A Review on Several Recent Studies on Alzheimer's Disease

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Abstract. The research on Alzheimer's disease (AD) has progressed in recent years. The potential risk factors for AD are multifaceted, which makes the diagnosis and treatment of AD extremely challenging. With the development of bioinformation other manipulations in the micro level, more and more research studies have revealed different aspects of the disease. This study summarizes current results on the etiology of AD as well as treatments for AD and their effectiveness by reviewing empirical findings. In the genetic level, some genes have been examined on mice model by inhibition or optogenetic activation and revealed pathways in the formation of AD. Apart from genes, proteomic studies on certain proteins have also revealed some related changes triggered by blood proteins. Meanwhile, researchers have tested non-invasive treatments such as affecting the brainwave of mice. However, the results do not always change into clinical treatments. The present study emphasizes the necessity to integrate these pieces of study and form a more comprehensive understanding of AD.

Keywords: Alzheimer's disease, impact factor, treatment.

1. Introduction

Alzheimer's Disease (AD) is a progressive neurodegenerative disorder that is paired with cognitive decline, such as memory loss and confusion, and behavioral deficits, such as motor difficulties. Most of the cases have a late onset time that occurs on people older than 65. In an aging society, it has become more and more necessary to find out the triggering factors of AD, and explore effective pharmacological treatments and behavioral interventions that are specific to AD. In this article, the author enclosed some recent research studies related to sign and treatments of AD.

2. Triggering factors of AD

The cause of AD is thought to be both genetic and environmental. The environmental cause of AD has been eliciting interest since it is changeable compared to the genetic cause. In a study conducted by Ehret et al., researchers used the mice model with the AppNL-F gene knocked in [1]. This specific gene contains mutations in the amyloid precursor protein that would lead to the development of amyloid beta plaques, which are the cause of cognitive symptoms of the Alzheimer's Disease. After about 18 months, the mice showed behavioral deficits that were common in AD, including rigidity in movements and reduction in behaviors. Then they were transferred to a new environment where there were rich stimuli for the mice. The transfer yielded an improvement in their metabolism, which included reduced blood glucose and triglyceride levels. Meanwhile, their behaviors were more individualized compared with before.

Meanwhile, neuroinflammation is also considered a risk factor for AD. One of the early signs of AD is mild cognitive impairment, which can be induced by neuroinflammation. In a study done by Engler-Chiurazzi et al., researchers explored how repeated neuroinflammation can damage cognitive ability and neural connections in mice [2]. They induced neuroinflammation on aging mice using lipopolysaccharide for several times, and then tested these mice on their performance of the Morris Water Maze, which evaluated their working memory. They found that mice that were repeatedly induced neuroinflammation showed less long-term potentiation in CA1 hippocampus. This led to the decrease in learning and memory in mice. This indicates that repeated neuroinflammation could be damaging for aging individuals and those with genetic vulnerabilities. They also found that mice in

the LPS group showed worse overnight retention of memory in the performance of Morris Water Maze task.

The genetic vulnerability of AD can be predicted by multiple gene variations. A recent study done by Bellenguez et al. has identified 83 gene variations that are associated with the development of dementia [3]. Based on this research, Yu et al. did a further study looking into the polygenic risk scores (PRS) of these variants [4]. The new gene model aims to explore more genetic vulnerability aside from the well-known apolipoprotein E (APOE) gene. By collecting data from 12,031 old European ancestry participants, the researchers were able to identify 3 PRSs, PRS-83SNP, PRS-SBayesR, and PRS-CS, to be related to the risk of developing dementia. When comparing the genetic vulnerability of these three PRSs to the common cause of dementia, PRS-23SNP, it is discovered that PRS-23SNP is still a more reliable predictor of the progression of dementia compared to the three PRSs studied above. In general, the study examined three gene variants related to dementia, and compared their effectiveness in predicting the disease to previously known variants.

3. Treatment

Studies of possible neuropathological treatments of AD have been focused on the two neural changes that are critical to the development of AD: extracellular aggregation of amyloid plaques and hyperphosphorylated Tau proteins within the cells [5]. Additionally, the immune response triggered by the abnormal aggregating amyloid proteins that involve microglia is also being investigated.

The proteomic analysis has allowed researchers to reach a molecular level and look closer into the substructures of proteins that are possibly responsible for the formation of AD. In a research study done by Merlini et al., researchers used proteomic analysis to track the activation of microglia by blood proteins on a molecular level, and pointed out that the blood protein called fibrinogen was critical to the initiation of microglia [6]. Blood proteins that can pass the blood brain barrier when the brain is damaged can act as messengers for the activation of microglial cells, which can cause neuroinflammation that is detrimental for the brain.

Based on this finding, researchers grew an interest in whether inhibiting fibrinogen could impact the whole process. They eliminated the gene of the protein motif that is connected to CD11b in fibrinogen in AD mice [7]. This prevented fibrinogen from passing the message to activate microglial cells, which inhibited the progression of AD symptoms eventually. This study points out the value of fibrinogen in the progression of AD, and thus points out a possible target for treatments of AD.

A study done by Eteläinen et al. targeted the Tau proteins that aggregate in AD patients [8]. The using of propyl oligopeptidase inhibitor effectively prevented Tau aggregation by upregulating protein phosphatase 2A (PP2A) in the Human Embryonic Kidney cell. Meanwhile, researchers found that the prolyl oligopeptidase was also directly linked to Tau aggregation as it interacted with the project domain of Tau and thereby increased its activity. The prolyl oligopeptidase inhibitor can inhibit the colocalization of prolyl oligopeptidase and Tau protein. When this inhibitor was applied to P301S mice models that expressed pathological Tau protein, the activity of PP2A was normalized. Their performances of the Barnes Maze test, a cognitive test, also improved. This research focused on treating the Tau pathology and showed an effective improvement in preventing Tau aggregation and also benefited cognitive ability in AD mice. Furthermore, it provides a possible effective treatment in the early onset of AD, while most other research studies focused on treatments before the onset of AD.

Although Tau protein is a main target for AD treatment, treatments that have been proven to be valid on mice were not always effective in humans. A research study by Wenger et al. has shown that the mice model was not effective in simulating important changes happening in late AD period, such as ubiquitination and acetylation [9].

One focus on the treatment of AD is the Tau tangles formed in AD patients' brains. In the AD patients, the entanglement of Tau proteins leads to declined cognitive ability. Therefore, drugs targeting Tau protein have been evaluated. However, even though some Tau-targeting drugs

successfully passed pre-clinical mice trials, they generally failed to work the same on humans. To evaluate the difference in human and mice on molecular level, Wenger et al. conducted a research study in 2023, evaluating the difference of brain structure between human and two commonly used mice models: P301S and P301L [9].

The investigation of early-stage post-translational modification reveals that Tau phosphorylation is the critical factor for the development of AD in both human and mice models. However, when entering the later stage, human AD patients showed ubiquitination and acetylation, which are not shown in both mice models in the later stage.

This study reveals the difference in biological progression of AD in mice and humans, and pointed out that mice model might not serve as a good model for simulation of AD progression in humans [9]. Further studies that include both early and later stage of AD need to be conducted to evaluate Tau-target drugs.

The pathogenic microglial cell is considered another major risk for neurodegeneration and has been considered as a potential target of AD treatment. Microglial cells are common in the brain and are often involved in aiding recovery of neurons. One signature of neuroinflammation is the blood extravasation caused by damage to the blood brain barrier. This activates the microglial cells to repair the damage. However, this increase in microglial activation has been linked to increased risk of the formation of amyloid plaques, which are harmful to our cognitive ability and are deemed as a signal to neurodegeneration. Therefore, preventing the activation of microglia cells can be an effective treatment to AD.

Apart from drug treatments, researchers are also looking at other alternatives. Another study utilizes the optogenetic technique to explore whether noninvasive methods can help in ameliorating neurodegeneration [10]. The experiment was based on the discovery that gamma oscillations between 20-50 Hz were found in some neurological diseases. Therefore, the researchers would like to examine whether mediating gamma oscillations can exert changes on the brain. They used 40 Hz flickering light as a stimulation on the interneurons in AD mice, and found that the amyloid-β plaques in their visual cortex were effectively reduced. They then proposed that this could be a possible way of treating AD. The results have been found to be applied on mice models with amyloid-β aggregates, and afterwards on Tau-mutated mice (TauP301S), which indicates that the effect can be generalized to AD with different causes.

In a further research study, the researchers were interested in 40 Hz stimulus in other sensory modalities [11]. They devised an auditory signal that induced 40 Hz gamma frequency neuronal activity within the auditory cortex and hippocampal CA1 region. This suggests that the stimulation of 40 Hz brainwave can be effective across modalities.

Another study on the effect of 40 Hz stimulation on brain functions found that the daily stimulation of gamma wave yielded reduced neuroinflammation caused by microglia, decreased neuronal loss, and improved the cognitive functions in mice [12].

In a recent study, researchers focused on the primary sensory and motor cortex, and evaluated how they were affected by the gamma wave [13]. The stimulation was given by the diaphragm of a speaker that vibrated in the frequency of 40 Hz, and the cage of mice was put on the diaphragm. The immunostaining of c-Fos (a marker of neural activity) showed that neurons increased activity significantly in the two brain regions. After that, they evaluated the effect of gamma wave on AD mice, and found that phosphorylated Tau proteins were reduced after the entrainment. Testing on the motor function of mice through the rotarod test and the grid-hang test also showed improvements for mice with AD. They concluded that the specific frequency of 40 Hz wave might be helpful in treating the progression of AD, and could be effective in motor improvements. The serial research on 40 Hz brainwave shed light on the possible non-invasive treatment for AD. However, its transferring effect on humans is still uninvestigated by now.

4. Behavioral intervention

Many behavioral interventions have utilized the development of technology nowadays. However, a research study pointed out that computerized cognitive trainings might not be as effective as people have expected [14]. In this randomized trial, researchers compared the effectiveness of withholding wellness education, computerized cognitive trainings, and yoga for 12 months. The effect of computerized cognitive trainings is found to be the least compared with other two. This might indicate that relying too much on technology is not the best option for an effective behavioral intervention.

5. Conclusion

In conclusion, the triggering factors of AD are multivariant and cannot be attributed to one single factor, which adds on the difficulty for doing early screening. There is a necessity that the diagnosis of AD could integrate different aspects to form a more comprehensive understanding of the disease. Meanwhile, pharmacological treatments targeting microglia and Tau proteins are facing the problem of transfer in human trials, while non-invasive treatments including 40 Hz gamma brainwave stimulation might be new pathways that can be applied as AD treatments.

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