

Mitochondrial-Targeted Small Molecules: A Promising Approach for Alzheimer's Disease Treatment and Neuroprotection

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Abstract:

Alzheimer's disease (AD) is a debilitating neurodegenerative condition characterized by memory loss, cognitive decline, and personality changes. Recent research has shed light on the critical role of mitochondria in AD pathogenesis, specifically their involvement in the production and aggregation of amyloid-beta ($A\beta$) and phosphorylated tau. Mitochondrial dysfunction is a hallmark of AD, with reactive oxygen species (ROS) playing a central role. Oxidative stress resulting from mitochondrial ROS production is closely linked to AD's early pathogenesis. Furthermore, the interaction between phosphorylated tau and $A\beta$ disrupts mitochondrial function, hindering energy production and leading to synaptic dysfunction. This article explores the promising advancements in mitochondria-targeted small molecules as potential treatments for AD.

Keywords: Alzheimer's disease, small molecules treatment, Mitochondria-targeted

1. Introduction

Alzheimer's disease (AD), the most popular cause of dementia in aging individuals, is a neurodegenerative disease leading to memory loss, change of personality, and cognitive impairment. It has been a prevailing disease in recent years, and the patients tend to be younger. The diagnosis cases would double every 20 years, and the number of people living with Alzheimer's will poke out 75.6 million in 2030. Till now, there is no specific and efficient way to cure AD. The overwhelming support indicates that $A\beta$ production and aggregation contribute to disease, and pathological accumulation of $A\beta$ occurs years before symptoms begin. Multiple factors cause cellular changes in AD, such as loss of synapses, cholinergic fibers, and memory loss. The purpose of this part of this article is to emphasize the current advance in mitochondria-targeted small molecules as AD treatment options. To be more detailed, the following articles will focus on how small molecules reduce synaptic disruption and cognitive decline via $A\beta$ and phosphorylated tau.

2. Mitochondrial dysfunction

2.1 Reactive oxygen species

Multiple symptoms of mitochondrial malfunction might be seen. Reactive oxygen species (ROS) are harmful chemicals that can start a chain reaction of oxidation-reduction reactions through their oxidant strength. Mitochondria serve a key role in generating 90 percent of endogenous ROS. When ROS outweighs mitochondrial and cellular antioxidants, oxidative stress, a precursor to aging, results. One of the main causes of the early

pathogenesis of AD is oxidative stress [1]. Additionally, the buildup of ROS and oxidative stress makes additional harmful chemicals possible to harm cells. Among these are tert-butyl hydroperoxide (t-BHP). This compound also leads to oxidative damage, and 3-nitropropionic acid, also known as (3-NP), is an endogenous toxin marker of mitochondrial failure in humans. Neurological condition [2].

2.2 phosphorylated tau + amyloid-beta

The cytoplasmic association of tau particles with microtubules serves as a conveyor belt for the movement of organelles. Age-related stress causes these tau particles to be phosphorylated, which changes the protein's conformation on the microtubule and slows the migration of organelles while also changing the cell's cytoskeletal structure [3]. This inhibits mitochondria from moving along the axon, depriving the axon and dendritic terminals of a source of energy. $A\beta$ and phosphorylated tau particles have also been shown to work together to boost one another's growth and to produce problems in the mitochondria and synapses.

2.3 interaction of VDAC1 with phosphorylated tau and amyloid beta

According to Reddy and Manczak, the voltage-dependent anion channel 1 (VDAC1) protein also binds to both A and phosphorylated A particles and blocks mitochondrial pores. In transgenic 3XTg AD mice, the researchers found that blocking the interaction of VDAC1, A , and particles, specifically a reduction in ATP production, played a role in the pathogenesis of AD.

2.4 Amyloid beta + ABAD

The protein amyloid combining alcohol dehydrogenase (ABAD) binds the coenzyme nicotinamide adenine dinucleotide (NAD⁺) by altering its structure in reaction to A. As a result of changes in permeability brought on by A β -associated ABAD's interaction with NAD⁺, poisonous aldehydes cannot be removed by the enzyme, which compromises respiratory enzymes [4].

3. Alzheimer's disease Therapeutics

3.1 cholinesterase inhibitors

Acetylcholine (ACh) neurotransmitters are produced in greater quantities by cholinesterase inhibitors (CHEI) in the central nervous system (CNS) [4]. Greater neural activity is made possible by the increased messages between neurons caused by the ACh buildup that results in the synapses. ACh serves as a neurotransmitter between the neurons involved in learning. These drugs, however, have proved to help AD patients keep their independence and reduce the neurodegenerative processes brought on by the disease. But risks associated with side effects include diarrhea, vomiting, abdominal pain, lack of appetite, bradycardia, headache, cramps, syncope, sleeplessness, and even hallucinations, all work together to lower quality of life.

3.2. Endogenous antioxidants

Antioxidants are particularly efficient *in vitro* when used experimentally because they target oxidative damage throughout AD pathogenesis. Antioxidants decrease ROS's capacity to oxidize. Endogenous antioxidants lessen ROS's potential hazard by converting them into less reactive molecules. The ETC's mitochondrial ubiquinone (Q) additionally serves as a built-in antioxidant for mitochondria [5]. Biomolecular mechanisms that block 3-NP's neurotoxic effects are started by the brain-derived neurotrophic factor (BDNF). In one experiment, administering antioxidants stopped the loss of almost half of the mtDNA copies in all organs studied after intragastric delivery of ethanol. Glutathione. A β tripeptide with antioxidant qualities is glutathione (GSH). GSH reduced the protein's sulfenic ion through covalent adduction, acting as an antioxidant. The reduction of free radicals in mitochondria has been effectively achieved by glutathione choline ester and N-acetyl-L-cysteine choline ester, which are products of the ester that links GSH and choline that directs GSH to the mitochondrion. In the mitochondria of AD cells or neurons injured by mutant APP, glutathione has been demonstrated to greatly reduce protein oxidation and prevent DNA breakage brought on by A-induced oxidative damage [6]. Nonetheless, endogenous antioxidants lose some ability to mitigate

oxidative damage with aging as mitochondrial dysfunction persists and multiplies. Antioxidant-rich diets are an efficient way to lessen oxidative damage.

3.3 Exogenous antioxidant: a diet high in antioxidants

Curcumin, green tea, vitamins C, E, A, and beta-carotene are natural compounds. Numerous studies have shown that vitamin E, particularly vitamin C, lowers the prevalence and incidence of AD in older individuals. A lipophilic and membrane-associated antioxidant, vitamin E, also known as tocopherol, maybe a helpful supplement for AD sufferers [7]. According to certain research, antioxidants may lessen or even counteract the negative effects of A or particles. A sleep-inducing substance called melatonin reduced A β polypeptide accumulation, aberrant protein nitration, and longevity in Tg2576 mouse brains. A cyclical aromatic alkaloid with antioxidant activity, huperzine A, was studied for its potential to treat AD patients. Coumarins, a class of polyphenol benzo, a pyrene compound derived from plants, have been shown to have anti-cancer properties by lowering oxidative stress and inflammation.

3.4 Mitochondria-targeted molecules

Similar to AD, Huntington's disease (HD) additionally leads to bioenergetic degeneration due to faulty enzyme complexes II, III, and IV in the mitochondria. A calcium cation imbalance in HD causes an increase in the permeability of the mitochondrial membrane, which is also similar to AD. Similarly, structural changes in the highly conserved regions of the GTPases Mfn1, Mfn2, and Opa1 that catalyze mitochondrial fission and fusion cause abnormalities in the mitochondria between HD and AD. The long-term effects of these abnormalities include excessive mitochondrial fragmentation and bioenergetics inhibition. Whether administered before or after A-42 inoculation, Mdivi 1 therapy in mouse neuroblastoma cells (N2a) with A-toxicity decreased A-42 levels.

3.5 MitoPBN

MitoPBN comprises positively charged, lipophilic triphenylphosphonium bromide and the anti-oxidant coenzyme Q (quinone), also known as PBN, a conjugated aromatic group. Due to its lipophilic and cationic nature, it is susceptible to rapid uptake by the mitochondria, similar to MitoQ and MitaVitE, even at doses of 2.2 to 4.0 mM. It is thought that mitoPBN inhibits O's ability to activate uncoupled proteins. In addition to acting as an antioxidant, LPBNAH, similar to MitoPBN and generated from phenyl-N-tert-butyl nitron, efficiently mitigates brain damage by preventing ROS damage from the mitochondrion. LPBNAH, which is far more potent

than PBN from which it was produced, can decrease free radicals in rotifers and lengthen their longevity.

Inhibitors of glutamate and cholinesterase prompt synaptic function but do not address mitochondrial damage. The blood-brain barrier prevents natural antioxidants from reaching the mitochondria directly. However, the topic's tiny molecules include antioxidant and regenerative characteristics and lipophilic and positively charged moieties. Mitochondria-targeted compounds shield neurons from oxidative stress brought on by aging and mitochondrial and cellular toxicities brought on by mutant proteins. After being treated with compounds targeting the mitochondria, cultured cells induced with neurodegenerative illness recover at the synapses. Mice who have been given a neurodegenerative illness and then treated with drugs that target the mitochondria live longer. Mitochondria-targeted molecules defend neurons from oxidative stress brought on by aging and mitochondrial and cellular toxicities brought on by mutant proteins. After being treated with compounds targeting the mitochondria, cultured cells induced with neurodegenerative illness recover at the synapses. Mice who have been given a neurodegenerative illness and then treated with drugs that target the mitochondria live longer.

It is interesting to notice that some of these molecules, like SS31, have shorter half-lives and metabolize more quickly than others, like MitoQ and Mdivi-1. SS31 hasn't yet demonstrated any unfavorable impacts in animal models or cell culture. The potential for mitochondria-targeted medicines to prolong the lives of people with neurodegenerative illnesses is encouraging.

4. Conclusion

In conclusion, the study of neuroscience and healthcare are still greatly hampered by Alzheimer's disease. There has never been a greater pressing need for efficient treatment alternatives, given the rising prevalence of AD. This paper examined prospective therapeutic approaches focusing on mitochondria-targeted small medicines and dug into the complicated terrain of mitochondrial dysfunction in AD. Cholinesterase inhibitors, in addition to endogenous antioxidants and exogenous antioxidants generated from natural sources, are currently used as therapeutic approaches. Even though these strategies have

shown promise in reducing some elements of AD, they frequently fall short of directly treating mitochondrial dysfunction, a key factor in the illness.

To confirm the safety and efficacy of mitochondria-targeted medicines, further research and clinical trials are necessary to develop new AD therapeutics. Because AD has many facets, a complete strategy is necessary, and these tiny compounds are an important complement to the available therapeutic alternatives. The development of mitochondrial-focused medicines offers hope for people affected by this severe ailment, even though the road ahead is still difficult.

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