Alzheimer’s disease and Glucose Metabolism
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Abstract: Alzheimer’s disease (AD) is one of the most common neurodegenerative disorders with a progressive memory decline and other cognition function weakness. There are around 35 million people worldwide suffering from this disease and AD related health cost is huge. The hallmarks of AD are intracellular plaques of amyloid beta (Aβ) deposits and intercellular neurofibrillary tangles (NFT) with highly phosphorylated Tau proteins. Gene mutations cause early-onset AD development at younger age, which accounted for less than 5% AD. The majority of AD are late-onset, sporadic with no clear understanding of mechanisms. It is well understood that cholinergic neuron malfunction is a leading event for AD development. The reduced acetylcholine releases lead to weaken cognition and later AD. The brain is an organ with highest basal glucose consumption. The interruption of glucose metabolism, especially by age-related oxidative stress, could lead to malfunction of brain neuronal system. As cholinergic neuron using acetyl-CoA as fuel and substrate, the improper glucose metabolism could deteriorate normal cholinergic functions and in turn play an important role in the AD development. This review gives a brief about the relationship between cholinergic neuron, glucose hypometabolism and AD.

Keywords: Alzheimer’s disease, glucose hypometabolism, cholinergic neuron

Introduction

BRAIN is the organ with highest energy, needs and consumes around 20% total energy of body. Most of the energy is provided by glucose except in a condition of starvation, in which ketone body can be transformed to acetyl-CoA to provide necessary energy [1]. Most of the energy for brain is used to maintain the balance of ions which are important for central nervous system functions. The precise control of energy metabolism in important for the brain. Disruption of it will lead to serious effects on the brain functions and cause disease. Alzheimer’s disease (AD) is a neuronal disease with deposits of Aβ deposits, intercellular neurofibrillary tangles (NFT) and reduced cognition functions. With the longer life for human, AD becomes a major health problem [2]. There is no clear conclusion about the cause for AD. The developing drugs can relieve the symptoms of AD but can’t cure it. In the AD, the over-production of Aβ and malfunction of cholinergic neurons are essential. Glucose metabolism produces not only the energy but also substrates for cholinergic neurons. Interruption in glucose metabolism had great influence on cholinergic neurons. In fact, the glucose hypometabolism was observed in AD [3, 4]. This review give a brief introductions for glucose hypometabolism and AD.

1. The roles of APP

Amyloid precursor protein (APP) is type-I transmembrane protein, encoded by app gene in chromosome 21. Because of alternative splicing, there are three major APP isoforms: APP695, APP751 and APP770. APP751 and APP770 are broadly expressed in most tissues, while APP695 is the dominant form in brain neurons. There are also two other APP like genes in human: APLP1 and APLP2. All undergo similar processing, while only APP contains Aβ domain [5, 6].

Physical roles of APP are still not clear even it was broadly expressed in all tissues [7-9]. The APP knock-out mice APP didn’t show significantly difference from wild type mice [10]. These mice were lighter and show weakness in the extremities with age. Based on conservative domain analysis, the extra cellular domain of APP could interact with many extra-cellular matrix components indicating possible roles for cellular adhesion for APP [11-13]. Another possible role for APP is the trophic function [14-16]. When treated with antisense APP, fibroblast cells grow slowly while addition of sAPP reverses such trends. Injection of sAPP into brain could increase synaptic density and improve memory retention in animals. The N-terminal heparin binding domain (28-123) also stimulates neurites outgrowth and promotes synaptogenesis. Injection of anti-APP antibody daily into brain leads to behavior impairments in rats. The The sAPP also could involve in the regulation of stem cells. sAPPα stimulated the differentiation of neural stem cells into astrocytic lineage. Combination of sAPPα and EGF stimulated the proliferation of EGF responsive neural stems cells in the subventrical zone of adult rodents’ brain [17-19]. Therefore, the APP may have autocrine and paracrine functions. As APP has very similar processing pathway as Notch receptors, there was suggestion that the C-terminal of it (AICD) could serve as translation factors [21-24]. AICD can form a transcriptional active complex with Fe65 and Tip60. There are several genes that could be target of AICD: tumor suppressor KAI1, nephrilysin (a neutral endopeptidase with Aβ degrading activity), LRP1 and EGF receptors. The latter two could link to in vivo phenotypes of presenilin activity and cholesterol metabolism. Another study reported that APP, TAG1 (in the out membrane) and presenilin act to suppress neurogenesis. Either APP or TAG1 deficiency animals have more neuroprogenitor cells. But the target for APP is still not clear.

2. APP processing & regulation

There are several cleavage sites in APP with two major processing pathways: non-amylodogenic and amyloidogenic processing [25]. For production of Aβ, APP is first cleaved by β-secretase with production of sAPPβ and C-terminal fraction C99. Further cleavage of C99 by γ-secretase in the transmembrane part will release Aβ and AICD [26]. In the non-amyloidogenic pathway, α-secretase cleaves APP within the Aβ domain to release sAPPα and C-terminal fraction C88. Further cleavage by γ-secretase
Several zinc metallocproteinase, such as TACE/ADAM17, ADAM9, ADAM10 and MDC-9, can cleave APP at the α-secretase site [27]. The major β-secretase is β-site APP- cleaving enzyme-1 (BACE-1), a transmembrane aspartyl protease. γ-secretase is a complex with four major subunits: presenilin-1/presenilin-2, nicastrin, APH-1 and PEN-2. There are two major cut sites for γ-secretase. Nearly 90% secreted Aβ is Aβ1-40, whereas Aβ1-42 accounts for less than 10%.

The most common forms of beta amyloid in AD plaques are Aβ1-40 and Aβ1-42. Aβ1-42 tended to form fiber more than Aβ1-40 and demonstrated more neurotoxicity. The insoluble fiber plaques are most common component of senile plaques in AD brain, which had been assumed to be the most toxic forms that contributed to AD development. In contrast to this assumption, it was found that neuro-degeneration appeared long before senile plaques formation. Therefore, there are other risk factors that induce the neuro-degeneration. The soluble Aβ oligomers could be the toxic components that lead to neuronal dysfunction and memory deficit in AD. It was suggested that Aβ oligomers are specific presynaptic ligand that inhibited hippocampal long term potentiation. In cellular and animal models, the Aβ oligomers demonstrated the ability to induce neurotoxicity, electrophysiological changes and disruption of cognitive functions.

Any factors that enhanced the production of Aβ, especially Aβ1-42 forms, increase amyloidogenic processing and could cause AD [5, 6]. The APP over-expression alone causes early onset AD. Down syndrome (DS) patients, which have extra copy of chromosome 21 and higher expression of APP, develop AD after middle ages. Over-expression of APP can also cause early onset AD. In sporadic AD, the expression of MiR-106b, which down-regulates APP, is decreased. The Swedish mutation of APP favored the cleavage by β-secretase and production of Aβ. Mutation of presenilin, part of γ-secretase complex, causes the most common type of familial AD. Another common factor is ApoE. There are 2-3 times of allele ε4 in late-onset AD than in cognitively normal person with increasing deposit of Aβ.

Because α-secretase cuts into the Aβ and leads to non-amyloidogenic processing, it is a target for prevention of AD [28-30]. Retinoic acid (RA) increases the expression of ADAM10 by activating the nuclear RA receptors. In AD, cholinergic and neuropeptide neuronal systems are weakened by impairing GPCR-induced α-secretase activation. Deficiency of M1 Muscarinic acetylcholine receptor (mAChR), a GPCR, increases Aβ production with decreased sAPPα.

3. Cholinergic neuron and AD

The basal forebrain cholinergic system extends to the cerebral cortex and hippocampus. The cholinergic neuron study focused on acetylcholine synthesis and degradation, choline acetyltransferase (ChAT), acetylcholine esterase (AChE), vesicular acetylcholine transporter (VACHT) for transferring of acetylcholine into vesicles, cholinergic nicotinic receptors (nAChR) and muscarinic (mAChR) for synaptic signaling, and neurotrophic supports such as NGF (nerve growth factor) mediated receptors for survival. With aging, cholinergic neuron undergoes moderate degenerative changes, leading to hypo-function, which may relate to progressing memory loss [31]. The normal aging is accompanied with gradual loss of cholinergic function caused by dendritic, synaptic, and axonal degeneration as well as a decrease in trophic support [2, 32-34]. Decrease in gene expression, weakened intracellular signaling and cytoskeleton transporting malfunction all add up regulate cholinergic cell atrophy that leading to aging related cognitive impairment. Loss of cholinergic function and cholinergic degeneration are displayed in different diseases. Therefore, the interference of early cholinergic changes is promising target for medical rescues.

In AD, the cholinergic neurons have similar but more severe changes as typical aging process. There is cholinergic neuron cell loss in AD [35]. As early as 1970s, there were reports that presynaptic cholinergic marker deficiency was found in late onset AD patients. The clinic study revealed a correlation between early dementia rates and levels of many cholinergic markers such as ChAT, nAChR, mAChR and acetylcholine by itself [36, 39]. In vivo PET scanning using AChE ligand indicated that there was mild loss of AChE activity with mild cognitive impairment (MCI) and early AD. Slightly increase of ChAT activity was observed in the hippocampus and frontal cortex of MCI patients. The increase of ChAT activity may partly contribute to the replacement of disconnected glutamatergic synapses by cholinergic synapses [37, 38]. P75 neurotrophin (p75NTR, a tumor necrosis factor receptor member) is mostly expressed by basal forebrain cholinergic neuron [31]. Aβ can bind to p75NTR and be internalized and removed by lysosome. In MCI patients, the trkA and p75NTR containing neurons, which are co-localized with ChAT, were significantly reduced. Therefore, the cholinergic neurons can both regulate the APP processing through Acetyl choline and Muscarinic receptors and help the removal of Aβ [32, 33, 38]. It suggested that the dysfunction of cholinergic neurons, instead of loss of it, might contributed to MCI and early AD [39]. Gene expression analysis of single basal forebrain demonstrated that trkA, but not p75NTR is reduced in MCI [34]. Pro-NGF and pro-BDNF expression are reduced in the cortex of MCI and AD [40]. In AD, the extracellular Aβ accumulation and intracellular neurofibrillary tangles may play some roles in mediating the changes of cholinergic pathway. There is evidence that Aβ indeed trigger cholinergic dysfunction through α7 nicotinic receptors, affecting NGF signaling, mediating Tau phosphorylation, interacting with acetylcholinesterase, and influence the proteasome in cholinergic neurons [41]. The trophic factors, such as NGF, play important roles in cholinergic neuron survive. Introducing of NGF by injection or genetic modification increases the trophic support to cholinergic neurons and delay cognition reduction with aging or AD patients in preliminary tests [42]. Even with above strong evidences supporting the role of cholinergic neurons in the initial stages of early onset and in the advanced stages of late onset AD, it is still not conclusive. Different from other neurons, the cholinergic neurons use acetyl-CoA not only as energy source, but also as substrate for acetylcholine synthesis. It responses more severe to glucose deprivation than other neurons. Targeting the cholinergic pathway could be good for AD patients.

4. Glucose hypometabolism and AD

Diabetic Mellitus (DM) is a complex metabolic disorder with chronic hyperglycemia. Glucose intolerance and diabetes mellitus are believed to be risk factors for development of AD. Rotterdam
initial study, religious order study, Mayo clinic Alzheimer registry, Hisayama study show increased AD risk for diabetes [43-46]. Among DM patients, there are 50-100% increase chances of development of AD. Diabetic patients show cognitive deficits including damaged verbal memory, diminished mental speed and mental flexibility, with glucose intolerance and insulin resistance. Streptozotocin induced diabetic mice formed neuritic plaques and neurofibrillary tangles [47]. In general, there are overwhelming evidences supporting the increased AD or dementia risks for DM patients.

On the other hand, 80% AD patients are with either impaired fasting glucose or diabetes. Disturbed brain metabolisms were widely observed in AD patients. Impaired glucose metabolism was observed in parietal, temporal and frontal cortex of AD patients [3, 4]. As early as 1983, De Leon et. al. found that elderly patient with dementia had lower cerebral metabolic rate of glucose, which is in accordance with cognitive performance [48]. One possible reason for glucose hypometabolism is the loss of nerve cells. However, glucose hypometabolism developed way before the cognitive loss. The presence of ε4 allele of the apolipoprotein E (ApoE4) greatly increased the chance to develop late onset sporadic AD. Those people displayed significantly reduced glucose metabolism in posterior cingulate, parietal, temporal and prefrontal regions even without clinical cognitive abnormal symptoms at early age [49, 50]. A similar trend was found in presenilin 1 mutant that tends to develop early onset AD [51].

The mechanism for glucose hypometabolism in AD is still not clear. Although some literatures focused on the toxic effects of ApoE4 fragments or Aβ protofibrils, others suggested that the disturbance of insulin-lipid-glucose is more central [52, 53]. In central nerve system, disturbed lipid metabolism inhibit membrane proteins such as glucose transporter and APP. The excessive insulin accelerates cellular damage in neurons [54]. Long term intranasal insulin administration in 4 months increased the cognitive functions in patients with mind impairments and early AD [55]. The extracellular accumulation of Amyloid Beta peptide also plays important roles in the synaptic dysfunction, which may represent the hypometabolic region of FDG-PET scanning. The downstream damage by hypometabolism included diminished production of acetyl-CoA and ATP, which are important for synaptic cholinergic neuronal activity and plasticity [56]. The decrease of acetyl-CoA and ATP will influence the synthesis of acetylcholine, protein misfolding and transport in the synapse. Insulin resistance and reduced ATP also increase the heperphosphorylation of tau, a major marker for AD. In SH-sy5y cells, high levels of glucose and insulin altered the processing of APP with increased Aβ[57, 58]. The insulin changed APP processing through phosphatidyl-inositol 3 kinase (PI3-K), suggesting that vesicle transport might be involved.

Brain is the organ with highest glucose consumption, most of the energy produced was used to maintain ion balance in synaptic transmission [1, 59]. Because the blood-brain barrier (BBB) has lower permeability for glucose and the brain contain little storage of carbohydrate storage, the active glucose transport plays important role in the maintenance of brain energy supply. Some reports suggested that lactate, produced by astrocytes is another major energy substrate for brain neuronal cells. Glucose transporter (GLUT) 1 is enriched in microvascular endothelial cells and astrocytes. Releasing of glutamate by neuronal activation could increase the uptake of glucose by astrocytes to produce lactate for neuronal usage. Under limited brain fuel supply or in pathological conditions such as AD, the glucose transport through BBB and/or neuronal membrane could become a rate limiting step [60]. For late onset, sporadic AD, ATP production decreased by 50% and continue to decrease with the worsen of the disease. The reduction of GLUT 1 and DLUT 3 in AD brain (expressed in brain neurons) corresponded with increasing tau phosphorylation (the major component of NFT) [61, 62].

Insulin receptors are rich in brain neurons, suggesting an important role for insulin in brain glucose metabolism and brain functions. Insulin resistance is known to be highly associated with decreasing cognition among old people. Insulin-PI3K-AKT signaling pathway played important roles in the phosphorylation of tau. Hyperphosphorylation of tau was related to reduced activity of several components in this pathway [63]. In AD and mild cognitive impairment (MCI) brain, the insulin receptors and signaling markers were reduced. At the same time, insulin also reduced the formation of highly toxic Aβ oligomer to reduce synaptotoxicity [64]. It is interesting that Aβ also regulate insulin signaling by directly bind to insulin receptors [65]. Aβ increased the phosphorylation of IRS-1 and induced insulin resistance. Because Diabetic Mellitus and glucose hypometabolism is strongly related to AD, it is a convenient target for AD prevention and treatment. Peroxisome proliferator-activated receptor (PPAR)-γ agonists, which was used for type II diabetes, inhibited Aβ stimulated secretion of pro-inflammatory products and decreased oxidative stress in both in vitro and in vivo models [66]. Increase of insulin levels by intravenous injection or nasal apply increased brain insulin levels with improved cognition [67]. There were also some success in both animal and human trials that increased memory performance by increasing energy in the brain [68].

Conclusion

With the life span of human increases, people has greater chance to develop aging related disease, such as mild cognitive impairment, dementia and AD. Glucose hypometabolism strongly related to AD and was a found well before the symptoms of AD. At the same time, the weaken of cholinergic neuron function and late lose of cholinergic neurons were found also in AD patients. The understanding of their relationship help us to understand the development of AD. It also provides useful targets for AD prevention and therapy.

Conflict of interest: None declared.

References


