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REVIEW ARTICLE

Prevention and Treatment of Basic Diseases: A Potential Direction to Intervene Alzheimer's Disease

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Abstract

As the life span of human beings increases, the number of dementia patients such as Alzheimer's disease (AD) is increasing. AD may be one of the major diseases faced by the whole world in the future. It is an unresponsive for single drug according to the current stage of AD pathogenesis and drug research. Combined use of various drugs may be the inevitable trend of AD drug research in the future. Personalized treatment of metabolic diseases, vascular diseases and chronic inflammatory risk diseases is a necessary step to intervene in AD. During the middle age, to strengthen immunity and to reduce the external environment to stimulate the susceptible gene, which is beneficial to suppress the formation of AD. In a word, the early prevention of AD is better than the later treatment.

Keywords

Alzheimer's disease, Metabolic disease, Cardiovascular disease, Chronic inflammatory disease

Alzheimer's disease (AD) is the most important neurodegenerative disease in the world. At present, there are about 49 million patients worldwide, whose incidence and prevalence are increasing year by year. Since the pathogenesis of AD is not clear, there is no other new drugs were approved for sale in the 15 years after FDA approved memantine in 2003. Many clinical trials of new drugs worldwide ended in failure. In May 17, 2018, Johnson announced the termination of atabecestat development. Pfizer, one of the largest pharmaceutical company in the world, announced to close all new drugs for Alzheimer's disease last year. More brutally, the French Ministry of Health recently confirmed that AD's existing four drugs did not achieve satisfactory medical results. The lack of clinical demand and new drug listing has been known as the biggest contradiction in the field. It is foreseeable that AD will be one of the major problems of geriatrics and socioeconomic problems facing the world in the future.

Aging is the Precondition for the Formation of AD

It is worth noting that dementia such as AD is not the exclusive disease of the modern people. The Chinese people had the corresponding literature more than 2000 years ago. Huang Di Nei Jing records that women aging begins at 35-years-old, while men aging begins at 40-years-old. This record is much more consistent with the incidence of AD in modern women than in men [1]. Moreover, studies have found that some people aged only more than 30 years can be observed higher level of β-amyloid in the brain [2]. While Individuals with Down's syndrome have been diagnosed with AD at the age of 30 to 40 [3]. Although these evidences do not prove that AD will be produced after aging, there is clear evidence that the prevalence of Aβ related to age [4]. More importantly, aging is closely related to skin barrier and organ function decline [5-8]. These changes reduce the body's resistance to external stimuli and may trigger immune responses and metabolic abnormalities. And then they induce the risk diseases of AD. Therefore, aging is the most critical risk factor for late-onset AD [9,10].

Basic Disease is the Necessary Condition for the Development of AD

AD is a complex neurodegenerative disease with many diseases involved in its formation. Type 2 diabetes

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mellitus (T2DM) has been recognized as an important risk disease for AD for many years [11]. Insulin and leptin signal all involve in T2DM. At the same time, they are involved in regulating the functions of nerve and synapse, and the production and clearance of Aβ [11]. Thus, AD and T2DM have the same cellular and molecular mechanism [12]. According to this, AD has also been known as type 3 diabetes mellitus [13]. A recent study found that triglyceride can induce leptin and insulin resistance through going across blood brain barrier (BBB) [14]. TG can inhibit leptin transport across BBB in a dose-dependent manner, while glucose and insulin promote leptin transport [15]. It suggests that these metabolic diseases such as obesity, T2DM and hyperlipidemia are major risk factors for AD. Studies have also shown that obesity induced by high fat diet can inhibit the metabolic activity of the BBB microvessels [16]. And then it causes macrophage invasion and cognitive decline [17]. These evidences suggest that metabolic diseases are one of the most important basal diseases of AD.

Neuroinflammation is an important potential factor in the pathogenesis and development of AD [18]. However, the role of neuroinflammation in the pathological process of AD is not clear. It may be caused by inflammatory factors intruded into the brain through aneretic BBB induced by persistent peripheral disease. It may also be aroused by insufficient local energy supply in the brain. Studies show that 20% of AD patients have allergic diseases such as allergic rhinitis, bronchial asthma [19]. And appropriate antiasthmatic treatment can improve cognitive ability in AD patients [20]. Unfortunately, there are no reports of allergic diseases and BBB damage. In addition, many studies have shown that rheumatoid arthritis (RA) are related to AD [21-24]. The gene and epigenetic regulation of inflammatory cascade is the point of association between AD and RA [24]. More importantly, recent studies have shown that RA patients have BBB dysfunction [25]. And the inflammatory factor TNF-alpha is a regulator of peripheral inflammation to amyloid pathology [26]. In conclusion, persistent peripheral inflammatory disease may be a major risk factor for neuro-inflammation.

The brain is an organ with high oxygen and energy consumption. The energy supply in the brain is directly related to the normal functioning of brain. In recent years, insufficient supply of AD brain has attracted wide attention [27-30]. In the decades before the symptoms of cognitive decline, AD patients showed chronic cerebral hypoperfusion and glucose hypometabolism [29]. A large number of studies have shown that vascular diseases such as atherosclerosis are the key risk factors for cerebrovascular disorders [31-32]. These cardiovascular diseases are also closely related to peripheral inflammation [33-35]. Thus, they are also one of the risk factors for BBB homeostasis and the development of AD.

Prevention and Control of Basic Diseases is the Fundamental Way to Prevent AD

Alzheimer's disease is a compound disease caused by many factors. Particulate matter [36,37], herpes virus [38], toxic substances and chemicals [39] are the external factors associated with AD formation. Second, patients may suffer from basic disease due to family inheritance, personal diet, living habits or environmental factors. They can cause a vicious cycle of oxidative stress, inflammation and energy metabolism, which can disturb BBB and even induce the activation of AD susceptible genes. A series of peripheral lesions will gradually form the same vicious cycle in the brain and accelerate the formation of AD typical pathology (Figure 1). Therefore, the protection of BBB is an important direction for the study of neurodegenerative diseases [40].

Aging is a prerequisite for the formation of AD, which runs through the whole process of AD lesions. On the premise of aging, the external environment invaded the body, leading to chronic inflammatory dis-

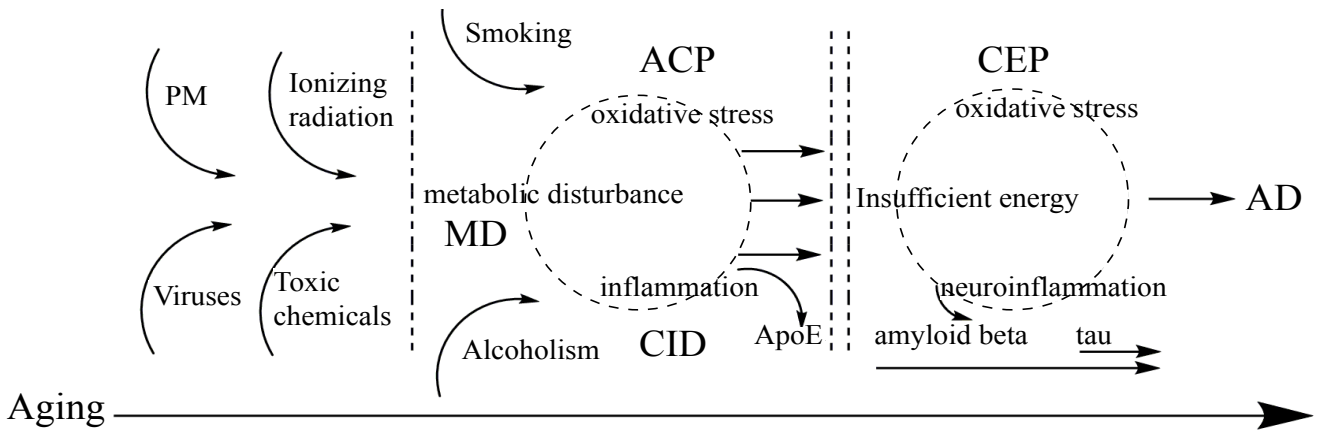

Figure 1: The evolution process of Alzheimer's disease.

eases (CID). At the same time, angiocardiopathy (ACP) and metabolic diseases (MD) are gradually formed due to personal habits and so on. These basic diseases form a vicious cycle of oxidative stress, inflammation and metabolic disorders. They then invaded the brain by disrupting BBB and induced a similar vicious cycle in the central nervous system (CNS). Subsequently, chronic encephalopathy (CEP) and AD characteristic lesions were induced, and finally AD was formed.

Although the research stage of AD has been moving forward in recent years, it has never been able to get rid of the influence of Aβ. At the same time, not all dementia has typical Aβ like lesions, and vice versa. Therefore, it is very important to put AD prevention research on basic diseases. On the one hand, their diagnosis compared with subjective cognitive decline is clearly. On the other hand, when treating basic diseases, we can intervene some external risk factors of patients and avoid the formation of AD as far as possible.

Multi Target Drugs or Combination of Multiple Drugs is a Potential Direction for AD Intervention

Clinically, AD patients are usually accompanied by a variety of basic diseases or other diseases. These diseases are cross-linked, so the failure of many effective laboratory drugs in clinical trials may come from here. Therefore, the therapeutic effect of single target drugs on AD is limited, and the existing treatment drugs are well proven it.

At present, the use of various natural medicines and ethnomedicinal medicine has attracted wide attention [41,42]. As the first country to record dementia, there are a large number of prescriptions have been handed down to the present in China. As we all know, Chinese medicine prescription is a combination of various natural medicines according to the rules of Chinese medicine prescription. In addition to interfering with peripheral risk factors, most of the prescriptions for treating AD consider intervening aging (Qi). Unfortunately! These prescriptions are not widely used in clinical since the different principles of treatment. Only part of the research results on animal models are published [43-47]. Anyway, the traditional Chinese medicine prescription may be a potential direction for treating AD in the future.

To sum up, prevention first, treatment second is the basic law to intervene AD. The treatment of basic diseases and the elimination of AD risk factors are the key steps in the treatment of AD. Multitarget drugs or combination of multiple drugs are potential directions for the treatment of AD.

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