Mechanisms of Hericium erinaceus in Alzheimer's Disease

Subjects: Neurosciences

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Alzheimer's disease (AD) is a neurodegenerative disorder, and no effective treatments are available to treat this disorder. *Hericium erinaceus* (HE), also known as the monkey's head mushroom, lion's mane mushroom, or Yamabushitake, is commonly found in East Asia. It is well-known for its diverse therapeutic activities, including neuroprotection and neuroregeneration, which are attributed to its neurogenesis, antioxidative, and anti-neuroinflammatory functions. Therefore, researchers have been investigating HE as a possible treatment for AD.

Hericium erinaceus | Alzheimer's disease | aging | memory | preclinical | clinical

1. Introduction

Several erinacines and hericenones have been isolated from the fruiting bodies and mycelia of *Hericium erinaceus* (HE), respectively [1]. Among them, 15 erinacines and cyathane diterpenoids were reported to possess various biological activities. Erinacines A–I were demonstrated to have neuroprotective properties through enhancing the release of neurotrophic factors, increasing the expression of insulin-degrading enzymes (erinacines A and S), reducing Aβ aggregation, and managing neuropathic pain (erinacine E) (**Figure 1**) [1]. The majority of hericenones were demonstrated to have been correlated with improved cognitive function through the activation of NGF synthesis in astrocytes, whereas erinacine B was found to prevent thrombosis, increase cerebral blood flow, and confer protection against cerebrovascular risk and vascular dementia [2][3].

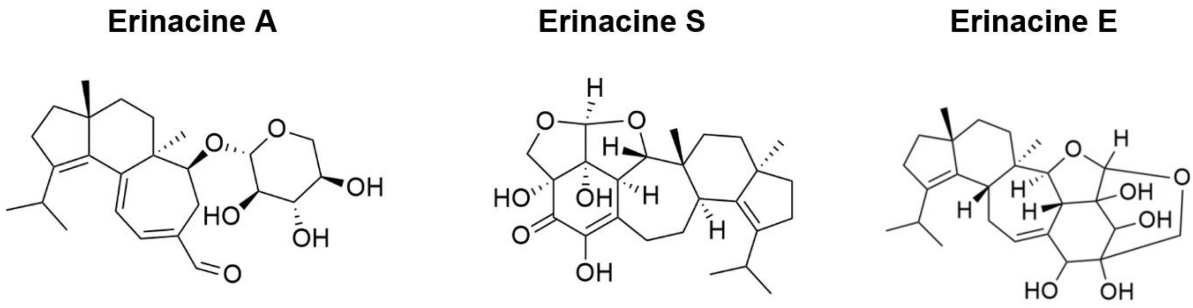

Figure 1. Bioactive compounds isolated from *Hericium erinaceus* with therapeutic effects on Alzheimer's disease.

2. Anti-Amyloidogenic Functions

Hericium erinaceus was reported to have anti-amyloid properties in reducing Aβ synthesis and accumulation and protecting neuronal cells against Aβ cytotoxicity [4]. Multiple mechanisms have been implicated in the clearance of Aβ plaque, including a reduction in CTF-β, SDS-soluble Aβ1-40, and SDS-insoluble Aβ levels [5]. Treatment with EAHEM reduced levels of Aβ1-42, which is the variant most prone to aggregation. Moreover, HE was found to prevent the deposition of Aβ peptides through the proteolytic degradation of Aβ and APP intracellular domain (AICD) by insulin-degrading enzyme (IDE) [6]. Farris et al. (2004) reported that IDE is a key proteolytic enzyme in Aβ reduction. Rats with partial loss-of-function mutation of IDE and an IDE-knockout mouse model demonstrated enhanced Aβ accumulation in the cerebral region [7]. In addition, a mouse model with AD-associated ApoE4 allele showed reduced levels of IDE associated with increased Aβ [8]. Remarkably, Tzeng et al. (2018) found that both HE-A and HE-S were able to increase the expression of IDE in AD animal models accompanied by a reduction in Aβ, as seen in the immunohistochemical analysis [5].

3. Anti-Oxidative Function

Several studies have suggested that the neuroprotective effects of HE result from upregulated antioxidant enzymes (e.g., glutathione peroxidase, catalase, and SOD) and reduced MDA levels that are implicated in the cellular defense mechanisms against ROS [9]. Furthermore, HE was shown to exert its antioxidant effects through the regulation of the transcriptional activity of nuclear factor-erythroid 2-related factor 2 (Nrf2) [10]. The Nrf2 signaling pathway regulates genes encoding various proteins that function as endogenous stress–response proteins, antioxidant enzymes, and redox-maintaining factors [11].

The antioxidant capacity of HE has been demonstrated in several preclinical animal studies. In a study by Lee et al. (2021), administration of increasing concentrations of EAHEM in SAMP8 mice over 13 weeks restored the level of TBARS, which is an index of lipid peroxidation [12]. This restoration is important considering that the long-term accumulation of lipid peroxidation is a key contributor to the aging brain and cognitive deterioration [13]. Besides, an ethanol extract of HE was also found to reduce apoptotic activity by inhibiting Bax/Bcl-2 and caspase-3 signaling pathways in a cellular model of glutamate-induced oxidative stress [14].

4. Anti-Neuroinflammation

Recently, Cordaro et al. (2021) demonstrated the anti-neuroinflammatory effects of HE by ameliorating NLRP3 inflammasome activation, which was found to involve the antioxidant properties of HE [11]. The inflammasome complex consists of various proteins, including DAMPS or PAMPS receptor (damage- or pathogen-derived molecular patterns), NLRP3 (NLR family pyrin domain containing 3), and pro-caspase-1 activated through ASC (apoptosis-associated speck-like protein containing a caspase recruitment domain) [11][15]. The NLRP3 inflammasome can sense a wide range of stimuli to trigger inflammation, mediating the activation of DAMPs or PAMPs, recruitment of ASC, and cleavage of pro-caspase-1 (pro-IL1β and pro-IL18) to generate pro-inflammatory cytokines [11][16]. The findings by Cordaro et al. (2021) revealed the anti-inflammatory mechanisms through the downregulation of the inflammasome network by decreasing the expression levels of ASC, NLRP3, and pro-

caspase-1. Additionally, HE was also shown to inhibit the activation of NF-kB, a pro-inflammatory transcription factor [11].

In addition, HE was found to reduce the inflammatory responses by regulating iNOS expression. Three nitric oxide synthase (NOS) isoforms (i.e., neuronal NOS (nNOS), endothelial NOS (eNOS), and inducible NOS (iNOS)) [12], and among these isoforms, increased iNOS expression has been correlated with oxidative stress and inflammatory processes [17]. Lee et al. (2021) observed a reduction in iNOS expression in mice administered EAHEM, which suggests that its neuroprotective effects were mediated through the attenuation of inflammation and oxidative stress.

5. Neurotrophic Mechanisms

Hericium erinaceus has been shown to stimulate the release of neurotrophic factors, including NGF and brain-derived neurotrophic factors, which are known to regulate the development, maintenance, function, and survival of neuronal cells [18]. Apart from being the major players in neuroplasticity, these neurotrophic factors can also activate neurogenesis and protect neuronal cells against apoptosis. HE extracts stimulate NGF release by promoting NGF mRNA expression in astrocytes via the c-jun N-terminal kinase signaling [19]. The increased levels of NGF released from astrocytes transmit into the nerve cells and have been associated with neurogenesis and neuroplasticity in the hippocampus, pituitary glands, and cerebral cortex [20][21]. The binding of NGF to tropomyosin receptor kinase A (TrkA) receptors results in the activation of extracellular signal-regulated protein kinase (Erk)-cyclic adenosine monophosphate (cAMP)-response element-binding protein (CREB) signaling cascade, which modulates proliferation, maintenance, and memory development in neural precursor cells [21]. Furthermore, NGF-mediated neuronal differentiation also promoted an extensive mitochondrial remodeling [22] and increased fusion proteins (Mfn2 and Opa1), Drp1-dependent mitochondrial fission, activation of Sirt3 and PPARγ, and mtTFA transcription factors, ultimately controlling bioenergetic capacity. Martorana et al. (2018) reported that NGF was important for mitochondrial remodeling and contributed to neurogenesis and nerve regeneration [22].

Various studies have shown that HE treatments can have long-lasting effects on increasing Ki67-positive, PCNA-positive, and BrdU immunoreactive cells in the dentate gyrus of the hippocampus, leading to the development of neural progenitor cells in the hippocampus [20][23]. Current evidence suggests that the regulation of hippocampal neurogenesis by HE involves NGF by increasing its mRNA and protein expression levels, which also demonstrates the ability of HE bioactive compounds to pass through the blood–brain barrier [20][23].

6. Neurotransmission

The mechanism by which HE modulates the expression of neurotransmitters has been investigated in preclinical studies. Treatment with HE was found to improve cholinergic function by enhancing ACh and choline acetyltransferase levels in AD mouse models [24]. Brandalise et al. (2017) found that dietary HE supplementation enhanced the release of glutamate neurotransmitter from the hippocampal mossy fiber terminals, as evident by the

increased spontaneous excitatory activities in the mossy fiber-CA3 synapses that were found to be dependent on glutamate release [25]. Further studies are required to examine the effects of HE on other memory-related neurotransmitters to better understand its modulating pathways.

Overall, the results of these studies indicate that HE treatments improved memory, which was accompanied with enhanced hippocampal neurogenesis and modulation of the anti-amyloidogenic, anti-oxidative, anti-neuroinflammatory, and neurotransmitter pathways (**Figure 2**).

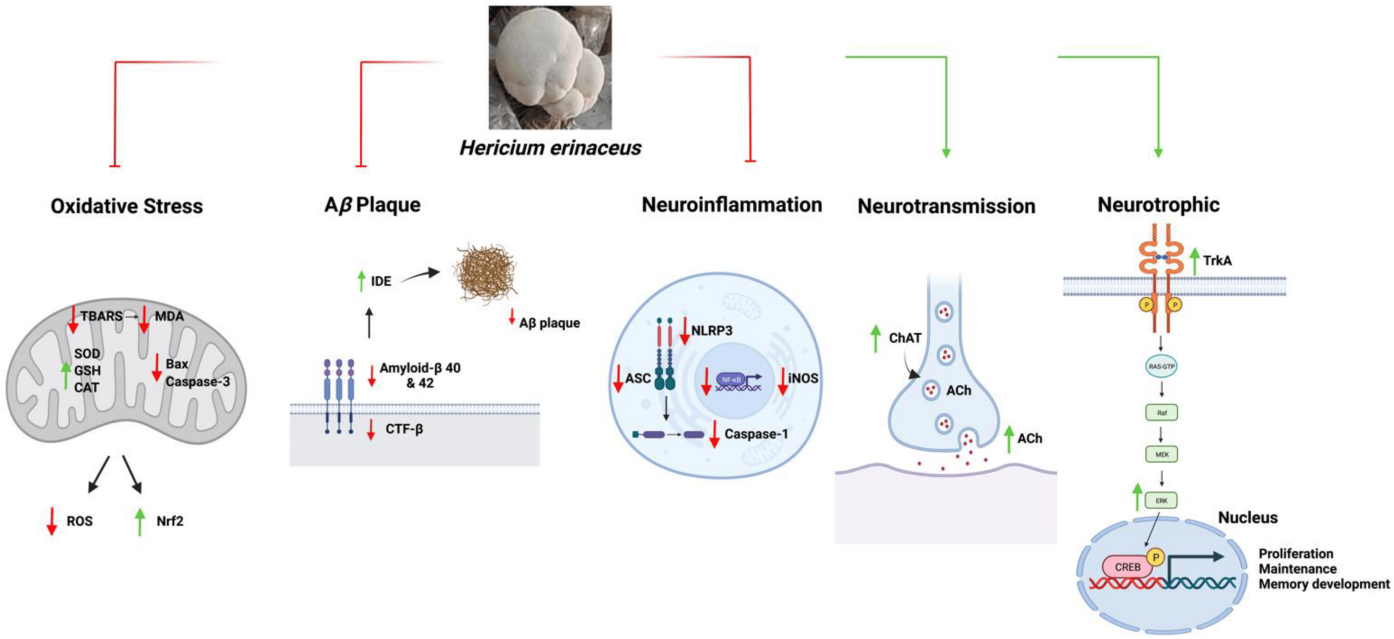

Figure 2. A schematic diagram summarizing the functions of *Hericium erinaceus* in AD. Abbreviations: ROS, Reactive oxygen species; BAX, Bcl-2- associated X protein; TBARS, Thiobarbituric acid reactive substances; MDA, Malondialdehyde; Nrf2, Nuclear factor-erythroid factor 2-related factor 2; SOD, Superoxide dismutase; CAT, Catalase; GSH, Glutathione; Bcl-2, B-cell lymphoma 2; SDS, Sodium dodecyl sulfate; CTF-β, Beta-carboxyl-terminal fragment; Aβ, Amyloid-beta; IDE, Insulin-degrading enzyme; iNOS, Nitric oxide synthase; ASC, Apoptosis-associated speck-like protein containing a caspase recruitment domain; NLRP3, NLR family pyrin domain containing 3; NF-kB, Nuclear factor-kappa B; ACh, Acetylcholine; ChAT, Choline acetyltransferase; TrkA, Tropomyosin receptor kinase A; RAS-GTP, Ras protein guanine triphosphatase; Raf, Rapidly accelerated fibrosarcoma; MEK, Mitogen-activated protein kinase; Erk, Extracellular signal-regulated kinase; CREB, cAMP-response element binding protein.

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