individuals with sporadic AD have late onset disease, occurring at age 65 or later, and similar to other chronic diseases, sporadic AD develops as a result of multiple factors rather than just from a single cause (Alzheimer's Association, 2015)

It has been shown by epidemiologic studies that insulin resistance and diabetes mellitus (DM) are risk factors for pathogenesis of dementia including AD (Bedse et al., 2015; de la Monte, 2014; Hao et al., 2015; Matsuzaki et al., 2010; Ohara et al., 2011; Sekita et al., 2010). Moreover, it was demonstrated through

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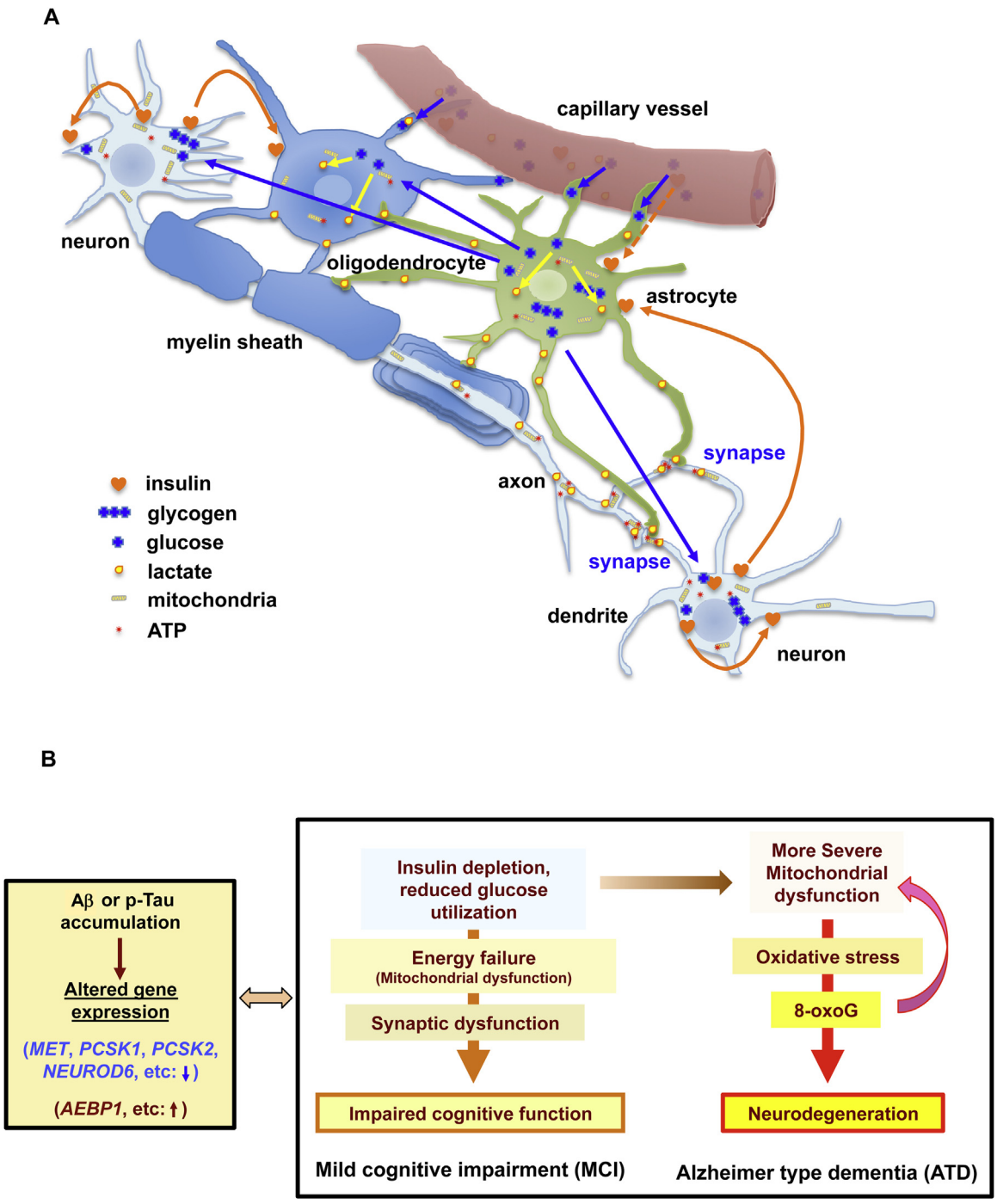

Fig. 1. Insulin production and glucose metabolism in normal brain and their impairments in AD brain. (A) Insulin production and glucose metabolism in normal brain. In normal brain, neurons in cortex and hippocampus produce insulin, which may regulate glucose utilization, glycogen storage or their metabolism in brain, probably mainly in astrocytes. (B) Impaired insulin production and glucose metabolism in AD brain may cause mitochondrial dysfunction and oxidative stress, which enhances the neurodegenerative process. In AD brain, up-regulation of *AEBP1* may cause a down-regulation of both *PCSK1* and *PCSK2*, which process proinsulin to insulin, resulting in a decreased insulin production in neurons, downergulation of *MET* further causes insulin resistance, and down-regulation of *NEUROD6* may cause mitochondrial dysfunction. In patients with mild cognitive impairment (MCI), such abnormality may induce synaptic dysfunction due to energy failure in neurons, thus resulting in impaired cognitive function. If such abnormality lasts long, mitochondrial dysfunction and oxidative stress might increase, resulting in a vicious cycle of oxidative damage and mitochondrial dysfunction, which may then trigger neurodegenerative processs similar to those in Alzheimer type dementia (ATD).

brain imaging by positron-emission tomography (PET) with use of ^{18}F-fluorodeoxyglucose (FDG) and Pittsburgh compound B (PIB) (FDG-PET and PIB-PET, respectively) that a significant decrease in cerebral glucose use in the precuneus region (known to be an area of early deposition of Aβ in both sporadic AD and inherited AD cases) was detected in mutation carriers 10 years before the onset of the expected symptom (Bateman et al., 2012). Though these data suggest that insulin resistance and DM may lead to the disturbance of glucose metabolism in the brain, the exact mechanisms on how insulin resistance and DM acts as risk factors for AD remain unclear.

The brain or central nervous system (CNS) utilizes a vast amount of energy to sustain its basic functions, such as maintaining or re-establishing of membrane potentials, signaling, and other essential cellular activities. While an adult human brain typically weighs