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A Study of HDAC6 for Ameliorating the Cognitive Function in Alzheimer's Disease

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Abstract. One of the most prevalent causes of dementia, Alzheimer's disease (AD) is characterized by gradual mental decline and memory loss over time. Several drugs are currently available for the treatment of AD, but they only address the disease's symptoms rather than its underlying pathogenesis. Researchers looked into epigenetic therapy and found that histone deacetylase 6 (HDAC6) could be an effective treatment for Alzheimer's disease. This paper uses a literature review approach to investigate the roles of HDAC6 inhibition in AD models and HDAC6 inhibitors, as well as the hypotheses surrounding the pathogenesis of AD. The amyloid cascade hypothesis, the tau hypothesis, and the role of oxygen species are identified as the most prominent pathogenesis hypotheses in this paper. A decrease in Hdac6 levels improves associative and spatial memory in an Alzheimer's disease mouse model and reverses the mitochondrial trafficking impairment in hippocampal neurons in vitro and in vivo. Therefore, inhibiting HDAC6 may represent a novel approach to treating AD-related cognitive decline. As a result of these issues, the FDA has yet to approve any HDAC6 inhibitor for use in the treatment of Alzheimer's disease (FDA).

Keywords: Alzheimer’s disease; Histone deacetylase 6; Pathogenesis; HDAC6 inhibitors.

1. Introduction

In the medical field, Alzheimer's disease (AD) is classified as a neurodegenerative disorder that causes progressive mental decline over time. Alzheimer's disease (AD), the most common type of dementia, is a neurodegenerative illness with a chronic and worsening course. Characteristic symptoms include slow mental processing and gradual memory loss. Neurofibrillary tangles (NFTs) and extracellular senile plaques (EPSPs) of agminated amyloid- (A) peptides are both hallmarks of this pathology [1-2]. The cause of Alzheimer's disease remains a complex mystery. Alzheimer's disease's cause has been debated, with various hypotheses positing roles for amyloid beta, hyperphosphorylated tau proteins, oxidative stress, and other factors [2]. Epigenetic regulation, including histone acetylation, was subsequently linked to the pathogenesis of Alzheimer's disease. Regulation of histone acetylation and deacetylation is mediated by histone acetyltransferases (HAT) and histone deacetylases (HDAC), respectively. Histone deacetylases and sirtuins make up the bulk of HDACs. In addition to histones, HDACs have a wide variety of non-histone proteins as substrates [3]. Because of this, some scientists hypothesized that a role for HDAC-regulated non-histone deacetylation in Alzheimer's disease, rather than histone acetylation. Although the exact cause of Alzheimer's disease remains unknown, numerous studies have shown that blocking HDAC expression can reverse cognitive deficits in animal models of the disease.

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However, there are currently no medications available that can alter the course of Alzheimer's disease and thus prevent or slow its progression.

Results from a review of literatures led the authors to the conclusion that blocking HDAC6 could have therapeutic benefits for people with Alzheimer's disease. The amyloid cascade hypothesis, the tau hypothesis, and the oxygen species hypothesis are briefly reviewed in this paper. Further, the paper elucidates the roles of HDAC6 inhibition in AD based on the results of animal trials and the current state of research involving HDAC6 inhibitors.

This paper covers a lot of ground, from previous hypotheses on AD's origins to potential new drug targets. The development of AD research and some fundamentals of this field can be quickly grasped by the reader. With some revisions, this paper could also be used as a springboard for scientists' subsequent investigations.

2. Hypotheses of AD pathogenesis

2.1 Amyloid cascade hypothesis

The Aβ hypothesis, which is linked to mutations in the amyloid precursor protein (APP) gene and the presenilin 1 (PS1) gene, has assumed a central role in many hypotheses of Alzheimer's disease (AD) pathogenesis, since all older individuals with this type of mutation develop AD [4]. When neurons are damaged, APP is overexpressed, leading to a pathogenic pathway that produces abnormally more Aβ [4]. The abundance of Aβ peptides form soluble oligomers, which eventually form β-plaques, leading to membrane deformation and cell structure changes [5]. Plaque deposition may influence the communication between nerve cells, thereby impeding signal transmission.

2.2 Tau hypothesis

Components of the neural cytoskeleton are microtubules that consist of tubulin and microtubule-associated proteins (MAPs). Tau protein is the most abundant MAP, and its primary function is stabilizing microtubules because of its role in dendrite and axon transport [6]. Tau protein contains a large number of phosphorylation sites, but hyperphosphorylated tau fails to bind to tubulin and aggregates to form neurofibrillary tangles, resulting in impaired axonal transport, mitochondrial and cytoskeletal dysfunction, synaptic loss, oxidative stress, and neuroinflammation. Hyperphosphorylation of particular phosphorylation sites also decreases tubulin acetylation, thereby destroying microtubule stability [7].

2.3 Oxygen species

Species of oxygen (OS) are internal oxides containing one or more unpaired electrons. However, when their number exceeds the body's capacity to eliminate them, disrupting the equilibrium between production and elimination, they will attack macromolecules, such as DNA, lipids, and proteins, and cause cell damage. Brain tissue is sensitive to oxidative stress, but the blood-brain barrier prevents some antioxidants from entering the brain, indicating a decline in antioxidant capacity and accumulation of OS [8]. Some researchers discovered that the number of mitochondria in AD model neurons decreased while the production of OS increased [6]. Moreover, the production of OS is related to the presence of Aβ, which can react with oxygen to generate reactive oxygen species [8].

3. The classes of HDAC

To date, researchers have cataloged 18 distinct HDACs found in mammals. Histone deacetylase and sirtuin proteins make up these HDACs. There are three groups within the family of histone deacetylases. Class I HDACs are most commonly found in the nucleus and include HDAC1, HDAC2, HDAC3, and HDAC8. Type IV HDAC11 has been identified. Sirtuins belong to class III of histone deacetylases [9].

Histone acetylation and deacetylation are controlled by the enzymes histone acetyltransferases (HAT) and histone deacetylases (HDAC), respectively. In addition to controlling the deacetylation of histones, HDACs can also regulate the deacetylation of non-histone proteins, such as the acetylation of a-tubulin

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at lysine 40 (a-tubulinK40ac), a major substrate of HDAC6. Therefore, many researchers have zeroed in on HDAC6, which has been linked to controlling cytoskeletal integrity, intracellular trafficking, and cell movement. HDAC6 is unique among HDACs in that it does not directly affect chromatin plasticity [10].

4. The functions of HDAC6 inhibition in AD models

Scientists linked HDAC6 to epigenetic treatments for Alzheimer's disease; subsequent animal experiments gradually revealed the roles of HDAC6 in Alzheimer's disease.

Scientists measured HDAC6 levels in adult mouse brain regions. In the hippocampus, cortex, and cerebellum, they compared Hdac6 mRNA and protein levels. They eliminated HDAC6 and got HDAC6-deficient mice. This type of mouse was compared to wild-type mice for Hdac6 mRNA, protein levels in the hippocampus and cortex, brain morphology, brain mass, Neuronal N and synaptophysin immunoreactivity, histone acetylation, HDAC family mRNA levels, and a-tubulin K40ac levels (Fig 1).

As a result, scientists gained fundamental knowledge about HDAC6. In the hippocampus and cortex, HDAC6 mRNA and protein levels were comparable, whereas they were lower in the cerebellum. Brain morphology, brain mass, Neuronal N and synaptophysin, and histone acetylation were normal in Hdac6-deficient mice, whereas a-tubulin K40c levels increased. Hdac6 is therefore expressed in the hippocampus and cortex, which are involved in memory function. And mice deficient in HDAC6 are viable [11].

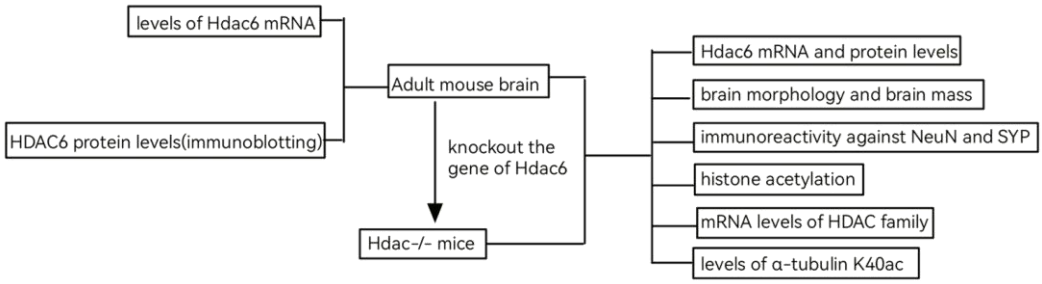


Figure1. Molecular detection in mice, HDAC6-/-, Hdac6 knockout, NeuN, Neuronal N, SYP, synaptophysin (original).

Then, the mice with Hdac6 knocked out and the wild-type mice were tested to see how they behaved. Motor coordination was tested using an accelerating rotarod, associative memory function was evaluated using electric foot shock, long-term associative memory was assessed using freezing behavior, spatial learning was assessed using the Morris Water Maze paradigm, and a subsequent memory test was administered (Fig 2).

Hdac6 knockout mice, in contrast to their wild-type counterparts, showed a striking increase in preference for the target region only in the subsequent memory test. Other experiment results have shown no differences between the two mouse strains. Therefore, Hdac6 deficiency has negligible effects on brain function [11].

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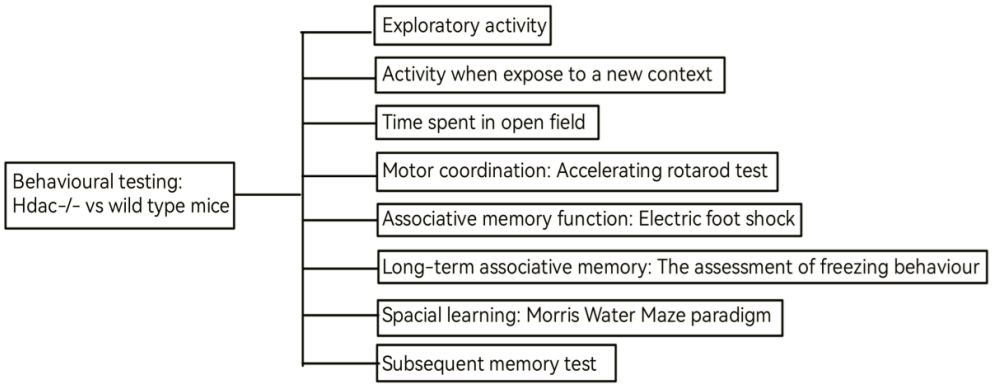


Figure 2. Behavioural testing in HDAC-/- mice and wild type mice (original).

Hdac6 knockout mice were crossed with APPPS1-21 mice, transgenic mouse models of Alzheimer's disease, to generate APPPS1-21-Hdac6-/- mice for the purpose of elucidating the role of HDAC6 in AD. Researchers evaluated the behavior of these three mouse strains using the same methods described in the section on mouse behavior testing (Fig 3).

In a test of associative memory, APPPS1-21-Hdac6-/- mice's normal freezing behavior restored APPPS1-21 mice's impaired freezing behavior. In a probe test to evaluate spatial memory, APPPS1-21 mice preferred the target quadrant less than APPPS1-21-Hdac6-/-mice. Hdac6 deficiency improved associative and spatial memory in an Alzheimer's mouse model [11].

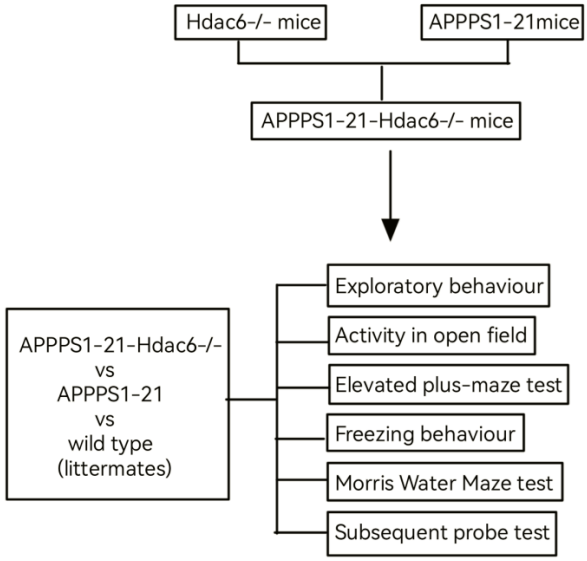


Figure 3. Behavioural testing in APPPS1-21-Hdac6-/- mice, APPPS1-21 mice and wild type mice (original).

Tubulin dynamics play a key role in dysregulated intracellular transport in Alzheimer's disease. Because HDAC6 is missing, intracellular transport may be dysregulated. Hdac6-/- mice were treated with amyloid -derived diffusible ligands before and after measuring mitochondrial trafficking. To test whether this finding is true in vivo, researchers examined Tom20 immunoreactivity in wild-type, APPPS1-21, and APPPS1-21-Hdac6/ mice (Fig 4).

Primary neurons from wild-type and Hdac6-/- mice did not differ in mitochondrial trafficking or moving mitochondria to total mitochondria. Wild-type hippocampal neurons were disrupted by ADDLs. In vivo experiments showed that the ratio of Tom20 immunoreactivity was dramatically increased in the nerve cells of APPPS1-21 mice compared to the nerve cells of the other two mouse strains, indicating

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impaired intraneuronal mitochondrial trafficking. In AD models, lack of HDAC6 increases mitochondrial trafficking in hippocampal neurons [11].

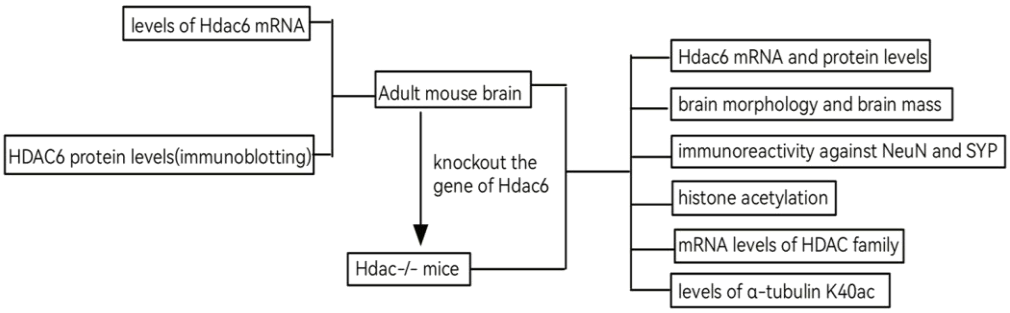


Figure 4. Further experimental process to prove the function of HDAC6 in intracellular transport (original).

5. Inhibitors of HDAC6

The Food and Drug Administration (FDA) has approved several anti-AD medications, including rivastigmine, galantamine, and memantine. Nonetheless, some of them were withdrawn due to clinical failure cases or their limitations, and none of the drugs were able to treat AD by targeting its pathogenesis [12]. In order to completely cure Alzheimer's disease, it is necessary for the treatment of AD to consider new angles.

Loss of HDAC6 is beneficial for Alzheimer's disease, as evidenced by the improvement of associative and spatial memory functions and the repair of mitochondrial transport in hippocampal neurons. And unlike other HDACs, researchers have demonstrated that HDAC6 inhibitors do not cause obvious toxicity when used in AD models [13]. Thus, some HDAC6 inhibitors could be considered therapeutic targets for Alzheimer's disease. Now, scientists are searching for HDAC6 inhibitors to determine the pharmacological viability of AD, and they have discovered selective and multi-target HDAC6 inhibitors.

However, none of the HDAC6 inhibitors are up to FAD standards and approved for the treatment of Alzheimer's disease. The majority of inhibitors are undergoing clinical testing, with some failing due to lack of efficacy or safety [12].

6. Conclusion

The treatment of Alzheimer's disease is a difficult problem that is being studied in greater depth. The pathogenesis of Alzheimer's disease is still unknown, but there are several hypotheses, the most prominent of which are the amyloid cascade hypothesis, tau hypothesis, and oxygen species. The Amyloid Cascade Hypothesis is associated with the overexpression of APP, which results in an abundance of Aβ peptides forming β-plaques and eventually inhibiting signal transmission between nerve cells. The central tenet of the tau hypothesis is that hyperphosphorylated tau proteins, the most abundant microtubule-associated proteins, aggregate to form neurofibrillary tangles, thereby causing numerous neuronal dysfunctions. The oxygen species hypothesis states that excessive oxygen species in brain tissue attack DNA, lipids, and proteins, causing cell damage. HDAC6 in epigenetics may be a therapeutic target for new Alzheimer's disease (AD) treatment strategies. Numerous animal studies have demonstrated that the absence of HDAC6, an enzyme that regulates the expression of -tubulin rather than histone acetylation, increases microtubule stability in the nervous system and improves cognitive function in AD patients, particularly in associative and spatial memory. In particular, the absence of HDAC6 may restore mitochondrial transport by regulating the expression of microtubule proteins. Additionally, they ensured that the HDAC6 gene has no additional negative effects on animal models. However, HDAC6 inhibitors have not yet been successfully developed and are currently undergoing clinical trials.

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Nonetheless, this study still has some limitations. There is substantial evidence that HDAC6 inhibitors would be an effective new strategy for treating cognitive impairment in Alzheimer's disease. This article has just mentioned that HDAC6 inhibitors are currently in clinical trials, and that some of these inhibitors have failed trials due to toxicity and efficacy issues. It did not mention the successful cases that approved the partial feasibility of HDAC6 inhibitors or explain why the inhibitors were ineffective in clinical trials. The paper must conduct additional research into the literature and human epidemiology studies in order to discover the answers to similar problems and the procedure for clinical trials in AD. After additional research and development, HDAC6 inhibitors will become effective therapeutic strategies for Alzheimer's disease in the future.

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