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HIF-1α as a possible therapy for Alzheimer's disease

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Abstract. The most significant pathology markers of Alzheimer's Disease (AD) are the tau protein and amyloid beta protein (Aβ). A transcription factor called hypoxia-induced factor 1α (HIF-1α) is in charge of helping cells and tissues adjust to low oxygen levels. Recent research points to HIF-1α as a possible therapeutic target for neurodegenerative disorders. On the one hand, it is hypothesized that HIF-1α causes neuroinflammation, which aids in the development of AD, by activating γ-secretase and inhibiting α-secretases, thereby increasing the processing of AβPP and the production of Aβ. HIF-1α, on the other hand, is able to fend off the harmful effects of Aβ and stop tau protein from becoming hyperphosphorylated. Icariin has numerous pharmacological actions as a medication that can decrease the clinical indicators of AD, including anti-depression, treatment of ischemic brain injury, anti-dementia, anti-aging, etc., and is closely related to HIF-1α. This article reviews the possible role of HIF-1α in the pathogenesis of AD and its future prospects.

Keywords: Alzheimer's disease, HIF-1α, tau protein, amyloid beta protein, icariin.

1. Introduction

AD is a degenerative brain condition that worsens with time. It is distinguished by changes in the brain that result in protein buildup. The brain constricts as a result of AD, and eventually brain cells fade away [1]. In recent years, with the aging of the population becoming more and more serious, the prevalence of AD is gradually increasing. More than 55 million people currently suffer from the disease, and that number is expected to rise to 139 million by 2050. This will greatly increase the burden on families. According to the survey data, 78% of people know that AD has a preclinical stage, but only 17% are willing to go to the doctor for this [2]. The causes of AD can be due to family history, such as autosomal dominant genes. Physical disorders include thyroid disorders, immune system disorders, epilepsy, etc. It can also be caused by head trauma.

Even the mere existence of medications like antidepressants, anxiety reducers, neurotransmitter-acting medications, and brain metabolic sedatives can help with some AD symptoms, such as memory loss. It must not be an elementary pharmacological therapy because the pathogenic components involve many different components. Nursing that is clinically rigorous and scientifically based is essential for patients' behavior modification and memory restoration. By studying several pathogenic factors of AD, it can be found that HIF-1α pathway plays a role in several of these factors, and regulating its expression level may achieve the purpose of treatment.

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The post-translational level of HIF-1α primarily controls the activity of HIF-1. Proline alkylase can hydroxylate HIF-1α under conditions of normal oxygen tension, and the ubiquitin protease system can then explain this process. Proline hydroxylase inhibitors can stop HIF-1α from causing apoptosis and damaging the mitochondria. The case for AD is very strong. HIF-1α is hydroxylated by PHDs, which results in its degradation and loss of activity [3]. This diminishes cell's ability to adapt to low oxygen levels, which makes cell poisonous. Studies have revealed that the primary mechanism of neuronal death in neurodegenerative disorders is oxidative stress-induced mitochondrial damage. Different types of hypoxia are thought to be a typical pathogenic process that can alter the pathogenesis of AD through the control of HIF-1α.

Icariin, a type of flavonoid, has been linked to numerous pharmacological activities, including antioxidant, anti-inflammatory, and anti-apoptotic activities. The substance has been demonstrated to be helpful in the treatment and prevention of a number of neurological illnesses, and it frequently improves learning and memory in animals. The generation and deposition of Aβ, one of the primary causes of AD, can be reduced to cure AD by using icariin [4]. Icariin appears to be another possible treatment for AD given that the dynamic binding of the HIF-1-Icariin complex within 100 ns showed that Icariin helped to the stability of HIF-1α.

This paper summarized it in this article, hoping to provide reference and guidelines for the treatment of AD as how HIF-1 is an important transcriptional activator and can involve in the hypoxia response and also how icariin may improve those AD patients' memory ability.

2. The possibility of targeting HIF-1α as a treatment for AD

Hypoxic signaling controls HIF-1α, an active subunit of HIF-1. The gene has 826 amino acids and is found on human chromosome 14 in the q21–24 region. The regulatory domain of hypoxia induction can be sensed by its two ends, which can also take part in regulation. For the creation of heterodimers and DNA binding, the alpha subunit's amino terminus has the Per/Amt/Sim (PAS) structure and basic Helix-Loop-Helix (bHLH) configuration [5]. The HIF-1α subunit must assemble with the HIF-1β monomer to form a heterodimer, which will operate as a factor in transcription. The HIF-1α component, in turn, regulates the activity of HIF-1. Cells are controlled by it so they can adjust to low oxygen environments.

When the oxygen level is normal, the proteasome swiftly breaks down HIF-1α, which is mostly expressed in the cytoplasm. HIF-1α's ability to degrade is inhibited in low oxygen environments, and the protein accumulates and is moved to the nuclear post where it joins the 8 subunits to create a dimer that is shared by many target genes' hypoxia response elements. The HRE's core sequence binds, activates downstream genes' expression, and causes a number of hypoxic adaptive reactions [5, 6].

It is widely acknowledged that amyloidosis and tau hyperphosphorylation are two pathological markers AD, and both of them are associating to HIF-1α.

2.1. The HIF-1α and Aβ decomposition

A short peptide containing 40–42 amino acids is the 4.2 kDa AB. The amyloid precursor protein (APP) serves as Aβ's precursor. When secretase is present, APP is cleaved on the cell membrane of brain neurons to create Aβ peptides. Additionally, an unsuitable buildup of Aβ leads to neurotoxicity in the brain. Neurological plaques are produced when monomeric Aβ forms insoluble oligomers. It has been demonstrated through experimental studies that an imbalance between Aβ synthesis and clearance causes problems metabolism [7, 8], which in turn causes misfolding of proteins, aggregation, and extracellular accumulation, ultimately leading to the development of amyloid plaques.

Numerous clinical studies have demonstrated that hypoxia may stimulate a variety of cell types to secrete Aβ, and that the amount of Aβ plaque in the brains of AD transgenic animals significantly rises.

First, in the brains of ischemia hypoxia model mice, APP mRNA and protein expression are upregulated. This rapid rise in APP may facilitate the creation of the neuroprotective protein sAPPα. Due to the absence of APP, the reaction of increased cerebral blood flow in hypoxia also vanished. As a result, the enhanced expression of the APP and BACEl genes during ischemia and hypoxia may have

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compensatory and protective effects that assist reduce stress [8]. However, the β pathway's substrate is also increased by the up-regulation of APP expression, which could lead to an increase in Aβ synthesis. The pathogenesis of AD is aided by hypoxia because it increases BACE1 transcription and expression, which increases AβPP processing and Aβ generation.

By inducing endoplasmic reticulum stress, increasing the expression of presenile protein 1 (PS1), and activating γ-secretase, hypoxia/ischemia reduces brain autophagy. Some studies suggest that PS1 regulates the induction of HIF-1. In response to hypoxia, APH-1A, serves as a component of the γ-secretase complex, is expressed, which ultimately leads to an increase in γ-secretase cleavage activity. The HIF-1α protein, it has been discovered, interacts with the γ-secretase complex and increases its activity without starting transcription [8]. It is important to note that the AβPP intracellular domain peptide and PS1 protein both have the ability to stabilize and activate HIF-1α.

The involvement of γ-secretase can be enhanced by the hypoxia-activated autophagy activity due to the increased expression of APH-1, and since the activity of β secretase will also rise during hypoxia, Aβ deposition will speed up [6].

In summary, hypoxia leads to increased APP expression, down-regulated a secretory enzyme expression, and up-regulated β and γ secretory enzyme expression, resulting in decreased a pathway products sAPPa and increased β pathway products CTFβ and Aβ production. The pathophysiology of Aβ and the development of AD can be slowed down by down-regulating the over-expression of HIF-1α. Hippocampal cells stimulated to apoptose by Aβ are successfully controlled by HIF-1α.

2.2. HIF-1α and phosphorylation of Tau protein

Under normal conditions, tau, a highly soluble microtubule-related protein, is abundant in neurons. However, when tau proteins are hyperphosphorylated, they form spiral filament pairs and eventually form neurofibrillary tangles, which impair the function of neuronal microtubules and cells. The major job of tau protein is to keep the axon microtubules stable. Detective tau proteins will cause dementia and neurological conditions like AD [9]. Hyperphosphorylation of Tau protein caused by hypoxia mainly exists in apoptotic neurons, which may be a downstream event caused by abnormal accumulation/deposition of Aβ.

The accepted theory is that tau proteins are over-phosphorylated, then theyare separated from microtubules, and finally aggregate to form NFTs. When NFT forms, the microtubules in neurons start to degrade and the cytoskeleton transport system collapses, ultimately impairing chemical communication between neurons and leading to neuronal death [6].

On Tau samples from AD brainfrontal and parietal cortex, researchers found changes at 43–55 different phosphorylation, 19 acetylation, 14–17 ubiquitin, and 4 methylation sites. Tau pathology begins in two separate brain regions (entorhinal cortex and hippocampus) in the progressive neurodegenerative illness AD and then spreads in a predetermined spatial pattern across the rest of the brain. Memory loss in AD patients and, consequently, the disease state is connected with the growth of Tau aggregations [3].

In AD, which reacts to Aβ alterations, tau migrates from an axon to the dendritic spine. So, in order to shift the Fyn's position, Tau might bind and isolate them. The excitatory GluN2B NMDA receptor is phosphorylated and is usually steady when the amount of Fyn rises with rising tau levels in the dendritic spine. This alteration enhances glutamate's signaling capacity, raising intracellular Ca2+ levels and raising the Aβ toxicity level [3, 5, 9]. Calcium-induced excitatory toxicity, which may also result in mitochondrial Ca2+ overabundance, membrane depolarization, oxidative stress, and death, can negatively impact post-synaptic sites.

GLUT1 and GLUT-3 are downregulated when HIF-1α levels are low, which affects glucose metabolism. This metabolic disorder will result in reduced O-glcn acylation levels, which are negatively correlated with tau phosphorylation sites and tau microtubule binding activity (Figure 1) [9]. It has been reported that elevated levels of HIF-1α reduce tau phosphorylation and neuronal inflammation, ultimately protecting neuronal death while there are still sound of opposition presenting.

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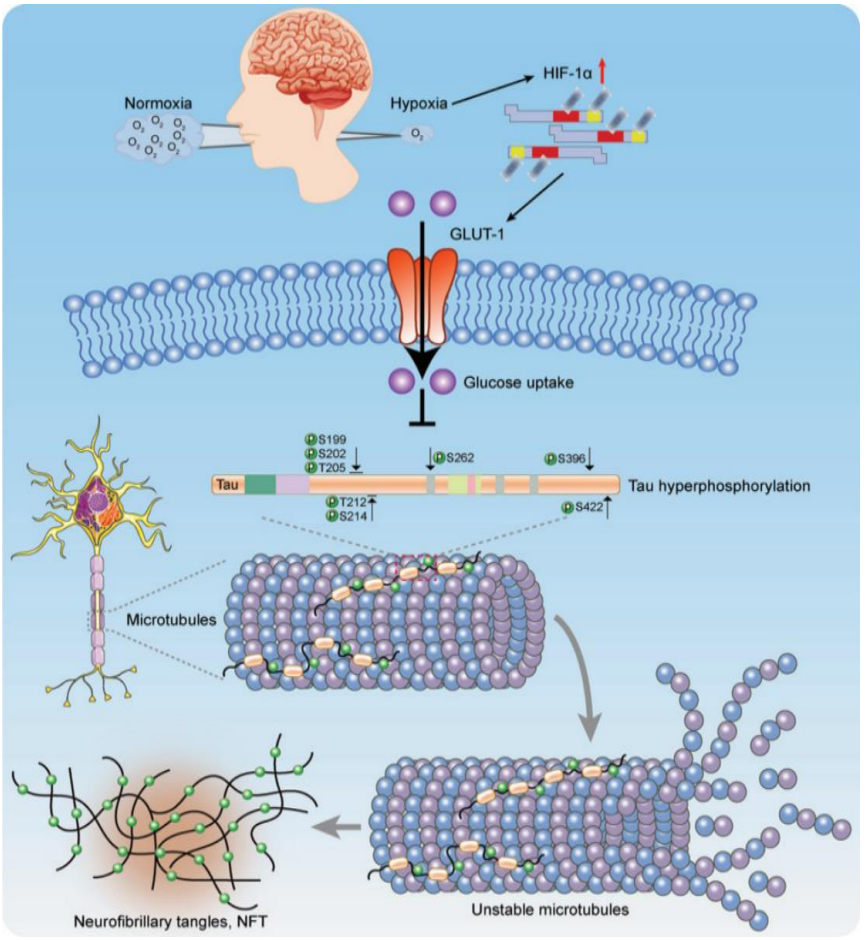

Figure 1. Role of HIF-1α in inhibiting hyperphosphorylation of tau protein [9].

3. HIF-1α as a potential target of Icariin

Icariin falls under prenylated flavonol glycoside classification and that makes it a flavonoid. Research shows that the compound has neuroprotective effects [5].

Numerous investigations have revealed that a large amount of amyloid deposition and intracellular neurofibrillary crosslinking occur in people with AD's brain, among which Aβ is the most crucial component of amyloid deposition in the brain. Icariin can resist the neurotoxicity caused by Aβ deposition by resisting oxidative stress damage, balancing intracellular calcium ion homeostasis, inhibiting β-secreting enzyme expression, and correcting the imbalance of energy metabolism. Icariin can reduce Aβ deposition further improve AD model symptoms [1, 7].

For resisting oxidative stress damage, HIF-1a is said to have an effect. Under normal oxygen partial pressure conditions, HIF-1α content in the cytoplasm is very low, does not show biological activity. When the oxygen partial pressure is reduced or other regulatory factors, the HIF-1α degradation pathway is going to be inhibited, and thus the accumulation and activation in the cytoplasm are transferred to the nucleus [10]. At this time, the content of HIF-1β in the cytoplasm is basically stable. So compared to HIF-1β. HIF-1α is included in significant part in hypoxia regulation.

HIF-1α is known to bind to hypoxic response elements of more than 60 genes. It plays a regulatory role in related genes. Under the hypoxic condition, the ubiquitin-albuminosomal system is suppressed, HIF-1α is stable, accumulates and binds to HIF-1β, transits from cytoplasm to nucleus, and forms a viable HIF-1 [11, 12]. These target groups, which include the glucose transporter albumin-1, glycozymolase, and vascular endodermal growth factor (VEGF), bind to the anoxic reaction components of the group and activate the transcription of these genes. These genes are necessary for cell

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survival in oxygen-deficient environments. However, too much HIF can encourage sugar fermentation, which gives cells energy, but it can also cause milk acid to build up and become toxic, which can cause horrible death [13]. In these model cells, icariin has been shown to lower HIF-1α levels, which has the effect of preventing neurotoxicity brought on by Aβ deposition (Figure 2) [11].

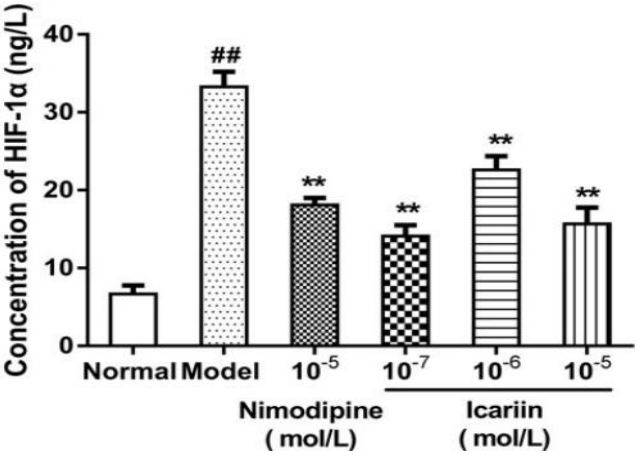

Figure 2. Effect of icariin on HIF-1a levels in cells [12].

However, there are still reports say that in order to increase the body's adaptation to hypoxia under long-term hypoxia conditions, the increased expression of HIF-1α factor regulates the kidney's production of erythrocyte increased cytogenetic factor. VEGF in plasma becomes erythropoietin, which stimulates increased production of bone marrow red blood cells and hemoglobin. This makes the blood sticky [12]. Will further aggravate the body hypoxia, this may just lead to the unwanted effect. Therefore, there are still others who disagree about how HIF-1α affects icariin in the treatment of AD.

4. Conclusion

In this paper, we conclude by studying the link between HIF-1α signaling pathway and two approaches to treating Alzheimer's disease. confirmed that HIF-1α may in fact be a therapeutic option for this neurodegenerative condition. The primary mechanism of neuronal death in neurodegenerative disorders is mitochondrial damage brought on by oxidative stress. Different forms of hypoxia are thought to be a characteristic pathogenic mechanism that, by regulating HIF-1α, can change the pathophysiology of AD.

Increased Aβ plaques may be brought on by hypoxia, aph-1 expression, or γ-secretase activity. Hif-1α expression downregulation can delay this result.

Additionally, when tau protein is hyperphosphorylated, it creates NFT, which ultimately results in neuronal death. Reduced tau proteins' microtubule binding activity and phosphorylation sites protect against neuronal inflammation and death when HIF-1α is increased.

In icariin, inhibiting HIF-1α expression both limits the fermentation of carbohydrates to supply energy to cells and lessens the deposition of Aβ.

However, there are lots of detrimental effects of adjusting HIF-1α, including:

-HIF-1α overexpression increased the production of β-secretase, which caused APP to be processed in an amyloidogenic manner following cerebral ischemia and stroke injury.

-An enhanced glucose energy metabolism may promote the growth of tumor cells.

-When HIF-1α expression was downregulated, hypoxia had no effect on the transcription of the human-site APP cleavage enzyme 1 gene.

-Hypoxia and ischemia decrease the expression of genes important for synaptic integrity and function. The inflammatory response of cells is simultaneously boosted by reactive oxygen species.

-When HIF-1α levels are low, GLUT1 and GLUT-3 are downregulated, which has an impact on glucose metabolism.

As a result, the side effects of HIF-1α have not been eliminated, future research should focus on eliminating such harmful consequence to enable successful treatments for Alzheimer's disease.

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