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Cerebro-spinal fluid (CSF) targeting through intra-nasal route by using nanotechnology emerging as a powerful technique for different brain diseases

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Abstract

The human brain, a highly sensitive organ, functions as the body's central control unit and is naturally protected to preserve neurological health. The Blood-Brain Barrier (BBB) presents a significant challenge to the delivery of drugs into the brain. Oral medications face low bioavailability and restricted brain exposure, compounded by rapid metabolism, elimination, unwanted side effects, and the necessity for high doses. These factors lead to inconvenience for patients and substantial costs for patients, their families, and society. The primary obstacle to effective brain penetration of these compounds is the BBB, which safeguards the brain from xenobiotics. Consequently, treating brain diseases such as Alzheimer's, Parkinson's, dementia, mood disorders, and bacterial infections is more complex. The intranasal route of administration offers a promising alternative for bypassing the BBB in brain drug delivery, facilitating drug transport from the nasal cavity to the brain via the olfactory and trigeminal nerves.

Keywords: Blood-Brain Barrier, Alzheimer's, intra-nasal, olfactory nerve, xenobiotics.

1. Introduction

The nasal route is a non-invasive method for administering active pharmaceutical ingredients intended for local, systemic, and central nervous system (CNS) effects. Intranasal drug delivery, a conventional approach for targeting the brain to treat neurological disorders, leverages this route for efficient drug administration (Hondadakatti et al., 2021). In recent decades, nasal drug delivery has emerged as a promising method for introducing drugs into the systemic circulation. This efficacy is attributed to the unique anatomy and physiology of the nasal passage, which features a large surface area, a highly vascularized epithelium, an endothelial membrane with pores, and the ability to bypass first-pass metabolism (Swamy & Abbas, 2012). Direct drug administration to the central nervous system (CNS) facilitates targeted therapeutic action. The blood-brain barrier significantly impedes the efficacy of most drugs, including antibiotics, neuropeptides, CNS stimulants, and antineoplastic agents. Recent studies indicate that nearly 100% of large-molecule drugs and 98% of small-molecule drugs are unable to cross the blood-brain barrier.(Mehmood et al., 2015). To facilitate direct delivery of drug molecules into the brain, the advanced nanoparticle drug delivery system (NDDS) is employed. This method has proven highly effective against several central nervous system (CNS) disorders (Mehmood et al., 2015). Using nano-vectors, drug delivery to the brain primarily occurs through two mechanisms: (i) via the nasal cavity, utilizing the olfactory and trigeminal nerve pathways, and (ii) through the spaces between cells (paracellular transport) or across the basal epithelial cells (transcellular transport). Lipophilic molecules are more suited for transcellular transport, while hydrophilic molecules prefer the paracellular route (Sorrentino et al., 2020).

2. Cellular structure of the human nasal cavity

Understanding nasal drug absorption and the pathways molecules must traverse to reach the brain necessitates a thorough knowledge of the nasal cavity's function and anatomical and cellular structure. The nose, responsible for various physiological functions such as respiration, consists of two symmetric cavities separated by the septum, which is aligned along the midsagittal plane (Crowe et al., 2018). The palatine bone separates the nasal cavity from the oral cavity. Both cavities

are lined with a mucosal layer, and the combined surface area of the nasal cavities is approximately 150–160 cm²(Lochhead & Thorne, 2012)(Mygind & Änggård, 1984)(Mygind & Dahl, 1998).

The trigeminal nerve transmits sensory information from the nasal cavity, oral cavity, eyelids, and cornea to the central nervous system through its ophthalmic (V1), maxillary (V2), and mandibular (V3) divisions (Clerico et al., 2003; Gray, 1978). Branches stemming from the ophthalmic division of the trigeminal nerve supply innervation to the dorsal nasal mucosa and the anterior region of the nose, while branches from the maxillary division innervate the lateral walls of the nasal mucosa. The mandibular division of the trigeminal nerve extends to the lower jaw and teeth, without direct neural connections to the nasal cavity. These three divisions of the trigeminal nerve converge at the trigeminal ganglion and proceed centrally, entering the brain at the level of the pons, ultimately terminating in the spinal trigeminal nuclei in the brainstem (Dhuria et al., 2010).

3. Advantages of Nasal Delivery

S. No.	Advantages	Factors
1.	Patient compliance improved	○ Trained person not required ○ Needle-free (painless) ○ Non-invasive ○ Self-medication
2.	Low dose required	▪ Avoids first pass metabolism ▪ Avoids GIT degradation ▪ Lower side effects ▪ High bioavailability
3.	Rapid onset of pharmacological action	○ Highly vascularized mucosa ○ Large mucosal surface area
4.	Avoid harsh environment	▪ Less chemical and enzymatic degradation.

Figure 1 Advantages of Nasal Delivery (Kaur et al., 2016)

4. Barriers to Nasal Drug Delivery

The scientific community continues to explore the full potential of the nasal route for drug delivery, leading to ongoing advancements and evolving theories. The preceding sections aimed to provide a foundational understanding of nasal drug delivery, highlighting that the challenges associated with nasal delivery vary depending on the intended objective, whether local, systemic, nose-to-brain, or vaccine delivery. Subsequent sections will address the specific challenges associated with each objective of nasal delivery. (Kumar et al., 2016).

i. **Low bioavailability:** polar drug molecules show lower bioavailability, for low molecular weight drugs it is 10% and for peptides, it would be less than 1%.
ii. **Mucociliary clearance:** due to mucociliary clearance, drugs administered via nasal routes have faster clearance in the nasal cavity.
iii. **Enzymatic degradation:** another factor for the lower bioavailability of proteins and peptides through nasal mucosa is the degradation of drug moiety by enzymes in the nasal cavity. (Swamy & Abbas, 2012)

iv. **Challenges and barriers to Nose to Brain peptide delivery:** In the early stages of 1937, Faber made the inaugural observation regarding the potential of a direct passage from the nose to the brain by introducing a dye into the nasal passages of rabbits. However, it wasn't until the late 1990s that the increasing interest in brain delivery spurred the scientific community to commence exploration of this alternative route. Mechanistic studies conducted in animal models have demonstrated that nasal-to-brain drug transport occurs through either extracellular or transcellular transport mechanisms along the olfactory epithelium or via the trigeminal nerve following drug administration into the nasal cavity. Despite the growing interest, the mechanisms underlying this direct nose-tobrain (N-to-B) pathway have not yet been fully elucidated (Samaridou & Alonso, 2018).

5. Barriers to Brain Targeting

The brain, being housed within the protective confines of the skull, poses a challenge for systemic drug delivery. One apparent route for delivery would be through the cardiovascular

system. With a high blood flow to the brain, approximately 750-1000 mL/min (equating to around 15% of total cardiac output), accessing it presents a unique challenge. Hence, it might be anticipated that such a high perfusion rate would adequately facilitate drug delivery into the brain. However, unlike in many other organs, the cerebral blood compartment does not freely communicate via diffusion with the interstitium of the brain. Barrier layers are established at three interfaces: the blood vessels of the brain (blood-brain barrier), the choroid plexus (blood-cerebrospinal fluid barrier), and the arachnoid layer of the meninges (blood-arachnoid layer) (Ghadiri et al., 2019; Jadhav et al., 2014).

A. **Blood Brain Barrier [BBB]:** The blood-brain barrier (BBB) serves as a distinctive partition that isolates the brain from the rest of the circulating blood. This crucial barrier safeguards the brain by inhibiting the entry of harmful toxins. Unlike the capillaries in other bodily organs, the blood capillaries within the BBB possess unique structural characteristics. While capillaries in other tissues allow for the free exchange of substances across cells, brain capillaries, characterized by tight junctions, restrict the movement of substances into the brain.

B. **Blood–Cerebrospinal Fluid Barrier [BCSFB]:** Another barrier between the brain and the circulating blood, the blood-cerebrospinal fluid barrier, presents limitations for drug delivery due to its relatively smaller surface area (approximately 5000 times less) compared to the blood-brain barrier (BBB).

   The blood-cerebrospinal fluid (CSF) barrier exists at various sites, including the choroid plexus and other circumventricular organs (CVOs). Choroid plexuses consist of networks of capillaries, which are microscopic blood vessels located in the walls of the two lateral ventricles (Pathol et. al 2001). The capillaries are enveloped by ependymal cells, which produce cerebrospinal fluid (CSF) from blood plasma through a combination of filtration and secretion. Due to the tight junctions between ependymal cells, substances entering the CSF from choroid capillaries cannot permeate between these cells; instead, they must traverse through the ependymal cells. This blood-cerebrospinal fluid barrier selectively allows certain substances to enter the fluid while excluding others, thereby shielding the brain and spinal cord from potentially harmful substances in the blood. Given that CSF can

exchange molecules with the interstitial fluid of the brain, the passage of blood-borne molecules into the CSF is meticulously regulated by the blood-CSF barrier. Once CSF is produced, it undergoes rapid movement via bulk flow over the cerebral convexities and is subsequently reabsorbed into the general circulation at the upper regions of the brain through the arachnoid villi. (Tiwari & Amiji, 2006)

C. **Blood-Tumor Barrier:** likewise, the blood-brain barrier and the blood-tumor barrier are similar and are located among tumor cells and micro-vessels of the brain. Targeting tumors in CNS is quite difficult because the occurrence of the BBB has clinical significance in the microvasculature of CNS tumors.

6. Approaches for targeting drugs to Brain

i. **Lipid nanoparticles:** Lipid nanoparticles (NPs) serve as effective vehicles for drug delivery systems. Compared to other colloidal carrier systems, they offer several advantages, such as drug entrapment, controlled drug release, enhanced physical and chemical stability, and efficient incorporation of lipophilic drugs into the lipid core of solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs). (Hondadakatti et al., 2021). Sorrentino et al. developed and optimized biopolymerbased nanoparticles for nose-to-brain delivery of serotonin to treat depressive diseases. The materials included mucoadhesive biopolymers, serotonin, and waterstable multi-walled carbon nanotubes functionalized with alginate. The method utilized ultrasonic and shear forces to break down the polymer bulk, followed by characterization using SEM, EDS, Raman spectroscopy, and ATR-FTIR. Successful production of monodisperse nanoparticles with diameters ranging from 30-70 nm was achieved, suitable for efficient drug delivery to the brain via the paracellular pathway (Sorrentino et al., 2020). Fatough et al. aimed to enhance brain delivery of agomelatine through intranasal administration using solid lipid nanoparticles (SLNs). The study screened different lipid types and concentrations, followed by a full factorial design to optimize the SLN formulation. The optimized SLN formulation, SLN-14, exhibited promising characteristics for enhanced drug delivery, with a particle size of 167.70 nm, negative

zeta potential, high encapsulation efficiency, and sustained release profiles (Fatouh et al., 2017). Seju et al. developed olanzapineloaded PLGA nanoparticles for nose-to-brain delivery to improve therapeutic outcomes in central nervous system disorders. Physicochemical properties and efficacy of the nanoparticles were evaluated using zeta potential measurement, MTDSC, X-ray diffractometry, and in vivo studies on white albino rats. The optimized formulation demonstrated high drug entrapment efficiency, small particle size, and stability, indicating potential for effective brain targeting (Seju et al., 2011). Rassu et al. devised a nose-to-brain delivery system for BACE1 siRNA using solid lipid nanoparticles (SLNs) for potential Alzheimer's therapy. Both uncoated and chitosan-coated SLNs with RVG-9R cell-penetrating peptide were prepared using a w/o/w double-emulsion technique. Results showed successful complex formation, low polydispersity, and altered zeta potential upon chitosan coating, suggesting a promising strategy for efficient siRNA delivery to the brain (Rassu et al., 2017). Zhang et al. investigated the efficacy of intranasal nanoparticles loaded with basic fibroblast growth factor (bFGF) for brain delivery in treating Alzheimer's disease.

Nanoparticles were prepared using the emulsion/solvent evaporation method, characterized for size and charge, and evaluated for drug release profiles. The nanoparticles exhibited a mean size of around 100 nm, high encapsulation efficiency for bFGF, and sustained release profiles in vitro, indicating their potential for brain delivery in Alzheimer's disease treatment (Zhang et al., 2014).

ii. **Polymeric micelles:** Polymeric micelles typically have a molecule size ranging from 10–100 nm, with water-insoluble drugs assembled in the core. These structures contribute to the enhanced bioavailability of the drug. Additionally, the shell formed by the micelle prohibits the interaction of drugs with non-target cells and serum proteins. (Hondadakatti et al., 2021).

iii. **Dendrimers:** Nanosized macromolecules referred to as dendrimers are commonly utilized as drug delivery systems due to their hyper-branched spherical structure. Unlike traditionally employed polymeric nano-vehicles, dendrimers possess a welldefined chemical structure and monodisperse nature. This specificity in dendrimer structure

provides advantages for drug transportation through either electrostatic adsorption or covalent conjugation, thereby enhancing therapeutic efficacy. (Jadhav et al., 2014).

Katare et al. enhanced the delivery of the water-insoluble antipsychotic drug Haloperidol to the brain using a dendrimer-based formulation. Their methodology involved preparing the dendrimer-Haloperidol formulation and evaluating its receptor binding and in vivo behavioral responses in rats. Results demonstrated improved solubility of Haloperidol in the dendrimer core, efficient binding to dopamine D2 receptors, and enhanced brain targeting compared to the control formulation, indicating the potential of dendrimers for targeted drug delivery to the brain (Katare et al., 2015).

Rishi Sharma et al. assessed the efficacy of dendrimer-mediated delivery of sinomenine in targeting neuroinflammation in traumatic brain injury. Their approach involved evaluating anti-inflammatory and antioxidant effects using RAW264.7 cells, assessing NF-κB translocation, and conducting real-time PCR analysis of inflammatory cytokines. Results indicated that D-Sino effectively inhibited proinflammatory cytokine secretion and NF-κB translocation, suggesting its potential for treating acute neuroinflammation in traumatic brain injury (R. Sharma et al., 2020).

Zarebkohan et al. synthesized and characterized a PAMAM dendrimer nanocarrier functionalized with SRL peptide for targeted gene delivery to the brain. Their materials and methods included the use of plasmid pEGFP-N1, peptide SRL, PAMAM G4 dendrimer, and various chemicals purchased from reputable suppliers. Results revealed successful attachment of PEG and SRL to the dendrimer, with an attachment efficiency of 80%. Confocal microscopy demonstrated the intracellular distribution of nanoparticles in brain capillary endothelial cells, suggesting potential for targeted gene delivery (Zarebkohan et al., 2015).

Nitin Diwedi et al. evaluated the potential of different generations (3.0G, 4.0G, and 5.0G) of PPI dendrimers loaded with donepezil for olfactory drug delivery. Their materials included acrylonitrile, ethylenediamine, MPEG-5000, DCC, and Raney nickel. Synthesis involved double Michel addition reactions and heterogeneous hydrogenation. Results indicated that the PEGylated 5.0G dendrimer exhibited the highest stability, entrapment efficacy for donepezil, and successful nasal diffusion compared to lower generations, suggesting its potential for effective drug targeting and sustained release behavior (Dwivedi et al., 2018).

iv. Liposomes: Liposomes are capsules with aqueous compartments formed by lipid bilayer membranes, with sizes typically ranging from 0.05 to 0.5 micrometers. They are designed for encapsulating both hydrophilic and hydrophobic drugs, facilitating their co-transportation. Liposomes find extensive use in transporting various pharmacologically active agents, including antineoplastic drugs, genetic material, and chelating agents(Jadhav et al., 2014).

Tiwari et al. investigated the potential of nanocarriers for enhancing drug delivery to the central nervous system (CNS), utilizing various nanocarriers like liposomes and solid polymeric nanoparticles. Through in vitro and in vivo studies, they demonstrated that these nanocarriers effectively transported drugs across the bloodbrain barrier, leading to improved drug delivery to the CNS with sustained release characteristics and reduced toxicity to peripheral organs.

Asmari et al. optimized, prepared, and evaluated an intranasally administered liposomal formulation of donepezil for enhanced drug delivery. Their study showed improved drug bioavailability and brain uptake with the intranasal liposomal formulation compared to oral administration, suggesting its potential as a promising drug delivery system for Alzheimer's disease treatment (Al Asmari et al., 2016).

Arumugam et al. delivered rivastigmine to the brain via intranasal administration using liposomal carriers. Their stability studies demonstrated promising results over time,

and the liposomal formulation exhibited good stability and drug content retention (Al Asmari et al., 2016).

Yuwanda et al. investigated the potential of valproic acid (VPA) liposomes for enhanced delivery to the brain via the intranasal route. Their study showed improved drug levels and sustained release with VPA liposomes compared to the free drug, indicating the potential of VPA liposomes for enhanced brain delivery and sustained drug release (Jufri et al., 2022).

Migliore et al. compared the effectiveness of cationic liposomes versus aqueous solution formulations for delivering proteins to the brain via the intranasal route. They found that cationic liposomes enhanced brain transport and extended brain residence time compared to nonliposomal solutions, suggesting their potential for improved brain delivery of proteins (Migliore et al., 2010).

Kumar et al. explored the potential of nanotechnology-based delivery systems for efficient nasal drug delivery, utilizing various nanomaterials such as carbon nanotubes, chitosan, and PLGA. Their study highlighted the successful formulation and application of nanotechnology in nasal drug delivery, emphasizing its potential for enhanced therapeutic outcomes (Kumar et al., 2016).

v. **Prodrug approach:** Typically, a prodrug is referred to as a promoiety. These are chemical substances that, before initiating the therapeutic action for which they are intended, undergo biotransformation. Following the crossing of membrane and enzymatic barriers, these compounds undergo enzymatic changes to release the therapeutically active substances.(Jadhav et al., 2014; M.Alagusundaram et al., 2022).

vi. **Microemulsion:** Lian Li et al. reported the rapid onset intranasal delivery of diazepam using an ethyl-laurate-based microemulsion. At a dose of 2 mg/kg, the maximum drug plasma concentration was achieved within 2-3 minutes, and the bioavailability (0-2 hours) after nasal spray compared with intravenous injection was approximately 50%.

These findings suggest that this approach may be beneficial during the emergency treatment of status epilepticus.

vii. **Nanocarriers:** While it has been widely acknowledged that particle size plays a crucial role in the ability of nanocarriers to traverse mucus barriers and epithelial layers efficiently, recent work by Ahmad et al. provided compelling evidence of this phenomenon. The authors investigated the biodistribution of nanoemulsions of varying sizes following intranasal administration in rats using fluorescence imaging. They concluded that nanocarriers with a particle size around 100 nm could be transported along the olfactory or trigeminal route, whereas nanoemulsions with larger droplet sizes were unable to follow the olfactory pathway. Additionally, several studies have reported the effectiveness of nanocarriers with sizes up to 200 nm in facilitating molecular transport in animal models. These findings align with morphological studies of the olfactory epithelium in different species, which have revealed that the average diameter of olfactory axons is approximately 200 nm, with many axons having diameters even less than 100 nm. In humans, this diameter range extends from 100 nm up to 700 nm (Samaridou & Alonso, 2018).

viii. **Solutions:** The physicochemical properties of a drug and its potency are crucial factors when formulating a solution for nasal delivery. For small lipophilic molecules, passive diffusion plays an important role in nose-to-brain delivery. The size of molecules intended for delivery via the nasal route to the brain is also an important factor. For example, a comparison of the absorption of dopamine (Molecular Weight 153 Da) to that of nerve growth factor (NGF) (Molecular Weight 27 kDa) revealed that brain concentrations were five-fold higher for the small molecule dopamine compared to the larger protein NGF when dosed at the same concentration.

On the contrary, larger molecules typically require more time to be transported from the nasal cavity to the brain. Following intranasal administration, brain concentrations were higher for small lipophilic drugs, often showing greater improvement in the brain compared to other routes of administration. Wang and colleagues studied raltitrexed, a hydrophilic small molecule with a logP of 0.98, for brain levels following intranasal

and intravenous administration. They demonstrated a 54–121 fold increase in the area under the curve (AUC) in the brain (depending on the section of the brain) after intranasal administration compared to the intravenous route in rats. This demonstrates that the molecular weight and lipophilicity of a drug significantly influence its efficiency in nose-to-brain delivery. Small, lipophilic drugs tend to have better brain penetration and higher concentrations following intranasal administration. In contrast, larger molecules require more time and may face more significant barriers to effective delivery (Wang et al., 2003).

ix. **Mucoadhesive agents:** Mucoadhesive and viscosity-increasing agents have been employed to prolong drug residence time in the nasal cavity, enhancing absorption. By augmenting the viscosity of the formulation with polymers like hydroxypropyl methylcellulose or polyvinyl alcohol, it becomes feasible to reduce mucociliary clearance. Mucoadhesive agents, such as pectin and chitosan studied by Charlton et al., effectively extended residence times at the olfactory epithelium. Additionally, it has been demonstrated that mucoadhesive and viscosity-increasing agents enhance bioavailability from nasal formulations designed for systemic delivery. To assess the impact of adding a mucoadhesive agent on drug absorption into the brain, Khan et al. (2009) compared brain concentrations of buspirone. They administered buspirone intravenously as a solution without chitosan or cyclodextrins, and intranasally as a solution with 1% chitosan and 5% hydroxypropyl β-cyclodextrin. The study revealed that the AUC in the brain was 2.5 times higher for buspirone in the mucoadhesive formulation compared to the intravenous solution, and twice as high as the buspirone solution when delivered intranasally. Additionally, cyclodextrins may have contributed to the increased brain concentration by enhancing the permeability of the drug through the tight junctions of the nasal epithelium (Khan et al.,2009).

x. **Nanoparticles (nanosuspensions, nanoformulations):** Nano suspension formulations are widely used across various routes of administration due to their ability to encapsulate drugs in polymeric carriers, offering benefits such as enhanced absorption, mucoadhesion, and increased stability. For instance, a nano suspension formulation of

donepezil, a cholinesterase inhibitor, has been developed to enhance brain exposure for the treatment of Alzheimer's disease (AD). Additionally, chitosan nanoparticles loaded with bromocriptine have been investigated in another study for their potential therapeutic application. These formulations represent innovative approaches to drug delivery, particularly for central nervous system disorders where crossing the blood-brain barrier efficiently is crucial for therapeutic efficacy (Md et al., 2014). Intranasally administered bromocriptine-loaded nanoparticles have demonstrated significantly higher brain area under the curve (AUC) values compared to intravenous administration of the nanoparticles, indicating enhanced drug delivery to the brain. Similar findings have been reported for other drugs such as lorazepam and rivastigmine, where nanoformulations have shown improved brain delivery compared to conventional routes. Additionally, pegylation and dendrimers are emerging nanotechnological approaches to enhance central nervous system drug delivery. These advancements in nanoparticle technology offer promising strategies for overcoming barriers to effective CNS drug delivery and improving therapeutic outcomes for various neurological disorders. The statement that pegylation may increase the cavity in the nasal cavity, as suggested by Kamiya et al., is intriguing. It's possible that Kamiya et al. propose this based on the concept that pegylation could modify the physicochemical properties of drugs, leading to changes in their interaction with the nasal mucosa. However, without further context or clarification from the source, it's difficult to fully understand the mechanism or rationale behind this claim. If Kamiya et al. provide experimental evidence or theoretical explanations to support this idea, it would be valuable to consider their findings in the context of nasal drug delivery research Kamiya et al. (2018).

xi. **Lipid based systems (micro emulsions, lipid based nanoparticles):** Microemulsions and solid lipid nanoparticles indeed offer promising avenues for enhancing drug delivery to the brain via the nasal route. The use of lipid components in these formulations can improve the solubility and permeability of hydrophobic drugs, facilitating their transport across biological membranes including the bloodbrain

barrier. Risperidone, formulated as solid lipid nanoparticles, exemplifies the potential of these lipid-based carriers for efficient nose-to-brain drug delivery. As reported in several articles, the application of solid lipid nanoparticles in direct nose-

to-brain drug delivery has garnered significant attention due to their ability to encapsulate drugs, protect them from degradation, and facilitate their transport to the brain tissue (Patel et al., 2011).

xii. **Co-administration with vasoconstrictors for improved delivery** That's a concise summary of the vascular supply to different regions of the nasal cavity. The differential blood supply between the olfactory and respiratory regions indeed has implications for drug delivery. Targeting the olfactory region can be advantageous for nose-to-brain delivery due to its relatively lower vascularity, potentially reducing systemic absorption and enhancing direct access to the olfactory nerve pathways for efficient drug transport into the brain. Khan et. al investigated the impact of phenylephrine, a vasoconstrictor used for nasal decongestion, on the brain-to-plasma AUC ratio when administering neuropeptides intranasally. They specifically examined brain concentrations after the nasal administration of hypocretin-1 and the dipeptide L-Tyr-D-Arg. The study found that phenylephrine significantly reduced the absorption of these drugs into the systemic circulation. Additionally, it increased the delivery of the drugs to the olfactory bulb. This suggests that using a vasoconstrictor can enhance the effectiveness of intranasal drug delivery to the brain by limiting systemic exposure and increasing the local concentration of the drug at the target site (Khan et al.,2009).

xiii. **Permeability enhancers:** The nasal epithelium can indeed serve as a rate-limiting barrier for the transport of drugs directly to the brain. To enhance drug delivery across this barrier, especially when targeting the systemic circulation, various permeation enhancers have been employed. These agents work by modifying the tight junctions between epithelial cells, thereby facilitating the passage of drugs through the nasal mucosa. Agents used to increase the permeability across a membrane are referred to as permeation enhancers. These enhancers are particularly valuable for improving drug delivery to the central nervous system (CNS) via the nasal route. The nasal epithelial

layer consists of tight junctions, which can impede the passage of therapeutic agents. Permeation enhancers that open these tight junctions can significantly improve the delivery of drugs to the brain (Erdő et al., 2018).

7. Intranasal application of different drugs for CNS indications

Numerous central nervous system (CNS) drugs encounter difficulty passing through the blood-brain barrier (BBB), and even when they successfully penetrate the brain, they may lead to adverse effects in peripheral tissues. (Wisniewski & Sadowski, 2008). These factors underscored the significance of discovering an alternative route of administration to directly deliver CNS drugs into the brain. This approach not only bypasses the blood-brain barrier (BBB) but also minimizes exposure to peripheral tissues, addressing concerns related to adverse effects. (Born et al., 2002),

In addition to factors such as first-pass metabolism, slow absorption, fast elimination, and plasma protein binding (Lindup and Orme, 1981), the route of administration for CNS-acting drugs is critical. Intranasal (IN) administration emerges as an alternative option compared to enteral or intravenous administration. Schiöth et al. (2012) reported that insulin-like growth factor 1 (IGF-1) exhibited significantly higher CNS exposure when administered intranasally compared to IV dosing. (Schiöth et al., 2012).

a.) **Learning and memory, neurodegenerative diseases:** Serexendin is an agonist of the glucagon-like peptide-1 (GLP-1) receptor, owing to its homology to a conserved domain in the glucagon/GLP-1 family. It is known to facilitate learning and has been demonstrated to decrease the occurrence of kainic acid-induced apoptosis in mouse models following intranasal (IN) administration. (During et al., 2003). The radioactive compound can be detected in the lymph nodes, blood, and olfactory bulb, indicating efficient uptake through the nose-to-brain route, in addition to the nose-toblood-to-brain path. Intranasal (IN) administration of NAP, an eight amino acid peptide (sequence: NAPVSIPQ) derived from activity-dependent neuroprotective protein (ADNP), has been shown to improve memory function in both normal and cognitively impaired rats. It also decreased anxiety in aged mice. (Gozes et al., 2000)(Alcalay et al., 2004). Gozes et al. demonstrated through reversed phase-HPLC that H-labeled NAP

reaches the brain unchanged within 30 minutes of administration. By the 60-minute mark, it reaches its maximum concentration in the brain cortex. (Gozes et al., 2000). In Alzheimer's disease (AD) models, chronic administration of [NAP] improved spatial learning and memory, increased soluble tau levels, and decreased neurofibrillary tangles in tauopathy. (Shiryaev et al., 2009). In a mouse model of schizophrenia, intranasal administration of NAP decreased hyperactivity and protected visual memory. (Gozes, 2011). Another study demonstrated that intranasal administration of NAP reduces oxidative stress in rats subjected to chronic hypoxia. (N. K. Sharma et al., 2011). However, the exact route of NAP was not detailed in these publications; only that NAP reached a sufficient concentration in the brain to exert its effects.

b.) **Eating regulation, obesity:** Although the blood-brain barrier (BBB) has the capability to transport leptin into the central nervous system (CNS) from the blood, this transport is impaired during obesity. (Banks et al., 1999), Intranasal delivery of leptin into the central nervous system (CNS) presents a potential strategy to regulate feeding behavior. A pharmacokinetic study of intranasally administered radioactive leptin showed that more than 80% was delivered unchanged into the brain within 30 minutes, with the highest levels observed in the hypothalamus. (Fliedner et al., 2006) In contrast, after intravenous administration, 125I-leptin was detected in a brain/serum ratio of a little less than 20%. (Hsuchou et al., 2013). Intranasal administration of leptin has also been shown to delay the onset of pentylenetetrazole-induced generalized convulsive seizures in mice. (Xu et al., 2008).

c.) **Auto-inflammatory diseases:** The anti-inflammatory cytokine interferon-beta-1b (IFN-β1b) was investigated as a non-invasive treatment for multiple sclerosis when administered intranasally. (Ross et al., 2004)(“Dale E. McFarlin Lecture,” 2004). At similar blood levels, intravenous IFN-β1b exhibited lower brain concentration compared to intranasal administration (Ross et al., 2004). Autoimmune responses to low-density lipoproteins (LDL) contribute to the development of atherosclerosis. Studies have shown that immunization with LDL can induce proatherogenic responses, similar to those observed with intranasal administration of apolipoprotein B-100

(apoB100) fused to the B subunit of cholera toxin. The treatment induced a protective mucosal immune response in a mouse model by attenuating atherosclerosis and inducing regulatory Tr1 cells that inhibit T effector responses to apoB-100.

d.) Antibodies: Antibodies demonstrate limited penetration into the brain when delivered peripherally. (Banks, 2004). One diagnostic indicator of meningitis is the presence of antibodies in the cerebrospinal fluid (CSF). Intranasal (IN) treatment with 22C4 singlechain variable fragment (scFv) antibodies resulted in a reduction of cerebral amyloid angiopathy and plaque pathology. Moreover, the single-chain Fv antibody was observed to bind to amyloid plaques in the brains of these mice. IN delivery of full-length antibodies against glutamate has led to anti-amnesic effects in rats previously injected with an amyloid beta (Aβ) fragment (Aβ25–35) into the nucleus basalis of Meynert. IN administration of the same antibody also improved retention of the conditioned passive avoidance response in rats with ischemic injury of the prefrontal cortex. However, neither study examined antibody pharmacokinetics within the brain. (Gorbatovet al., 2010;

Romanova et al., 2010)

d.) Gene vectors tumors and stem cell therapies: Intranasal (IN) administration of gene vectors could serve as a solution to bypass the blockade of the blood-brain barrier (BBB) and deliver therapeutic transgenes to the brain. (Lochhead and Thorne, 2012). For instance, a growth-compromised herpes simplex virus type 2 mutant ΔRR encoding the anti-apoptotic gene ICP10PK has been effectively delivered to the brain via the intranasal (IN) route. This delivery method prevented kainic acid-induced seizures, neuronal loss, and inflammation in both mice and rats. There was also a study to investigate whether a brain tumor could be targeted with the telomerase inhibitor GRN163. The results demonstrated successful delivery of the drug to the tumor cells without significant accumulation either in healthy brain cells or in the body. Stem cells represent potential treatment options for many diseases due to their ability to replace dead cells or deliver trophic factors to damaged areas. Intranasally administered mesenchymal stem cells (MSCs) have been utilized to treat ischemic brain damage in neonatal mice.

Mesenchymal stem cells (MSCs) stimulate endogenous cerebral repair by up-regulating repair-promoting factors in the ischemic brain. Intranasal MSC treatment also showed promise in the treatment of subarachnoid hemorrhage in a rat model (Erdő et al., 2018).

8. Conclusion

In summary, an analysis of the available literature has revealed that brain targeting via nasal drug delivery is an attractive and promising approach for treating neurological disorders. The blood-brain barrier (BBB) significantly limits the effectiveness of many treatments for neurological conditions, making CNS drug delivery particularly challenging. Intranasal drug delivery offers a novel method for delivering drugs directly to the brain, bypassing the BBB and increasing systemic drug exposure and bioavailability.

This method leverages various endogenous transporter mechanisms, including receptormediated transport and efflux pump-mediated transport, to facilitate drug penetration across the BBB.

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