

Nose-To-Brain Targeted Drug Delivery: Impact of Nanoparticles in Alzheimer's Disease Treatment

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ABSTRACT: Alzheimer's disease is a chronic, progressive neurological disorder that is the most common type of dementia linked with memory loss. The Blood-Brain Barrier restricts traditional brain drug delivery. To achieve the desired therapeutic effect, an optimal target was chosen where the drugs are not subjected to systemic circulation. For this purpose, several intrusive and non-intrusive approaches have been examined. Among these, drug delivery from the nasal to the brain via the olfactory and trigeminal nerve system was regarded as the most efficient. Additionally, drug formulation into nanoparticles allows for brain targeting, in addition to controlled release. Nano medicines have attracted immense attention because they can increase drug bioavailability, shorten absorption time, and increase solubility in blood. This review examines the intriguing realm of nanoparticles, which enhance the delivery of drugs from the nose to the brain for the treatment of Alzheimer's disease. The coming years will see the enhancement of human well-being with the inclusion of increasingly advanced methods in drug delivery systems.

Keywords: Alzheimer's disease, neurological disorder, drug delivery, nose to brain delivery, nanoparticles, nano medicines

I. INTRODUCTION

Alzheimer's disease (AD) is the most prevalent type of dementia, affecting millions globally and entailing a stupendous socioeconomic cost. ^[1] AD is defined by the progressive accumulation of amyloid-beta (A β) plaques and neurofibrillary tangles (hyperphosphorylated tau protein), leading to neuronal dysfunction, synapse loss, and diffuse neurodegeneration. ^[2] The only modest, symptomatic treatments available are not improving symptoms, and there is a dire need for disease-modifying treatment. ^[3]

One of the biggest hurdles to successful AD drug development is the Cerebrovascular barrier. This physical physiological barrier, which consists of tightly sealed endothelial cells, pericytes, and astrocytes, carefully controls the entry of molecules into the brain, shielding it from toxic substances and pathogens. ^[4] Although vital for brain homeostasis, the BBB inadvertently prevents more than 98% of small molecules and nearly all large molecules from entering, including many potential anti-AD drug candidates. ^[5] Systemic drug administration typically requires high doses to reach therapeutic levels in the brain, resulting in extensive systemic side effects and decreased patient compliance. ^[6]

In view of such challenges, the nasal to brain delivery route has proven to be an immensely promising non-invasive method of bypassing the BBB to reach the CNS directly. This novel method leverages the peculiar anatomical fixation between the nose and the brain, providing a direct pathway for therapeutic molecules. ^[7] The incorporation of nanotechnology further broadens the promise of nasal to brain delivery since nanoparticles (NPs) exhibit properties that enable them to surpass numerous pitfalls related to free drug delivery through this route, including rapid ciliary clearance and Biodegradation by enzymes. ^[8]

This review attempts to provide a detailed summary of nose-to-brain (N2B) targeted drug delivery. This review aims to be all-encompassing, with a special emphasis placed on the use of nanoparticles to treat Alzheimer's disease. We will explore how N2B transport occurs, the benefits and constraints of this method, the different types of nanoparticles used, and how they are used to deliver anti-AD agents such as Rivastigmine and EGCG.

II. ANATOMICAL AND PHYSIOLOGICAL BASIS OF NOSE-TO-BRAIN DRUG DELIVERY

The nasal passage is an intricate anatomical pathway that offers various routes for immediate delivery of drugs to the brain, avoiding the BBB.^[7, 9] The main routes of involvement in nasal to brain delivery are:

2.1. Olfactory Pathway

The olfactory neuroepithelium, located in the upper back part of the nasal cavity, contains Olfactory receptor neurons whose axons project directly to the olfactory bulb and then to other parts of the brain, i.e., hippocampus and entorhinal cortex (regions most severely impacted by AD).^[10] Medications delivered into this area can be delivered through:

- Intracellular (axonal) transport: Drugs may be internalized by the olfactory sensory neurons and delivered along their axons to the olfactory bulb and beyond. This route is especially applicable to nanoparticles and high-molecular-weight substances.^[11]
- Extracellular (paracellular) transport: Low-molecular-weight, hydrophilic molecules can pass through the tight junctions between olfactory epithelial cells into the submucosa and subsequently enter the CNS through the perineural space.^[9]

2.2. Trigeminal Pathway

The trigeminal nerve supplies the whole nasal cavity, with branches reaching up to the brainstem and other CNS structures.^[12] Drugs can be carried along these nerve tracts or through perineural routes, providing an alternative direct route into the brain, albeit typically less widespread than the olfactory route for direct targeting of brain parenchyma.^[13]

2.3. Systemic Circulation (Indirect Route)

Although the major benefit of nasal to brain delivery is avoiding systemic circulation, a portion of the drug still has the possibility of being absorbed into the systemic circulation via the highly vascularized respiratory epithelium in the lower nasal cavity. This component would then be subjected to the difficulties of BBB penetration, the same as oral or intravenous delivery. Nevertheless, with optimized delivery and deposition in the olfactory area, systemic absorption can be minimized and hence peripheral side effects reduced.^[6]

III. ADVANTAGES AND DISADVANTAGES OF NASAL - BRAIN DRUG DELIVERY

The nasal to brain pathway presents several strong advantages over the treatment of AD:

3.1. Advantages

- Non-invasiveness and Compliance of the Patient: Intranasal drug delivery is easy, convenient, and patient-friendly, enhancing compliance over injectable routes.^[14]
- BBB Bypassing: Direct brain delivery obviates the significant barrier offered by the BBB, enabling potential drug candidates to access therapeutic levels in the CNS.^[5]
- First-Pass Metabolism Avoidance: Drugs avoid hepatic first-pass metabolism, achieving increased bioavailability and less degradation as compared to oral delivery.^[15]

Quick Onset of Action: Direct entry into the brain may cause a faster onset of action, important for severe conditions or where a fast neurological impact is desired.^[16]

- Lower Systemic Side Effects: By limiting systemic exposure, N2B delivery can lower off-target effects and toxicity due to elevated systemic drug levels.^[6]
- Targeted Delivery: The proximity of anatomy permits more localized delivery to given brain areas implicated in AD, e.g., the olfactory bulb, hippocampus, and cortex, which might enhance the efficacy of drugs.^[10]

3.2. Challenges

Nasal to brain delivery is not without challenges despite its benefits:

- Mucociliary Clearance: The nasal mucosa contains an effective mucociliary clearance system that quickly washes away foreign substances, including drug products, to restrict their dwelling time and absorption.^[17]
- Enzymatic Degradation: Enzymes in the nasal mucosa (e.g., peptidases, proteases) can break down drugs, especially peptides and proteins, before they enter the brain.^[18]
- Limited Absorption Area: The olfactory area, which presents the most direct route to the brain, is very small (2-10 cm²) relative to the overall nasal surface area.^[9]
- Low Permeability of Nasal Mucosa: The nasal epithelium's tight junctions and other efflux

transporters (e.g., P-glycoprotein) may limit drug permeation.^[19]

- **Formulation Requirements:** Formulations should be specially optimized for nasal delivery based on pH, viscosity, osmolality, and deposition patterns to allow effective delivery with no irritation or damage to the nasal mucosa.^[20]
- **Dose Reproducibility:** Reproducible and consistent administration of the drug to the olfactory area may be difficult owing to anatomical differences in the nasal passages as well as breathing habits among individuals.^[21]

IV. NANOPARTICLES: A GAME CHANGER FOR NOSE-TO-BRAIN DELIVERY

Nanoparticles (NPs) are colloidal systems with sizes usually falling in the range from 1 to 1000 nm (although typically 10-200 nm are optimum for nasal to brain delivery). Due to their novel physicochemical characteristics, they are perfect carriers for alleviating the challenge of N2B drug delivery to the brain in AD therapy.

4.1. Why Nanoparticles are best for Nose to Brain delivery

- **Increased Drug Solubilization:** NPs can encapsulate hydrophobic as well as hydrophilic drugs, enhancing the solubilization and stability of poorly soluble anti-AD drugs.^[22]
- **Prevention from Degradation:** Nanoparticle entrapment saves drugs from enzymatic degradation in the nasal passage and systemic circulation.^[23]
- **Greater Mucosal Permeation:** Due to their small size, NPs can interact better with the nasal mucosa and, thus, potentially cross tight junctions using paracellular or transcytosis routes, or directly through contact with nerve endings.^[24]
- **Extended Residence Time:** Some NP systems, particularly those mucoadhesive (e.g., chitosan), can extend residence time on the nasal mucosa, which can maximize absorption.^[25]
- **Targeted Delivery:** NPs may be surface functionalized with targeting ligands to bind to particular receptors on olfactory neurons or brain endothelial cells (for indirect BBB transport if required), enabling directed uptake and buildup in target regions of the brain.^[26]
- **Controlled and Sustained Release:** NPs can be designed to deliver sustained release of the

entrapped drug, sustaining therapeutic levels over an extended time and decreasing dosing frequency.^[27]

4.2. Mechanisms of Nanoparticle Transport to the Brain

NPs enter the brain via the olfactory and trigeminal nerves through several postulated.

- **Intranasal axonal transport:** NPs are taken up by olfactory or trigeminal neurons and transported along their axons into the brain.
- **Perineural transport:** NPs move through the perineural spaces surrounding the olfactory and trigeminal nerves into the CNS.
- **Transcellular transport:** NPs travel directly across the nasal epithelial cells through endocytosis/transcytosis.
- **Paracellular transport:** Small NPs may traverse tight junctions between epithelial cells, particularly if they are co-formulated with permeation enhancers
- **Receptor-mediated endocytosis:** When NPs are surface-functionalized with ligands (e.g., transferrin, lactoferrin, insulin), they can be recognized by specific receptors on the nasal epithelial cells or brain endothelial cells to be internalized and transported^[28]

4.3. Nanoparticle types for nasal to brain AD delivery

Nanoparticle systems of varying types have been investigated for N2B delivery in AD, and each has its strengths:

- **Polymeric Nanoparticles:** Polymers that are biocompatible and biodegradable (e.g., PEGylated polymers, PLGA, PLA, chitosan) are particularly versatile owing to ease in drug loading, controlled release, and surface modification. Chitosan's mucoadhesive and cationic nature make it a favorite for delivery through the nose.^[29]
- **Lipid-based Nanoparticles:** These include liposomes, solid lipid nanoparticles (SLNs), and nanostructured lipid carriers (NLCs). They offer good biocompatibility, high drug encapsulation efficiency for lipophilic drugs, and can enhance permeation across biological membranes.
- **Inorganic Nanoparticles:** While less common for direct N2B delivery of small molecules, materials like gold or silver nanoparticles are explored for diagnostics or as carriers for large biologics, though toxicity is a concern.^[30]

- Nanogels: Cross-linked polymeric networks that swell in aqueous environments, providing high drug loading and controlled release. Mucoadhesivenanogels have the potential to enhance nasal retention.
- Nanoemulsions and Nanosuspensions: Liquid dispersions of ultrafine drug particles or oil droplets with good stability and possibly improved absorption.

V. APPLICATION OF NANOPARTICLES IN DELIVERING ANTI-ALZHEIMER'S AGENTS

Nanoparticles have been the focus of intense exploration for the delivery of different anti-AD drugs through the nasal to brain route to enhance their brain bioavailability and therapeutic effectiveness.

5.1. Rivastigmine Loaded Nanoparticles

Rivastigmine is an acetylcholinesterase inhibitor (AChEI) commonly used for mild to moderate AD symptomatic treatment.⁴⁰ Its oral route, however, is plagued by a short half-life, limited brain bioavailability following extensive first-pass metabolism, and gastrointestinal side effects.^[31] Delivery of Rivastigmine nanoparticles via N2B is extremely promising.

- Chitosan Nanoparticles: Chitosan nanoparticle-based nanoparticles are extremely desirable for the delivery of Rivastigmine. Their mucoadhesive characteristics enhance residence time in the nose, and their cationic character may allow binding to the negatively charged nasal mucosa. Rivastigmine-loaded chitosan nanoparticles have been demonstrated in studies to attain brain concentrations of the drug higher than intravenous or oral delivery, while bringing about better cognitive function in animal models.^[32, 33] Careful control of particle size and zeta potential is important to ensure the best brain targeting. For instance, cationic Rivastigmine-loaded nanostructured lipid carriers (NLCs) integrated in an in-situ gelation system showed improved brain delivery and pharmacodynamics in the models of AD.
- Other Polymeric/Lipid NPs: Scientists have also studied PLGA nanoparticles and lipid-polymer hybrid nanoparticles for Rivastigmine. These systems have exhibited enhanced encapsulation efficiency, extended release profiles, and enhanced brain targeting, overcoming the drawbacks of systemic

delivery.^[34, 35] Surface modification of these nanoparticles (e.g., with PEG or targeting ligands) increases their circulation time and brain uptake further.

5.2. EGCG-Loaded Nanoparticles

Epigallocatechin gallate (EGCG), one of the primary polyphenols of green tea, has attracted significant interest for its multifaceted neuroprotective activities, including antioxidant, anti-inflammatory, anti-amyloid, and metal-chelating activities. EGCG is plagued, however, by low bioavailability, instability, and poor BBB permeability upon oral intake. Nanoparticle-mediated nasal to brain delivery can overcome these issues.^[36]

- Chitosan Nanoparticles: EGCG-loaded chitosan nanoparticles present a very promising way to enhance their brain delivery. Chitosan may preserve EGCG from degradation, improve its penetration through the nasal mucosa, and promote its transfer to the brain. Evidence has shown that intranasally delivered EGCG-loaded chitosan nanoparticles may result in increased levels of EGCG in the brain, decreased oxidative stress, and improved cognitive function in AD animal models. The synergistic action of EGCG's neuroprotection administered directly into the brain using mucoadhesive nanoparticles may be therapeutically significant.^[37]
- Other Nanocarriers: Lipid nanocarriers, such as solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs), have also been investigated for the delivery of EGCG through the intranasal route. These systems boost the stability of EGCG, enhance its solubility, and enable its brain uptake, showing promising neuroprotective activities in preclinical models. Liposomes and polymeric micelles have also demonstrated promise for encapsulating EGCG and transporting it into the brain, taking advantage of their capacity to preserve the compound and aid its transport across biological barriers.^[38]

5.3. Combination Therapy

The multifactorial nature of AD pathology makes it likely that combination therapies addressing more than one pathway will prove more successful than single-agent treatment.^[39] Nasal to brain delivery of Rivastigmine and EGCG using nanoparticles together is an especially enticing approach. Rivastigmine targets the cholinergic

deficiency, whereas EGCG addresses oxidative stress, inflammation, and amyloid pathology. Nanoparticles may facilitate the co-encapsulation of both medications and their simultaneous delivery to the brain, with a possible synergistic therapeutic effect enhancement. Optimization of such dual-loaded nanoparticle formulations for nasal to brain delivery is an area that should be addressed in future studies.^[40]

VI. RECENT ADVANCES AND FUTURE DIRECTIONS

The research in the area of N2B nanoparticle delivery for AD is progressing very quickly with some very promising advances:

- **Surface Functionalization:** In addition to mucoadhesion, NPs are being designed with several targeting ligands (e.g., transferrin receptor antibodies, lactoferrin, ApoE, angiopep-2 peptides) to utilize receptor-mediated transcytosis at the BBB or direct neuronal uptake, adding to brain specificity.
- **Smart Nanoparticles:** Construction of stimulus-responsive nanoparticles (e.g., pH-sensitive, enzyme-sensitive) capable of releasing their contents in a controlled fashion at the pathological location within the brain is picking up momentum.^[41]
- **In-situ Gelling Formulations:** The addition of nanoparticles to in-situ gelling systems for nasal delivery increases nasal residence time, with more time for nanoparticles to engage with the nasal mucosa and be transferred to the brain.
- **Nasal Device Technology:** Improvements in nasal spray and nebulizer devices are enhancing the accurate deposition of nanoparticle formulations in the olfactory area, resulting in more predictable and efficient brain delivery.
- **Clinical Translation:** Although the majority of studies are preclinical, the clinical efficacy of intranasal insulin (albeit non-nanoparticle-based) has given a high level of justification to the nasal-to-brain approach. There is continued interest in transitioning promising nanoparticle-based intranasal formulations of anti-AD drugs into human clinical trials, though an important barrier still lies ahead in proving strong efficacy and safety in humans.
- **Imaging and Biomarkers:** Development of more sensitive biomarkers for AD and sophisticated neuroimaging will be important for tracking the in vivo brain targeting of

intranasally administered nanoparticles and their therapeutic outcome.^[42]

VII. CONCLUSION

The nasal-to-brain targeted drug delivery approach, especially when coupled with nanotechnology, promises a paradigm shift in the management of Alzheimer's disease. By leveraging the direct anatomical connections between the nasal cavity and the brain, this non-invasive pathway efficiently bypasses the powerful blood-brain barrier - a significant challenge to conventional systemic therapies. Nanoparticles, due to their advantageous physicochemical characteristics, offer an ideal platform to overcome the drawbacks of the nasal pathway, including short mucociliary clearance and enzymatic degradation, while improving drug solubilization, stability, and targeted delivery to the CNS.

Preclinical trials with Rivastigmine and EGCG-loaded nanoparticles have shown encouraging outcomes, exhibiting increased brain bioavailability, lowered neuroinflammation, decreased amyloid burden, and improved cognitive function in animal models. The ability to co-deliver several anti-AD agents further establishes the versatility of this technique. Although substantial obstacles still exist, especially in translating these results into effective clinical outcomes, persistent developments in nanoparticle design, surface functionalization, and nasal delivery devices are moving us even closer to the full therapeutic potential of nasal-to-brain drug delivery for Alzheimer's disease. Ongoing robust research, including careful safety evaluations and properly designed clinical trials, will be imperative to advance these promising nanoparticle-based treatments from bench to bedside, providing new hope for millions suffering from this terrible neurodegenerative disorder.

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