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Review Article

Novel therapeutic delivery for neurodegenerative diseases: Strategies to overcome CNS barriers

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ABSTRACT

The incidence of central nervous system (CNS) diseases is expected to rise significantly due to increasing lifespan and changing population demographics. Among CNS diseases, neurodegenerative diseases (ND's) entail a significant challenge since they frequently involve neuronal loss and age-related progressive deterioration in brain function. Although the mechanisms and pathogenesis of neuronal disorders including Parkinson's disease (PD), Alzheimer's disease, and Huntington's disease (HD) have been extensively studied, effective treatment strategies remain limited. Drug delivery to the CNS is particularly challenging and poses a significant obstacle in the management of neurodegeneration. The present review focuses on the challenges associated with neuronal disorders, especially concerning the delivery of macro molecules containing proteins and nucleic acid. Additionally, we highlight opportunities to enhance therapeutic delivery for the treatment of ND's. As our understanding of the biological aspects of ND's continues to grow, there is a growing potential for therapeutic interventions. Therefore, these delivery strategies play a vital role for the future transition of CNS therapies from research labs to clinical practices.

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1. Introduction

Central nervous system (CNS) disorders affect a substantial number of individuals worldwide, with an estimated 1.5 billion population experiencing these conditions currently. The situation is projected to worsen in the 21st century as the aging population increases, leading to a higher prevalence of CNS disorders, particularly Alzheimer's disease(AD), which typically manifests around the age of 70.[1] Currently, CNS disorders account for 11% of the worldwide burden of disease, a figure expected to rise to 14% by 2020, primarily due to population aging. Neurodegeneration is a common underlying factor in various CNS diseases, including AD, Amyotrophic Lateral Sclerosis (ALS), Huntington's disease (HD), Parkinson's disease (PD), epilepsy, and stroke.[2] These conditions have life-threatening consequences and impose a substantial economic burden, with annual costs exceeding several hundred billion dollars in the United States alone. Unfortunately, existing treatments for ND's are inadequate, primarily addressing symptoms rather than modifying the course of the diseases. Moreover, the high doses and long-term administration of drugs often result in significant side effects that can significantly impact patients' quality of life.

The potential of a new generation of biological therapeutics that utilize peptides, proteins, and nucleic acid constructs shows promise in overcoming the limitations of

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current treatment methods.[3] These advanced therapeutics have the potential to directly target disease-causing molecules, thereby offering the possibility of modifying the progression of diseases. Several protein-based therapeutics, such as nerve growth factor (NGF), glial cell-derived neurotrophic factor (GDNF), brain-derived nerve growth factor (BDNF), and basic fibroblast growth factor (bFGF), have demonstrated potential in halting disease progression and restoring neuronal function.[4] Moreover, gene therapy shows promise in neurodegenerative disorders by delivering genes that encode neurotrophins, enzymes, antioxidants, anti-inflammatory agents, and anti-apoptotic molecules, thereby providing potential protection against these disorders. Another area of great interest in the field of neurodegenerative diseases is the use of small interfering RNA (siRNA) to target specific genes, such as β-amyloid and α-synuclein in AD and PD, respectively.[5]

The current review explore the challenges associated with CNS therapeutics, particularly the delivery of biological macromolecules, and emphasize strategies that have the potential to improve therapeutic delivery for the treatment of ND's. The growing understanding of the biological mechanisms underlying these diseases opens up exciting opportunities for developing novel therapies, and the optimization of drug delivery strategies is crucial for translating these potential treatments from the laboratory to clinical practice.

2. Neurodegenerative Diseases

2.1. Alzheimer's disease

AD is a common neurodegenerative disorder characterized by the development of plaques and neurofibrillary tangles, which consist of β-amyloid and tau proteins, respectively. Age is the biggest risk factor for this dementia . AD affects 10% of adults over 65, and it is anticipated that by 2050, there will be three times as many AD sufferers in the US. Presently, all available therapies focus on symptom management rather than modifying the underlying disease process.[6]

The current FDA-approved medications for AD include acetylcholinesterase inhibitors and the NMDA receptor antagonist meantime. Although off-label use of antipsychotics has been explored, their efficacy in AD treatment has been called into question. Investigational approaches involve investigating the potential benefits of curcumin, an anti-inflammatory compound found in Indian curry spice, and omega-3 fatty acids in reducing amyloid plaque burden. Ongoing research is focused on the development of novel therapeutic agents for AD. Some candidates aim to manage symptoms, while others directly target disease progression.[7] The recombinant DNA drug etanercept has shown promise in preventing the tumour necrosis factor alpha (TNF), pro-inflammatory cytokine from reaching the AD-associated increased levels. NGF gene therapy has been investigated in clinical trials to prevent cholinergic neuron degeneration, leading to cognitive improvement in some patients Monoclonal antibody bapineuzumab is being developed to bind and clear β-amyloid plaques from the CNS.[8] Despite the extensive efforts in AD treatment, no therapies have successfully halted disease progression. Therefore, a combination of treatment approaches targeting both symptoms and disease modification may be necessary for effective therapy. This comprehensive approach may involve the simultaneous use of multiple treatment options to achieve optimal outcomes in AD patients.

2.2. Parkinson's disease

The dopaminergic degeneration in the substantia nigra accompanied by the misfolding of α-synuclein in dopaminergic neurons is feature of PD.[9] PD is a movement disorder that includes symptoms such as tremors, bradykinesia, and akinesia.[10] Currently, there is no proper management options for PD, and available strategies provides symptomatic relief rather than slowing disease progression. Treatment options for PD include levodopa, dopamine agonists, COMT-inhibitors, anti-cholinergics, MAO inhibitors, and amantadine.[11] Growth factors have demonstrated potential in neuroprotection for PD, including BDNF and glial cell-derived growth factor. A new generation of nucleic acid constructions has also appeared, capable of silencing α-synuclein, a protein associated with PD. RNA interference (RNAi) has been explored as a potential treatment strategy, demonstrating success in animal models. To effectively deliver these novel therapeutics, advanced delivery methods are required to facilitate their entry into the CNS. Approaches such as intranasal administration and the use of nanocarrier devices offer protection against degradation and clearance, while also enhancing the enrty of macromolecules across the BBB. These delivery strategies hold promise for enabling the therapeutic effects of these agents in the treatment of PD.[12]

2.3. Huntington's disease

Huntingtin protein in neurons, resulting in impaired neuronal function and eventual cell death. The hallmark symptom of HD is chorea, abnormal involuntary movements experienced by patients. HD is the result of an autosomal dominant mutation and currently lacks a cure. The existing treatments mainly aim to manage the symptoms rather than targeting the fundamental disease process.[13] Depression, psychosis, and epilepsy are commonly observed neurological problems in HD patients, which are treated with neuroleptics and anticonvulsants.[14] Additionally, Parkinsonism symptoms can be present in

HD patients, and levodopa is often used for their treatment. Despite the fact that there is not yet a medication that can be used to specifically target the mutant huntingtin protein, there are ongoing efforts to develop disease-modifying therapies. Recombinant adeno-associated viruses have been utilized to deliver RNA interference (RNAi) therapeutics, resulting in reduced pathology in preclinical models of HD. Another approach involves neural implantation of cells that secrete ciliary neurotrophic factor, which has shown promise in improving HD symptoms. The development of new therapeutics for HD must focus on protecting the deteriorating nervous system. Neuroprotective and disease-modifying treatments offer promising avenues for intervention in HD. One potential strategy involves the use of novel delivery methods, such as small interfering RNA (siRNA), to specifically target and eliminate the mutant huntingtin protein in the CNS, thereby halting the progression of the disease.[15] Advanced delivery techniques can enhance the effectiveness and specificity of these therapeutic interventions, offering hope for the future treatment of HD.

3. Barriers to CNS Delivery

Drug delivery to the CNS is a significant challenge in the field of ND's. The majority of micro-molecular drugs (98%) and all proteins and nucleic acid therapies are unable to effectively reach the CNS due to various barriers. The main obstacles include the blood-brain barrier (BBB), the blood-cerebrospinal fluid (CSF) barrier, and the dilution effects caused by systemic distribution of drugs.[16]

4. Blood Brain Barrier

The BBB serves as a defence system to keep chemicals out of the brain. Paul Ehrlich, who noted that water-soluble dyes put into the circulatory system stained all tissues save the brain and spinal cord, was the first to discover its presence. Additional research identified a physical barrier made of tight connections between the endothelial cells of the brain's microvasculature.[17] They consist of combination of claudin and occludin proteins, creating an almost impenetrable barrier. Additionally, the BBB possesses active mechanisms such as P-glycoprotein (P-gp) and multidrug resistance-associated proteins, which actively exclude compounds from entering the brain. Metabolizing enzymes like those from the cytochrome P450 family are also present in high levels at the BBB.[18] These properties contribute to the function of the BBB, making it challenging for drugs to penetrate. Drugs attempting to cross the BBB should ideally have a molecular weight below 500 Daltons, fewer than 10 hydrogen bond donors/acceptors, and minimal affinity for the BBB enzyme and efflux systems, as well as low binding to plasma proteins.[19]

4.1. Blood CSF barrier

Likewise, the BBB, the blood-CSF barrier blocks the passage of substances into the central nervous system. It serves as a picky filter, letting only specific chemicals enter the cerebrospinal fluid.[20] Tight connections between choroid plexus epithelial cells provide the barrier. The capillaries that supply the choroid plexus feature fenestrae rather than tight junctions, in contrast to the BBB.[21] Drugs can readily flow via these fenestrae, yet the tight connections still prohibit them from entering the CSF. However, the blood-CSF barrier is less relevant in terms of drug delivery compared to the BBB, as it has 1,000 times less surface area.[22]

4.2. Systemic distribution and clearance

Systemic distribution and clearance of drugs in peripheral tissues also pose a barrier to CNS delivery that is often overlooked. When lipophilic compounds are used to increase CNS permeability, they more easily penetrate other tissues in the body upon administration into the systemic circulation. This results in the need for higher doses to achieve therapeutic levels in the brain, leading to non-specific systemic effects and increased toxicity. Moreover, high plasma protein binding affinity further complicates CNS drug delivery, as less free drug is available to diffuse into the CNS. However, novel drug delivery systems that encapsulate therapeutic agents in carriers can help address these issues by altering the release and pharmacokinetic profiles of the drugs.[23,24]

5. Strategies to Enhance CNS Delivery

Various strategies have been explored to overcome the barriers to CNS delivery. These strategies can be broadly categorized into invasive and non-invasive approaches, as well as systemic and local administration methods.

5.1. Intracranial delivery

Intracranial delivery is an invasive approach that involves direct administration of the drug into the brain parenchyma through intracerebral infusions or implants. This method allows for localized delivery to the targeted site, but diffusion to other areas of the brain is limited. Intracranial delivery has shown positive outcomes for specific targets, such as local tumor delivery or direct treatment of failing neurons in PD.[25] For example, neural implants releasing GDNF have improved movement disorders in aged rats. Direct striatal injections of GDNF have also prevented neurodegeneration in PD models. However, intracranial delivery is not suitable for broad distribution of therapeutic agents across neural tissue, as desired for the treatment of conditions like AD or HD.[26] Additionally, the invasive nature of this approach carries risks and variability in

drug administration. Clinical trials of intracranial delivery have been conducted, including the use of recombinant methionyl human GDNF in PD patients.[27] However, unexpected adverse effects were observed, such as catheter repositioning, removal, and even a hemorrhagic stroke. This led to the discontinuation of the trial. Intracranial implants, such as genetically engineered cells encapsulated in a polymer matrix, have also been used in HD patients but did not demonstrate significant clinical benefits, possibly due to variable drug release.[28]

Non-invasive approaches include systemic administration, which involves delivering drugs through the bloodstream, and local administration, which targets specific regions of the CNS. Systemic distribution poses challenges such as dilution effects and limited CNS penetration due to the BBB. Strategies to enhance systemic CNS delivery include increasing lipophilicity of drug molecules, utilizing prodrugs, or employing carrier systems like nanoparticles or liposomes to improve drug stability and transport across the BBB.[29] Local administration methods include intranasal delivery, which takes advantage of the nose-to-brain pathway, and intrathecal injection, which targets the CSF for drug delivery. In clinical trials, intracranial injection of NGF for AD treatment has shown a decrease in the rate of cognitive decline. However, there have been potentially lethal side effects associated with this approach. These examples highlight the complexity and challenges in finding effective CNS delivery strategies.[30,31]

6. Disruption of the BBB

Transient disruption of the BBB is another approach to enhance drug penetration into the CNS. One method involves the administration of hyperosmolar agents like mannitol directly into the carotid artery. This causes temporary openings in the BBB, allowing drugs to enter the CNS. However, this approach introduces potentially neurotoxic molecules and plasma proteins to the CNS and is associated with significant pain and patient mortality. The use of organic solvents and certain surfactants can also transiently disrupt the BBB[32] Co-administration of drugs with ethanol or dimethylsulfoxide has been shown to affect the BBB and increase drug activity in the CNS. Non-ionic surfactants such as polysorbate 80 have also demonstrated BBB-altering effects in vitro, specifically affecting efflux transporters. Immune adjuvants, like Freund's adjuvant, have been utilized to disrupt the BBB for the treatment of AD.[33] They induce an immune response and inflammation, which opens the BBB and facilitates the penetration of antibodies into the CNS. Ultrasound has shown promise in opening the BBB, allowing dyes and drugs to penetrate into the CNS. However, the duration of BBB opening and the potential effects on healthy neural tissue need to be carefully considered.[34]

Despite the potential benefits, transient BBB disruption methods have limitations and risks. The duration of BBB opening should be controlled to prevent accumulation of toxins in the brain. The risks associated with introducing foreign compounds and the potential for toxic effects must be carefully evaluated before considering these methods for the treatment of chronic ND's. Furthermore, the long-term treatment schedules for ND's do not align well with BBB disruption, as each disruption carries the risk of harmful substances entering the CNS. For example, the failed β-amyloid immunization led to encephalitis. The transient BBB disruption methods hold promise for enhancing drug delivery to the CNS, significant improvements are needed to ensure their safety and efficacy in human trials. The risks and challenges associated with these approaches must be carefully considered, and alternative strategies may be required to achieve widespread and targeted drug delivery to the brain.[35,36]

6.1. Intranasal delivery

Intranasal delivery is an emerging approach for delivering drugs to the central nervous system (CNS) and has attracted significant interest. The nasal cavity is of particular interest because nerves that project into it have been observed to penetrate the BBB, potentially allowing direct drug passage into the brain tissue, bypassing the BBB. The olfactory epithelium, located just below the cribiform plate of the ethmoid bone, separates the nasal cavity from the cranial cavity. The olfactory sensory cells, which are bipolar neurons, have dendritic processes extending from the cell body to the mucosa's apical surface. These neurons terminate into axons that form bundles and penetrate the cranial cavity through small holes in the cribiform plate.[37]

The exact mechanisms by which drugs delivered intranasally reach the brain and cerebrospinal fluid (CSF) are not fully understood. However, three distinct pathways are believed to play a role. The systemic pathway involves the absorption of small, lipophilic drugs into the capillaries of the olfactory epithelium, followed by their crossing of the BBB. The other two pathways are slower but are more likely involved in the uptake of large molecular weight solutes like proteins and nucleic acids. These pathways include intracellular axonal transport by olfactory sensory neurons and paracellular transport through clefts between olfactory epithelial cells.[38] Paracellular transport, which occurs between cells, is considered a rapid route and may account for a significant portion of protein uptake observed shortly after intranasal delivery. Studies have shown that peptides and proteins administered intranasally can rapidly reach the cerebrospinal fluid in humans and animals. For example, neuropeptides were detected in human subjects' CSF within 80 minutes of intranasal administration. Insulin administered intranasal yielded concentrations in the brain over 400-fold higher than those achieved through

subcutaneous delivery, and uptake occurred within 10 minutes.[39,40]

In animal studies, various peptide molecules and growth factors have been successfully delivered to the brain via the nasal route, demonstrating neuroprotective effects in disease models. For instance, intranasal delivery of insulin-like growth factor-1 (IGF-1) bypassed the BBB, distributed throughout the brain, and exerted neuroprotective effects in stroke models. NGF delivered intranasally reversed cognitive deficits in an AD model, and basic fibroblast growth factor showed protective effects in a PD model.[41] Despite its promise, intranasal delivery for CNS therapeutics in humans is controversial and has limitations. Although the olfactory route lacks a BBB, tight junctions and metabolic enzymes present in the nasal epithelium act as barriers. Additionally, anatomical differences between rodents and humans can impact the efficacy of treatments, and the small volumes and short residence time of drugs in the nasal mucosa pose challenges. To improve intranasal delivery, advanced strategies such as nanoparticles, dry powders, or mucoadhesive gels are being explored.[42] These formulations can enhance residence time, decrease drug degradation, facilitate nose-to-brain transport, and increase drug availability in target tissues and cells. Further preclinical evidence, including studies in non-human primates, will be necessary to better understand the benefits and limitations of intranasal delivery, especially for large molecular proteins, peptides, and nucleic acid constructs.

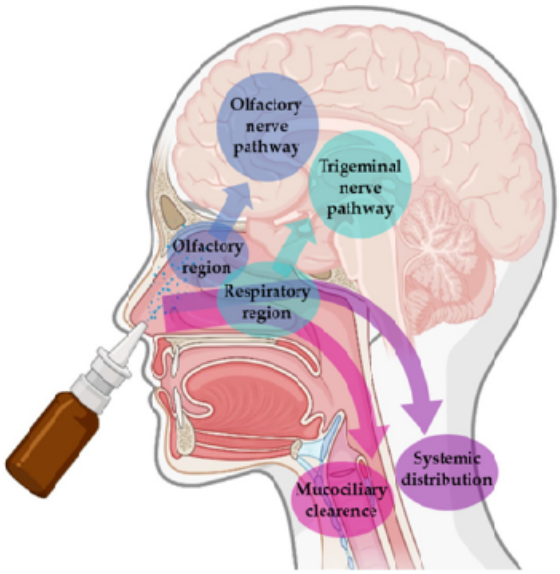

Fig. 1: Common pathways for nose-to-brain drug delivery

6.2. *Nanotechnology for CNS delivery*

Nanotechnology plays a crucial role in the development of pharmaceutical products, including CNS delivery. Nano-sized carriers like liposomes, emulsions, solid-lipid nanoparticles, and polymeric nanoparticles are designed to efficiently package therapeutic or imaging payloads and facilitate transport across the BBB.[43] These carriers allow drugs to be delivered specifically to the CNS while minimizing systemic distribution. Additionally, these systems enable the concentration of various agents within the nanocarrier, enhancing their effectiveness. However, it is important to consider the potential disruption of the BBB by certain components of these delivery systems, such as polysorbate 80. Furthermore, the elimination and toxicity of nanoparticles used in drug delivery need to be carefully evaluated to ensure minimal harm. Extensive toxicity studies are necessary for each delivery system to assess their safety and potential adverse effects on CNS tissues.[42,44]

6.3. *Liposomes and nanoemulsions*

Liposomes are well-established drug delivery systems that resemble cell membranes. While traditional liposomes have limited success in treating CNS diseases, immunoliposomes have been effective in delivering compounds to the CNS. By attaching antibodies to the liposome surface, they can be targeted to the endothelial cells of the BBB, enhancing CNS absorption. This targeted delivery allows for increased drug delivery to the CNS and reduces non-specific distribution and side effects.[45] However, off-target uptake still occurs, highlighting the need for CNS-specific drugs. Immunoliposomes have shown success in delivering antisense RNA to the CNS, where the drug can have its intended effects. Additionally, natural ligands and chimeric proteins can act as molecular vehicles to transport drugs across the BBB and into the CNS. These strategies hold promise for achieving safer and more specific targeting of CNS therapies.[46]

Liposomes and nanoemulsions are effective drug delivery systems. Liposomes are composed of phospholipids and can be modified with antibodies to target endothelial cells of the BBB, enhancing drug delivery to the CNS and reducing non-specific distribution. On the other hand, nanoemulsions are emulsion systems with a nanometer-sized inner phase. They can improve oral absorption of drugs and increase CNS penetration. For example, nanoemulsions systems have been used to deliver saquinavir to the CNS, resulting in increased brain uptake.[47] This effect is attributed to the use of oils rich in omega-3 fatty acids in the nanoemulsions formulation, as these fatty acids are preferentially transported into the brain. With further advancements in emulsion distribution, these delivery systems hold promise as effective strategies

for treating CNS diseases by bypassing the BBB.[48]

6.4. Solid-lipid nanoparticles (SLNs)

SLNs are lipid-based colloidal dispersions that solidify upon cooling. They offer advantages over polymeric nanoparticles, including biocompatibility and ease of large-scale production. SLNs resemble oil-in-water emulsions and can efficiently carry hydrophobic compounds. Modified SLNs, such as poly (ethylene glycol)-modified SLNs, have demonstrated the ability to penetrate the BBB and improve drug delivery to the central nervous system (CNS). Thiamine-coated SLNs have shown increased uptake in the CNS, indicating their potential for treating malignant gliomas. Due to their stability and manufacturing feasibility, SLNs hold promise as a promising approach for CNS drug delivery.[49,50]

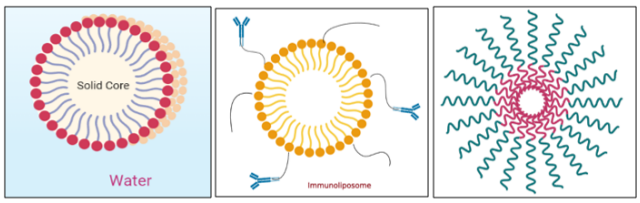

Fig. 2: Commonly used nano formulations

6.5. Polymeric nanoparticles

Polymeric nanoparticles are solid particles made from biocompatible polymers and are utilized for drug delivery. Poly-butyl cyanoacrylate nanoparticles coated with polysorbate 80 have shown the ability to deliver drugs to the brain. The mechanism of how polysorbate 80 facilitates BBB transport is still debated, but its ability to disrupt the BBB may contribute to the nanoparticles' BBB penetration. Polysorbate 80 modification has also been found crucial for transporting polylactic acid nanoparticles across the BBB. Despite the need for polysorbate 80, these systems hold potential for treating ND's.[51,52]

7. Conclusion

The conclusion highlights the urgent need for improved therapeutics that can effectively modify the progression of ND's rather than just alleviating symptoms. While biological macromolecules have shown promise in preclinical models, their translation into clinical practice is challenging due to limited brain availability following systemic delivery. The conclusion explores various strategies to enhance the delivery of these macromolecules to the brain, ranging from invasive approaches such as intracranial delivery and temporary disruption of the BBB to non-invasive methods like intranasal administration and nanotechnology-based delivery systems. The advantages and disadvantages of each approach are discussed, along with relevant examples from scientific literature. It is emphasized that delivery strategies should be integrated early in the development of CNS therapeutics. Furthermore, a combination of different delivery strategies may offer synergistic benefits and improve the availability of therapeutic agents in the CNS.

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None.

9. Conflict of Interest

None.

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