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Review

Intranasal Therapeutics for Alzheimer's Disease

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ABSTRACT

Alzheimer's disease (AD) is an age-related, irreversible, and progressive neurodegenerative disorder that accounts for 70% of all dementia cases worldwide, with approximately 35 million individuals affected. The neurodegenerative effects caused by AD are among the leading causes of disability and mortality in the elderly population. Current treatment strategies for AD are limited and primarily rely on approaches such as cholinergic replacement therapy and the inhibition of glutamate excitotoxicity. However, these treatments provide only symptomatic relief and are insufficient in halting disease progression. This limitation has increased interest in the potential role of neuroprotective drugs in the management of AD. Recently, the direct intranasal delivery of drugs to the central nervous system (CNS) has emerged as a therapeutically viable alternative to oral and parenteral administration methods. This review focuses on the potential efficacy of neuroprotective therapies in AD models. Additionally, it aims to discuss the mechanisms of intranasal drug delivery to the CNS and its role in the management of AD. In light of recent findings, the review seeks to contribute to advancements in this field by summarizing key studies on intranasal drug delivery.

Keywords: Alzheimer's disease, clinical applications, cognitive functions, intranasal therapy, neurodegenerative diseases, targeted drug delivery.

Alzheimer's disease (AD) is an age-related, irreversible neurodegenerative disorder that accounts for 70% of all dementia cases worldwide, affecting approximately 35 million individuals. This disease leads to a significant decline in cognitive functions, profoundly impacting the quality of life. To date, the management of AD has primarily relied on cholinergic replacement therapy and the inhibition of glutamate excitotoxicity. However, these approaches have limited efficacy and fail to halt disease progression. Consequently, neuroprotective drugs and innovative delivery methods are gaining increasing attention in the treatment of AD.[1]

In recent years, intranasal drug delivery methods targeting the direct transport of therapeutics to the central nervous system (CNS) have emerged as a promising alternative to traditional oral and parenteral routes, which are often limited by various constraints. Intranasal administration bypasses the blood-brain barrier (BBB) by facilitating the direct transport of drugs to the CNS via the olfactory and trigeminal nerve pathways. This approach enables the direct nose-to-brain delivery of neurotherapeutic agents and is considered a promising strategy for the treatment of neurological disorders such as AD.[2]

Various formulations have been developed for intranasal drug delivery in the treatment of AD. One such formulation is an oil-in-water nanoemulsion (NE) loaded with donepezil, designed to enhance drug delivery from the nose to the brain. *In vivo* studies have demonstrated that NE is effectively transported to the brain and exhibits high retention levels in Sprague Dawley rats. Furthermore, the characterization of the developed NE in terms of parameters such as particle size, zeta potential, and *in vitro* release performance highlights its potential as an innovative approach for AD treatment.[3]

In light of this information, further research is needed to explore the potential efficacy of intranasal drug delivery in the treatment of AD and the

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feasibility of administering neuroprotective drugs through this route. This review aims to evaluate the mechanisms, advantages, and clinical potential of intranasal administration in AD treatment.[1-3]

INNOVATIVE DRUG DELIVERY SYSTEMS IN ALZHEIMER'S DISEASE

The Role of Nanocarrier Technologies and Intranasal Administration

Alzheimer's disease is an irreversible and progressive neurodegenerative disorder that affects millions of people worldwide. It is characterized by complex pathological mechanisms such as the accumulation of amyloid-β plaques, the formation of neurofibrillary tangles, and insulin signaling dysfunction. Due to the presence of the BBB and the complex pathogenesis of AD, developing effective treatment approaches remains a significant challenge. In recent years, intranasal drug delivery has emerged as a promising non-invasive alternative for delivering drugs to the brain. This method has the potential to solve the problem of crossing the BBB by directly delivering drugs to the CNS via the nose-to-brain pathway. Specifically, nanocarrier systems have shown remarkable results in CNS-targeted drug delivery. Innovative carriers such as polyelectrolyte complexes, polyethylene glycol-poly(lactic-co-glycolic) acid nanoparticles, dendrigraft poly-l-lysines, and serum albumin nanoparticles enable the effective intranasal delivery of peptide- and protein-based drugs to the brain.[4-7]

Nanocarrier systems can exhibit multifaceted effects on mechanisms associated with the pathogenesis of AD. For instance, nanoparticle formulations have shown neuroprotective effects in AD models; treatments with basic fibroblast growth factor and insulin-based therapies have improved synaptic plasticity and cognition, thereby slowing the progression of the disease. Additionally, nanocarrier systems containing therapeutic agents such as rapamycin and β-secretase (BACE1) siRNA have inhibited Aβ aggregation and reduced oxidative stress.[5-8]

Given the critical roles of insulin signaling dysregulation and mitochondrial dysfunction in the pathogenesis of AD, insulin-based therapeutic approaches have gained significant attention. Therapeutic agents integrated into nanoparticles have been shown to improve mitochondrial respiration, reduce oxidative stress, and alleviate cognitive impairments. Moreover, formulations such as the newly developed B1R/B2R-TRIOZAN™ nanoparticles demonstrate high efficacy in crossing the BBB, offering the potential to revolutionize CNS-targeted therapies. This review summarizes the current status of intranasal drug delivery systems and nanotechnological approaches for AD. It also discusses how these strategies exert their effects through multiple mechanisms, providing a paradigm shift in the management of the disease. The development of innovative drug delivery systems for AD treatment holds promise for altering the course of the disease and improving the quality of life for individuals affected.[6-8]

Molecular Targets, Next-Generation Sensing, and the Role of Intranasal Administration

BACE1 sensing and inhibitor screening

One of the most critical targets in understanding the molecular mechanisms of AD and developing therapeutic strategies is the BACE1 enzyme. The BACE1 acts on amyloid precursor protein and leads to the production of Aβ. Therefore, the precise detection of BACE1 and the development of its inhibitors are of great importance in slowing the progression of AD. In this context, a WS2 nanosheet-based fluorescent sensing platform has been developed to monitor BACE1 activity. This system is based on the principle that a fluorescent peptide substrate is hydrolyzed by BACE1. In the absence of β-secretase, the peptide substrate adsorbs onto the WS2 nanosheet surface, quenching the fluorescent signal. In the presence of BACE1, the peptide fragments formed as a result of hydrolysis cannot interact with the WS2 nanosheet, and the fluorescent signal is restored. This innovative sensing platform can detect BACE1 with a detection limit of 66 pM, demonstrating high sensitivity and specificity. Furthermore, it has been shown to be an effective tool for screening BACE1 inhibitors.[9]

Strategies for tau protein aggregation

Tau protein has gained increasing attention as an alternative target to Aβ in the pathogenesis of AD. Abnormal phosphorylation and aggregation of tau lead to neurotoxicity and disease progression. Next-generation nanotechnological approaches developed against tau protein aggregation show promising potential in the treatment of AD. Polymeric micelles decorated with tau-binding peptides have been used to create multifunctional nanoinhibitors that effectively inhibit tau protein aggregation. These nanoinhibitors not only recognize tau aggregates but also prevent the deposition of these aggregates on neuronal surfaces, significantly reducing cytotoxicity.

Furthermore, the ease with which the nano inhibitor-tau complexes can be broken down has enhanced the therapeutic efficacy of this strategy.[10]

Reduction of Aβ aggregation and neurotoxicity

The formation and accumulation of Aβ plaques is one of the most characteristic pathological features of AD. Aβ aggregates into toxic forms that can form cross-β-sheet structures, leading to oxidative stress, neuroinflammation, and neurodegeneration. In this context, molecules that inhibit Aβ aggregation or convert its toxic forms into non-toxic ones show promise for AD treatment. Chitosan oligosaccharides (COS) are among the significant compounds in this area. It has been demonstrated that COS inhibits Aβ42 aggregation and reduces its toxicity by directly binding to the protein. Furthermore, the ability of COS to effectively cross the BBB enhances its applicability in AD treatment. Notably, the COS monomer with DP6 has been found to be the most effective in preventing the transition to β-sheet-rich structures. These effects of COS have significantly reduced Aβ-induced toxicity to neuronal cells.[11]

Neuroinflammation and the effects of *Notopterygium incisum*

Neuroinflammation plays a central role in the pathogenesis of AD. Specifically, microglial activation is a critical factor in the regulation of neuroinflammatory processes. The root extract of Notopterygium incisum (NRE), used as a traditional remedy in Chinese medicine, has shown inhibitory effects on neuroinflammation associated with ADNotopterygium incisum has reduced the production of proinflammatory cytokines in vitro in microglial cells activated by Aβ and lipopolysaccharide. In *in vivo* studies, long-term administration of NRE suppressed microglial activation in neuroinflammatory mouse models and provided neuroprotective effects. These results suggest that NRE holds promise as an agent for slowing the progression of AD and alleviating damage associated with neuroinflammation.[12]

Based on this information, these multifaceted approaches to AD treatment offer innovative solutions tailored to the complex pathophysiology of the disease.

Strategies such as β-secretase sensing platforms, chitosan derivatives that inhibit Aβ aggregation, nano inhibitors targeting tau protein aggregation, and plant extracts that suppress neuroinflammation have the potential to make significant advancements in the management of AD. These innovations not only have the potential to slow the progression of AD but also to enhance the quality of life for patients.[13]

Nanotechnological Carrier Systems and Targeted Drug Delivery for Alzheimer's Disease

Effective treatment of AD requires more specific and targeted approaches. Nanotechnological carrier systems offer a promising solution in this field, holding great potential for AD treatment. Nanotechnology-based carrier systems provide innovative therapeutic options for AD's complex pathophysiology. In particular, targeted drug delivery methods, such as lipid-based nanocarriers, enable more effective distribution of drugs in the brain by bypassing the BBB. The BBB is a significant barrier that limits the efficacy of drugs in the brain and reduces therapeutic effectiveness. Nanotechnological carrier systems overcome this barrier, enhancing the effectiveness of neurological treatments.[14]

The use of functional DNA nanostructures also enhances the potential of nanotechnology in AD treatment. These systems, with targeted components such as ultra-small nanopores and DNA aptamers, specifically carry neurological targets like acetylcholinesterase. DNA aptamers enable precise delivery of neurological targets with a low detection limit and high signal-to-noise ratio. This approach effectively detects and transports target proteins at low concentrations in complex biological samples.[15,16]

Another promising approach developed for AD is dual-functional nanotechnology carrier systems. For example, β-sheet breaker peptide H102 (TQNP/H102)-loaded nanoparticles, combined with various targeting peptides, aim to cross the BBB and reach specific targets in the brain. These carrier systems offer high bioavailability and a low side effect profile, contributing to the recovery of neurological damage. Clinical studies have shown that TQNP/H102 significantly improves spatial learning and memory in AD mice.[17]

In recent years, new nanocarrier systems have been developed that surpass the limits of traditional drug development methods, along with nanotechnology. Boron-based carrier systems, for example, enhance the bioavailability of antimicrobial and antioxidant agents and increase therapeutic efficacy in neurodegenerative diseases. Boron nitride nanoparticles offer self-assembling nanocarrier systems by integrating different drug components. These systems effectively load drugs like memantine

and β-lactamase, reducing cellular damage caused by AD and providing neuroprotective effects.[18] Overall, nanotechnological carrier systems offer significant advantages over traditional drug delivery methods in AD treatment. The targeted drug release provided by nanotechnology, overcoming the BBB, enhancing bioavailability, and reducing side effects, are all factors that lead to promising results in AD treatment. However, further research and development are required for the effective application of these systems in clinical settings. Additionally, more studies should be conducted on the safety and long-term effects of nanotechnological carrier systems.[18-21]

INNOVATIVE STRATEGIES

Intranasal treatment methods enable the delivery of biological agents directly to brain tissue via the nasal pathway. This approach allows for more effective delivery of drugs that struggle to cross the BBB. Additionally, extracellular vesicles such as exosomes or carrier systems, with their low immunogenicity, small size, and high bioavailability, show promising results in AD treatment.[22]

The Effect of Exosomes Derived from Multipotent Mesenchymal Stromal Cells on Spatial Memory

The intranasal administration of exosomes derived from multipotent mesenchymal stromal cells significantly improved spatial memory in mice mimicking the sporadic form of AD. Since spatial memory involves learning and understanding the environment, this improvement could reverse the cognitive decline seen in the early stages of AD. The low immunogenicity of exosomes minimizes the risk of immune rejection, providing a safe treatment option. Furthermore, the direct delivery of these exosomes to brain tissue shows accumulation in areas such as the hippocampus and neocortex, which play a crucial role in learning and memory processes. This suggests that the treatment is beneficial in areas severely affected by AD.[23]

Intranasal Treatment of TNF-α Receptor 1 Deficiency and KA-Induced Neurotoxicity

Studies conducted on mice with tumor necrosis factor-alpha (TNF-α) receptor 1 (TNFR1) deficiency have shown that this receptor plays a protective role against kainic acid (KA)-induced neurotoxicity. Intranasally administered KA resulted in more severe seizures, behavioral changes, and hippocampal neuronal degeneration in the mice. It was found that TNF-α reduces neurotoxicity by regulating the nuclear factor kappa-light-chain-enhancer of activated B cells signaling pathway. The more severe neurotoxicity exhibited by TNFR1-deficient mice indicates that this signaling pathway plays a critical role in the progression of AD. This suggests that intranasal treatment may offer an effective intervention against neurodegenerative processes.[24]

Intranasal Delivery and Bioavailability with Curcumin-Coated Carrier Systems

Curcumin (CUR) hydroxypropyl-β-cyclodextrin (CUR/HP-β-CD) encapsulated complexes and chitosan-coated poly(lactic-co-glycolic acid) nanoparticle (CUR-CS-PLGA-NP) formulations have been administered intranasally. These formulations enhance the bioavailability of CUR and ensure its stability in brain tissue, offering an effective therapeutic solution. *In vitro* studies revealed that the stability of the CUR/HP-β-CD complexes was maintained at a high rate of 95.41%, demonstrating superior cellular uptake compared to CUR-CS-PLGA-NP formulations. Both formulations suppressed AD-associated inflammation by reducing inflammatory responses through their antioxidant properties.[25]

The Role of 3D Graphene Scaffold-Based Exosomes in Reducing Amyloid-β Accumulation

The capacity of exosomes derived from cells cultured on 3D graphene scaffolds to reduce amyloid-β accumulation has been emphasized. These exosomes regulate the expression of α-secretase and β-secretase, thereby decreasing Aβ production. Experiments conducted in transgenic mice showed that these exosomes improved cognitive functions and exhibited neuroprotective effects. This presents an effective therapeutic strategy to combat the fundamental pathology of AD.[26-28]

In conclusion, intranasal applications have the potential to alleviate neurodegenerative damage by enabling targeted drug delivery directly to the brain via the nasal route. This method offers a non-invasive approach that could slow the progression of the disease and support cognitive functions. Intranasal treatment methods are considered a promising alternative in the management of AD. Further research and studies in clinical applications will support the broader use of these innovative approaches in the future.

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