Main hypotheses, concepts and theories in the study of Alzheimer’s disease

Yuhui An*, Chao Zhang, Siyu He, Chunxia Yao, Limei Zhang, Qian Zhang

Department of Biochemistry and Molecular Biology, Basic Medical College, Zhengzhou University, Zhengzhou, Henan 450052, China

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Abstract

The incidence of Alzheimer’s disease (AD) is 25 millions worldwide in 2000 and it is expected to increase to 63 and 114 millions in year 2030 and 2050, respectively. Nowadays, such aging disease has caused enormous medical and financial burden to the community, which effective prevention and treatment are urgently needed. In this study, we have reviewed different hypotheses, concepts and theories of AD. These include hypothesis related to the loss of cholinergic neuron, calcium, oxidative imbalance, microtubule instability and amyloid cascade; the concepts about mild cognitive impairment and the regulation and interference of original molecule; and the theories of nitric oxide and glutamate neurotoxicity. Although genetic tests have existed for the research of AD, they are considered useful only for the small number of families with a history of early-onset illness. Because AD is a genetically heterogeneous disorder, it is classified as familial and sporadic. We hope this review can briefly provide a summary of the general knowledge about sporadic AD, and help to promote the research on AD or related prevention and treatment. [Life Science Journal. 2008; 5(4): 1 – 5] (ISSN: 1097 – 8135).

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1 Introduction

According to a report of world health organization (WHO)[1], the incidence of Alzheimer’s disease (AD), a feature of memory dysfunction with a progressive loss of learning and memory, is drastically increasing along with human aging. The population of AD will be related to 60% of over-60-year-old population worldwide. In 2000, the incidence of AD is 25 millions. It is estimated that it will reach 63 and 114 millions in year 2030 and 2050, respectively. It is clearly a pressing problem and burden in both the medical and financial view of the society. In this review, different hypotheses, concepts and theories of AD have been summerized. These include hypotheses related to cholinergy, calcium, oxidative imbalance, microtubule instability and amyloid cascade; the concepts about mild cognitive impairment and the regulation and interference of original molecule; and the theories of nitric oxide and glutamate neurotoxicity.

Although genetic tests have existed for the research of Alzheimer disease, they are considered useful only for the small number of families with a history of early-onset illness. Because AD is a genetically heterogeneous disorder, it is classified as familial and sporadic[2]. We hope this review can briefly provide a summary of the general knowledge about sporadic AD, and help to promote the research on AD or related prevention and treatment to the next level.

2 The Cholinergic Hypothesis

The cholinergic hypothesis was firstly proposed by Sims et al in 1981. They postulated that the synthesis of acetylcholine, a neurotransmitter, was low in the neocortex of the brain in AD patients[3,4]. In supporting this notion, the level of choline acetyltransferase was clearly found downregulated in the hippocampus and frontal cortex, and cholinergic neuron counts in the nucleus basalis was generally lowered in AD condition[5]. For the above reasons, the “cholinergic hypothesis” was suggested to

*Corresponding author. Email: yuhuan@zzu.edu.cn
describe the low level of acetylcholine in the brain of AD patients. Based on this hypothesis some drugs were put under investigations for that they could generally increase the cerebral level of acetylcholine. These include the acetylcholinesterase inhibitor, the cholinergic neuron agonist, the acetylcholine releasing agent and the cholinergic neuron proliferation agents etc. Tacrine was the first drug that had launched into the market for treating the loss of memory and intellectual decline in AD patients. However, its side effect such as hepatic toxicity and the lack of ability to delay the progression of disease had resulted in poor outcome and popularity. To date, nerve growth factor (NGF) is being studied on its protective characteristic on neurons for AD patients. It is a neuron proliferation agent that can elevate cholinergic neuron counts and protect neurons, particularly cholinergic neurons, from degeneration. Since it is a big molecule which cannot pass through the blood brain barrier, research is ongoing which aims to improve the drug delivery strategy for NGF. So it might become one effective agents used in gene therapy for treating AD.

3 The Conception of Mild Cognitive Impairment

In clinical research of AD, Petersen et al suggested “the conception of mild cognitive impairment (MCI)”(13). It postulated a state between normal aging and AD. At the state, patients with MCI are yet to reach the pathological standard of AD, but they are people of higher risk to develop AD. About 15% of MCI sufferers will finally develop AD every year. Research has shown that MCI represents an early point of decline on the continuum of AD that is different from normal aging of various aspects. These include reduction of learning ability, rapid loss of short-term memory, elevation of intrusion errors, and poor recognition discriminability. The proposed adjustments and additions (neuropsychological instruments and the incorporation of depressive symptoms) in the diagnostic flowchart of Petersen may serve as useful tools for clinicians when making a diagnosis of MCI.

4 The Hypothesis of Oxidative Stress and Oxidative Imbalance

In recent years, studies have revealed a close association between increased oxidative stress and AD. It is well recognized that oxidative imbalance and stress can play a crucial role in the pathogenesis of neuron degeneration and death. Increasing evidence have also supported a role of oxidative imbalance, characterized by impaired antioxidant enzymatic activity and increased reactive oxygen species (ROS) production in AD. Those ROS include the free radicals (e.g. superoxide and hydroxyl radicals), nonradical oxygen species (e.g. hydrogen peroxide and peroxynitrite), and reactive lipids and carbohydrates (e.g. ketoaldehydes, hydroxynonene). In general, oxidative damage to DNA can occur via various pathways such as the oxidative modification of the nucleotide bases, sugars, or simply by forming crosslinks. Such modifications can lead to mutations, pathologies, cellular aging and death. Moreover, oxidation of protein appears to play a causative role in many chronic aging diseases including cataractogenesis (21), rheumatoid arthritis (22), and various neurodegenerative diseases including AD (23).

5 Nitric Oxide Theory

Nitric oxide (NO) theory is another hypothesis in molecular etiology of AD. NO and other reactive nitrogen species appear to play several crucial roles in the brain. These include physiological processes such as neuromodulation, neurotransmission and synaptic plasticity, and pathological processes such as neurodegeneration and neuroinflammation. NO is synthesized by the nitric oxide synthase (NOS), which is present in the mammalian brain in three different isoforms, two constitutive enzymes (i.e. neuronal nNOS, and endothelial eNOS) and one inducible enzyme (iNOS). Nitric oxide synthase neurons are abundant in the human cortex, and their distribution differs between different cortical regions, and there are differences between normal aging and Alzheimer patients in the frontal cortex and the hippocampus. All three isoforms are aberrantly expressed in Alzheimer’s disease giving rise to elevated levels of nitric oxide apparently involved in the pathogenesis of this disease by various different mechanisms including oxidative stress and activation of intracellular signalling mechanisms. In AD cases, aberrant expression of eNOS (NOS-3) in cortical pyramidal cells was highly co-localized with nitrotyrosine. Furthermore, iNOS (NOS-2) and eNOS were highly expressed in astrocytes in AD. eNOS overexpression can result in apoptosis accompanied by increased levels of p53, p21, Waf1, Bax, and CD95. However, iNOS has been found to be a major contributor to initiation/exacerbation of the central nervous system (CNS) inflammatory/degenerative conditions through the production of excessive NO which generates reactive nitrogen species (RNSs). The up-regulation of NOS expression, suggesting overproduction of NO, can causes a decrease in cerebral blood flow, involving microvasculopathy with impaired NO release.
which in turn results in regional metabolic dysfunction[31]. NO is thermodynamically unstable and tends to react with other molecules, resulting in the oxidation, nitrosylation or nitration of proteins, with the concomitant effects on many cellular mechanisms. NO intracellular signaling involves the activation of guanylate cyclase but it also interacts with MAPKs, apoptosis-related proteins, and mitochondrial respiratory chain or anti-proliferative molecules[32]. NO can be scavenged in a rapid reaction with superoxide (O\(_2^−\)) to generate peroxynitrite (ONOO\(^−\)), with a half-life less than 1 second. ONOO\(^−\) is a potent oxidant and the primary component of nitroxidative stress. At high concentrations (> 100 nM), ONOO\(^−\) can undergo homolytic or heterolytic cleavage to produce NO\(_3^−\), NO\(_2^−\), and OH\(^−\), highly reactive oxidative species and secondary components of nitroxidative stress. The high nitroxidative stress can initiate a cascade of redox reactions which can trigger apoptosis and evoke cytotoxic effects on neurons and endothelial cells[33]. NO also induces tau hyperphosphorylation at Ser396/404 and Ser262 in HEK293/tau441 cells with a simultaneous activation of glycogen synthase kinase-3beta (GSK-3beta)[34].

6 The Theory of Glutamate Neurotoxicity/Calcium Hypothesis

The theory of glutamate neurotoxicity and the calcium (Ca\(^{2+}\)) hypothesis belong to the same theory. Simpson et al[35] found that glutamate-containing nerve terminals are severely reduced in AD. Glutamate can increase the intracellular Ca\(^{2+}\) activity. This finally leads to a Ca\(^{2+}\) influx via NMDA receptor of glutamate, an excitatory amino acid, which can act on the NMDA receptors on spinal cord neurons, channels[36] and results in dysregulation of multiple Ca\(^{2+}\)-dependent processes including learning or memory loss. Based on this observation, the calcium hypothesis was suggested[37], and antagonist of NMDA receptor was being investigated for its application as a novel therapeutic approach for AD[38].

7 The Hypothesis of Microtubule Instability

The hypothesis of microtubule instability comes from the observation to the phenomena in which tau protein promotes microtubule assembly and stabilizes microtubules, yet hyperphosphorylated tau did not[39]. Hyperphosphorylated tau-induced disruption of microtubule network results in both axonal and dendritic neurodegeneration seen in AD patients[40]. It is known that the state of tau phosphorylation is mainly regulated by maintaining the balance between tau phosphatase(s) activity and tau kinase(s) activity. Since many studies have shown that hyperphosphorylation of tau in the brain of AD might be due to a decrease of tau phosphatase(s) activity[41,42]. The related enzymes became potential target candidate that might be employed in the treatment of AD.

8 The Amyloid Cascade Hypothesis

Beta-amyloid (Abeta), a 4200-dalton peptide isolated from extraparenchymal meningeal vessels, neuritic plaques, and neurofibrillary tangles, has been revealed as an important pathological factor in the neural system[43]. An investigation which studied the amyloid deposition in the brain and other organs in 105 consecutive autopsy cases, aged 59 to 101 years, had verified a close relationship between Abeta and AD[44]. Nowadays, a pathological cascade was suggested for AD. This started with the Abeta deposition, then leads to tau phosphorylation and tangle formation and finally neuronal death[45]. It is generally believed that a beta fibrils deposited in amyloid plaques will lead to the formation of beta-derived diffusible ligands (ADDL). The ADDL will bind to synaptic sites or near NMDA receptors which results in synaptic loss, oxidative damage, and AD-type tau hyperphosphorylation[46]. However, some studies in somatostatin cells have revealed an independent status of Abeta deposition and hyperphosphorylation of tau which could not be explained by the amyloid cascade hypothesis[47]. Therefore, such hypothesis is still controversial, yet it is mostly accepted as one of the implications in the pathological aging processes including AD[48].

9 The Conception of Regulation and Interference of Original Molecules

Neurotoxic molecules, which can generate neurotoxicity to nervous cells, can induce AD. We have summarized in the above sessions that ROS, NO, tau protein, Abeta are endogenous neurotoxic molecules. Our genuine question should be about the origin of those molecules. For ROS, it is obvious that they came from oxidative reaction where oxidative enzyme and substrates should count as their origin[18–23]. For NO, there is no doubt that its original substances are L-arginine and nitric oxide synthase[24–34]. Furthermore, tau kinase and tau phosphatase are the original molecule of hyperphosphorylated tau, yet it needs an imbalance of the state to make it pathological[39–42]. For the formation of Abeta, amyloid precursor protein (APP), a membrane protein of 695 amino acids[49], β- and γ-secretase can be regarded as the original molecules. APP involves in the initial of a cascade, in which when hydroly-
sis of β- and γ-secretase occurs, the neurotoxic molecule Abeta will be induced\[^{56,51}\]. Therefore, we are suggesting here that if the formation of the original molecules are regulated in an purpose to reduce their generation of neurotoxic molecules, the condition of AD might be curable or slowed down in progression. Based on this, we have previously suggested a conception of “regulation and interference of original molecules” (RIOM)\[^{52}\]. Thereafter, several studies have positively evaluated this concept. For example, an inhibitor of cysteine protease and secretase was found to reduce Abeta production\[^{53}\]. The regulatory effects of acidic peptide on the levels of N-methyl-D-aspartate receptor, the NGF and the Abeta peptide have evidence to interfere with original molecule\[^{54}\], and lead to an effective therapy to AD\[^{55}\]. Furthermore, okadaic acid was also found to reduce mint-1, mint-2, and APP overexpressionin neurons\[^{56}\]. The plasma concentration of NO in the AD patients was also found to be decreased with an artificial increase of homocysteine\[^{57}\]. Similarly, NADPH oxidase was down-regulated by an introduction of heme oxygenase-1 in vivo, that resulted in a decrease in oxidative stress\[^{58}\]. All of the above demonstrated either regulation or interference on the original molecules, via an interaction with enzymatic activity and gene expression. It is a valuable platform for further investigation which would be carried out to reveal if any of the interferences might be helpful in reducing the occurrence of AD. Those reagents or substances which successfully cause the interferences might as well serve as a novel therapeutic strategy in treating aging diseases in the near future.

### References