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A review on Intranasal Drug Delivery System for Brain Targeting

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ABSTRACT: There are many challenges associated with both acute and long-term pharmaceutical therapy for different neurodegenerative and psychiatric diseases. Oral drugs come with a lot of drawbacks, including high dose needs, quick metabolism, rapid elimination, limited brain exposure and bioavailability, unpleasant side effects, and expensive expenses to the patient, their family, and society. The chemicals' limited brain penetration may be explained by the fact that they need to pass the blood-brain barrier, which protects the brain from xenobiotics. Intranasal drug delivery is one of the most promising ways to get beyond the blood-brain barrier, minimize the medication's systemic adverse effects, and use lower concentrations. Furthermore, nasal drug delivery usually yields a greater brain exposure at same doses, less side effects, and a better bioavailability when compared to oral drug delivery. The primary objective of this paper is to provide an overview of the intra nasal drug delivery system, with their limitations as well as highlighting the main advantages and disadvantages of this delivery method for CNS drugs targeting. In this paper the authors describe methods to enhance nasal drug delivery through the nasal epithelial route and also elaborate *in vitro, ex vivo*, and in *vivo models* for studying intranasal drug delivery, which are based on the most recent research in the area.

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INTRODUCTION:

Interest in intranasal medication delivery has grown since the 1980s. A non-invasive method of administering active medicinal components for local, systemic, and central nervous system activity is via the nasal channel. Despite the nasal epithelium's appearance of being a tight barrier, leaky epithelial tissue causes the intercellular junctional complex of the nasal mucosa to be less tight [1-2]. Furthermore, a prime absorption surface for drug administration is provided by the considerable vascularization of the mucosa, lamina propria, and leaky epithelium [3-4]. For CNS acting medicines, the direct

absorption of the molecules from the nasal cavity via the trigeminal and olfactory pathways offers a direct access to the brain and a favorable pharmacokinetic/pharmacodynamics (PK/PD) profile. Additionally, this mode of administration circumvents the two primary physiological barriers—the blood-cerebrospinal fluid barrier (B-CSF-B) and the blood-brain barrier (BBB) to allow highly potent and effective CNS-targeted drugs to reach the brain parenchyma. This is a novel and promising alternative to enteral and systemic drug administration. The blood-brain barrier (BBB), which restricts the entry of foreign substances into the brain, is formed by the brain's capillary endothelial cells enclosing pericytes and astrocyte end feet as well as the basal lamina.

The interface between the brain and cerebrospinal fluid, or B-CSF-B, is located at the surface of the cerebral ventricles and restricts the amount of liquid (CSF) that may be transported between the brain parenchyma. The medications are sent straight onto the brain by molecular diffusion that gets across these obstacles at the nasal cavity via addition to having a local and/or systemic impact, active pharmacological components absorbed via the nasal mucosa may also be employed to directly target the brain [5-7]. Compared to oral or intravenous drug administration, the nasal route offers a number of benefits, such as non-invasiveness, self-administered, a quicker time to effect start, and better bioavailability since hepatic first-pass metabolism is avoided. Furthermore, avoiding the BBB could make the medication more available in the central nervous system (CNS) [8-10].

Subsequently, a few studies assessing medication intranasal penetration for various central nervous system indications will be presented. Ultimately, the strategies to enhance nasal medication delivery will be compiled, and a critical assessment of the nasal drug administration route will be provided, taking into account both the benefits and drawbacks of this approach [11-14].

An overview of the nose-to-brain pathway is provided in this article, with particular attention paid to the structure of the nasal cavity and the cellular and molecular processes that are crucial to the administration of drugs via the nose and their absorption into the brain. Following this introduction, a number of *in vitro, ex vivo*, and in *vivo models* for studying intranasal drug delivery will be discussed, all of which are based on the most recent research in the area.

ADVANTAGES AND LIMITATIONS OF INTRANASAL DRUG ADMINISTRATION:

Brain-blood barrier (BBB): a thin layer of blood arteries with densely packed endothelial cells that divide the brain from the circulatory system. It shields the brain from the entrance of undesirable or dangerous elements including poisons and other compounds [15]. Lipophilic medications, such as antidepressants, anxiolytics, and numerous hormones, may more readily pass the endothelium cells than hydrophilic compounds, charged molecules, proteins, and peptides. Chronic dosage was necessary for patients with neurological diseases, which resulted in adverse effects in organs that were not the intended focus. Patients with neurodegenerative illnesses and brain tumors have fewer therapeutic choices since most medications that were formerly effective in treating neurological disorders have been shown to be compromised by the BBB. Drug delivery to the brain without intrusive methods is crucial for treating neurological conditions and brain cancers that require long-term care [16-17]. When treating chronic disorders, olfactory and trigeminal pathways provide dependable alternatives to maximize therapeutic benefits at lower dosages while avoiding negative effects. Drug administration via the mucosa via the olfactory or trigeminal pathways, which circumvent the blood-brain barrier, is known as direct IN drug transfer to the brain. The brain can only communicate with the outside world via this pathway [18].

In addition to its benefits, nose-to-brain delivery has drawbacks that have been documented. These drawbacks include the relatively small volume of drugs that can be administered, the olfactory epithelium's limited surface area, the short retention time for drug absorption, and the impact of nasal secretions on drug delivery [18].

Advantages:

- Non-intrusive.
- little danger of infection.
- Simple self-management.
- comparatively big absorption area (rats: 13.4 cm^2, humans: 160 cm^2).
- large region of the olfactory epithelium, particularly in rodents (12.5 cm^2 for humans against 6.75 cm^2 for rats).
- Quick assimilation.
- There are several vascular and limphatic vessels in the nasal submucosa.
- There is no hepatic first pass drug metabolism.

- Direct medication administration that gets beyond the blood-brain barrier to the brain.

Limitations:

- Limited to powerful drugs.
- Small amounts, 25 to 200 µL in humans.
- An active mucociliary clearance.
- Short amount of time invested.
- Proteases, peptidases, and nasal cytochrome P450 (pseudo first pass effect)-induced enzymatic degradation.
- Drugs that are hydrophilic permeability are low.
- It is necessary to use absorption enhancers.
- Low nose epithelium's pH.
- Individual variations.
- Minimal CNS protein delivery.

Nasal anatomy and physiology:

The nasal cavity, which forms the nasal channel meant for breathed air from nostrils to the nasopharynx, is a significant component of the respiratory system. The primary purpose of the nasal septum, which separates the nasal cavity from the nasopharynx longitudinally, is breathing [21].

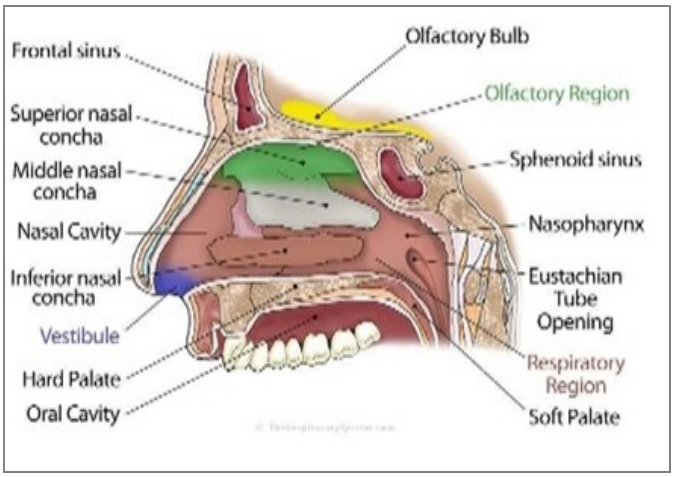

Fig 1. The anatomy of the human nasal cavity.

A cartilage called the nasal septum divides and shapes the nostrils. The nasal cavity of humans is 12 to 14 cm long and 160 cm in size, with inferior, middle, and superior conchae, or turbinates, making up the absorbent surface area [22].

This helps the inspired air to become warmer, more humid, and filtered. Four types of lung function include squamous, respiratory, transitional, and olfactory epithelia that are found in the nose. The submucosal layer of the nasal cavity is made up of blood artery networks, mucus, and cellular components such as blood plasma that are secreted by glands. The main parts of the nasal cavity are the olfactory, respiratory, and nasal vestibule regions [23].

Vomer to the anterior region of the conchae is where the nasal vestibule extends. The squamous epithelium that lines it, on the other hand, has sweat and sebaceous glands. as well as rough hairs [23].

Between the squamous and respiratory epithelium lies the non-ciliated transitional epithelium. However, the emphasis of intranasal medication delivery is on the respiratory and olfactory pathways. The olfactory region is the most delicate part of the nasal cavity responsible for the sense of smell. It is made up of pseudostratified columnar epithelium with a surface area of less than 10 %. It greatly affects taste perception because it includes turbinates communicating posteriorly with the mouth. The olfactory region of the nasal cavity contains the Bowman's glands and olfactory receptors. Mucus secretion is the result of these Bowman's glands. The bipolar cells that house the odorant-responsive receptors found in the olfactory cilia are known as olfactory sensory neurons. To generate nerve bundle cells that connect to the central nervous system, the axons of olfactory sensory neurons converge with those of other olfactory sensory neurons [24].

Mechanism of drug absorption:

Passage via mucus is the initial stage of medication absorption from the nasal cavity. Small, unmodified particles may go across this layer with ease. Nevertheless, large or It could be more challenging for charged particles to cross. The main protein in mucus, mucin, has the ability to adhere to solutes and prevent diffusion. Environmental changes (such as pH, temperature, etc.) may also cause structural alterations in the mucus layer [25].

There are several ways for a medicine to be absorbed via the mucosa once it has passed through the mucus. These consist of paracellular transport by cell-to-cell migration, transcytosis by vesicle carriers, and transcellular or simple diffusion across the membrane. Potential metabolism prior to entering the systemic circulation and a short duration of residency inside the cavity might be barriers to medication absorption. Although several processes have been suggested, the two that follow have received the majority of attention [26].

The first mechanism, referred to as the paracellular pathway, is an aqueous route of transport. This path is passive and sluggish. The molecular weight of substances that are soluble in water and intranasal

absorption have an inverse log-log relationship. inadequate bioavailability was noted for medications whose molecular weight was more than 1000 Daltons [27].

The second mechanism, which is also referred to as the transcellular process, involves transport of lipophilic medicines that exhibit a rate dependence on their lipophilicity via a lipoidal pathway. Medications additionally traverse cell membranes by tight junction openings or an active transport pathway mediated by carriers [27].

Models for testing direct Nose-to-brain delivery:

Narcotic nasal route drug distribution to the central nervous system (CNS) has been shown in AD, brain tumor, epilepsy, pain, and animal models. There may be paracellular, transcellular, and neuronal transport involved in the nose-to-brain pathway via the olfactory and respiratory epithelium [5].

Models of nasal drug delivery may be utilized for PK/PD research, drug transporter interaction, nasal barrier evaluation, toxicological and electrophysiological studies, and detection and testing of nasal drug absorption and penetration [5].

Ex vivo, *in vivo*, and *in vitro* models are often employed in nasal drug delivery research. Numerous investigations may make use of the various models. Permeation and diffusion studies may be conducted using in vitro methods; nasal absorption can be characterized and a drug's pharmacokinetic profile can be determined using in vivo models; and nasal perfusion can be studied using ex vivo methods [5].

***In vivo* models:**

Sufficient in vivo models are crucial for effectively researching the nasal administration methods. When choosing an animal model for an in vivo nasal absorption investigation, it is crucial to examine the architecture of the animal's nasal cavity. The initial animal model was a rat, which was introduced in the late 1970s. Later, as nasal absorption investigations progressed, mice, rabbits, dogs, sheep, and monkeys were also included [6].

While rabbit, dog, and sheep models are more often employed for pharmacokinetic research, mouse and rat models are highly helpful for early investigations of nose-to-brain drug absorption [7].

However, due to the anatomical and physiological variations in their nasal cavities, the outcomes of research conducted using animal models may not necessarily match well with those conducted using human subjects. There are two main categories for the direct drug transfer from the olfactory mucosa to the central nervous system: transfer outside the nerve and transfer inside the nerve axon. There is a chance to get across the blood-brain barrier (BBB) via either route [7].

Due to the restricted capacity for absorption, the limiting factors are often the drug's potency and solubility. It is crucial to remember that straight absorption from the nose to the brain prevents dilution from distribution and protein binding, preabsorption metabolism, and the first pass impact. It is possible to administer and absorb a dose as little as 0.01 to 1 % of the oral dosage to the olfactory area or neuronally. The drug's solubility in the few microliters that will be used for intranasal administration is also crucial. As a result of the quick clearance inside the nasal cavity, drugs that must dissolve before absorption often do not have enough time to do so [7].

When administering medication by nasal formulation, a pipette or a polyethylene tube connected to a micropipette is often used. The tube is introduced around 3 (in mice) or 5 mm (in rats) into the nose. The medication was given into the right nostril (right-sided administration) in the Westin et al. trial, with a 5 µL received volume for mice and 50 µL for rats during intranasal treatment. This allowed the left olfactory bulb to function as a control. To maximize the likelihood that the medicine reaches the olfactory area, or the top section of the nasal cavity, which has direct access to the brain, it is crucial to maintain the animals in a supine posture. About 10 % of the nasal cavity in humans is occupied by the olfactory area, which has restricted access. However, the olfactory area occupies almost half of the nasal cavity in mice and rats. Similar to the human olfactory area, the monkey olfactory region is located in the upper nasal cavity. Dogs and rabbits both have comparable nasal structure, with branching complicated conchae within the nasal cavity. However, dogs' nasal cavity has a greater surface area, and the olfactory region is largely concentrated on the ethmoidal conchae [8].

Factors Affecting Nasal Drug Delivery:

Physiochemical Properties:

***Particle Size*:**

The most important and crucial component affecting the drug's nasal administration to the brain is particle size since smaller particles have less resistance to mucus migration throughout the absorption route as well

as penetration. Large-sized particles are held in the nasal mucosa and have a tough time migrating through the nose. It is easy for nanoparticles in the 100 to 200 nm size range to pass through olfactory epithelium cells. The process of cerebral transit is very size-dependent. Particle morphological features must be taken into account in addition to size in order to prevent grittiness and irritation of the nasal mucosa [22].

***Surface Charge*:**

Due to the negative charge of the nasal mucosa, it is feasible for positive charge particles or polymers to interact with the mucosa via electrostatic forces. This results in increased residence duration and bio-adhesion. Most often, polymers such as chitosan and its derivatives are employed to create nanoparticles. Since the normal pH of the nasal cavity is positive, chitosan-like polymers have the potential to target the brain by nasal administration [24].

According to some research, the trigeminal and olfactory nerve routes may be preferred by positively charged particles and negatively charged particles, respectively. The medication's physicochemical properties, such as its pH, molecular weight, partition coefficient, pka, perfusion rate, and drug concentration, all influence how the drug is delivered from the nose to the brain [24].

***Molecular Weight*:**

The primary factor used to calculate the rate of permeability via mucosa is the molecular weight. Compounds with a molecular weight of 300–500 Daltons may go from the nose to the brain with ease. conveyance of the High molecular weight substances, such as proteins and peptides, target the brain at a low level via the nasal route. Drugs with a large molecular weight may also be delivered by this route by using permeation enhancers (sodium lauryl sulphate, sodium glycocholate, etc.). When it comes to polar medications, the primary factor influencing how quickly the drug passes through the nasal barrier is its molecular weight. Hydrophilic compounds with molecular weights under 300 Dalton are readily transported by carrier-mediated transport or the paracellular pathway. Passive diffusion is used to move the molecules, which are lipophilic and have molecular weights between 300 and 1000 Dalton (big molecules) and even less than 300 Dalton. Particles that are too small to be delivered to the brain via the nasal pathway may be readily deposited in the lungs [24].

***Polymorphism* [25]:**

When developing new products and for nasal medication administration, it is crucial to take the drug's polymeric form into account. Various polymorphs have an impact on both the drug's absorption via the nasal cavity and its disintegration. The drug's many polymorphic versions vary in their ability to pass through the nasal membrane. It is necessary to take into account the stability and purity of polymorphic forms for the nasal formulations.

***pH*:**

The medicine's nasal distribution to the brain is influenced by the pH of the nasal mucosa and the drug itself. To avoid mucosal damage, bacterial development, and nasal discomfort, the formulation's optimal pH has to be between 4.60 and 6.50. Only the drug's non-ionized portion may infiltrate via the mucosa of the nose.[26]

***Partition Coefficient*:**

High molecular weight and hydrophilic chemicals are removed via mucociliary clearance, which prevents them from passing through the nasal mucosa. The nasal mucosa contains hydrophilic and lipophilic components; however, lipophilic medications need greater transit across the nasal epithelium than hydrophilic drugs do. With hydrophilic moieties, the prodrug method works well for drug transport from the nasal cavity. Levodopa's prodrug is designed to improve absorption via the nasal mucosa. The enzymes found in the nasal mucosa break down a variety of substances, including proteins and peptides, but the prodrug method protects these substances from breaking down. One such prodrug is acyclovir, which is also known as L-aspartate β-ester. The nasal mucosa may be readily penetrated by the medicine when it is in its salt or ester form [26].

Formulation Related Factors:

***Tonicity*:**

A significant factor influencing nasal mucosal permeability is tonicity. Through the reduction of nasal epithelial cells, the hypertonic solution facilitates nasal mucosal permeability. As a result, it promotes nasal mucosal permeability. Furthermore, in the case that hypertonicity continues, it inhibits ciliary motility, which obstructs mucociliary clearance. Because the hypertonic solution shrinks nasal epithelial cells, it facilitates nasal mucosal penetration. Moreover, it reduces mucociliary clearance [27].

Mucoadhesives:

Excipient lengthens the medication's period of residence in the nasal cavity, resulting in a longer-lasting release. The mucus and the mucoadhesives are joined by techniques for diffusion, adsorption, electrostatic interaction, and wetting. Many mucoadhesive compounds are available, including hyaluronic acid, poly-methacrylate, chitosan, polyacrylic acid, and carbopol [27].

Approaches to improve the Absorption of Drug in the Nasal Route for Effective Delivery to The Brain:

The nasal cavity includes a number of features, including complications, high enzymatic activity, quick physical clearance via mucociliary action, and limited mucosal permeability. Because of the intricate structure of the nasal cavity, linked to drug deposition. Each of these elements creates a barrier to the effective delivery of medications to the brain. There are several methods for addressing these restrictions [29].

Chemical Modification of Therapeutic Agents:

To improve stability, provide improved membrane permeability, and improve the absorption of active substances, the structure is chemically modified. Prodrugs, lipidization, PEGylation, and amino acid replacements are examples of chemical alterations. Lipidization and PEGylation are two methods that may change a material's hydrophilicity and hydrophobicity. The specificity of the target might be accomplished by surface functionalization and chemical alterations [29].

Enzyme Inhibitors:

Increased mucosal reductase and protease activity in the nasal cavity's olfactory area affects a variety of enzymes involved in drug metabolism. The nasal cavity contains a variety of enzymes, including glutathione S transferases, CYP450 isomers, oxidative and conjugative enzymes, exo/endopeptidases, alkaline phosphatases, and Glucuronyl transferases, aldehyde dehydrogenases, carbonic anhydrases, etc. These enzymes cause a variety of medications to break down or metabolize, which results in the pseudo-first pass effect. Adding protease inhibitory compounds as a formulation element is a workable way to break through the nasal cavity's enzymatic barrier. By blocking the enzymes that cause degradation, the use of enzyme inhibitors is another effective strategy to improve the stability of medicinal medicines at the absorption site [29].

Permeation Enhancers:

The most adaptable functional formulation elements that improve a drug's or therapeutic agent's permeability across biological membranes are called absorption enhancers or permeation enhancers. There are several agents that possess characteristics that improve permeability, such as fatty acids, hydrophilic polymers, cyclodextrins, surfactants, bile salts, etc. Enhancers of permeability break apart the intricate structures that connect neighboring epithelial cells, interact with the phospholipid membrane, and make the material more viscous . In the end, olfactory epithelium, olfactory bulb, and CNS are the targets of penetration enhancers. This reversible tight connection opening is the most practical method for absorbing hydrophilic, polar molecules [30].

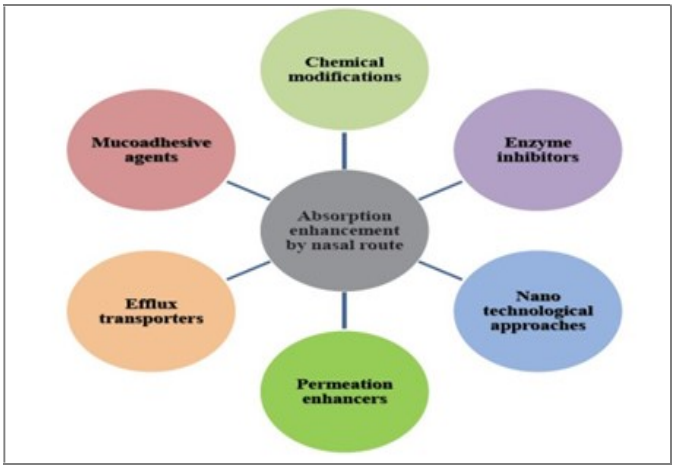

Fig 2. Absorption Enhancement by Nasal Route.

Efflux Transporters [30]:

The main obstacle to medication delivery to the brain is efflux transporters. Efflux transporters facilitate the brain's increased absorption of drugs. Glycosylated membrane proteins, which are found in the P glycoprotein, many bodily tissues, such as the nasal and respiratory mucosa. A wide range of hydrophilic and hydrophobic compounds are detoxified by PgP-mediated efflux transporters in the nasal mucosa. It contributes significantly to the decrease in the drug's CNS permeability. A greater penetration of the central nervous system is achieved by inhibiting it. For example, rifampicin with a P-glycoprotein efflux inhibitor improves medication absorption in the brain.

Mucoadhesive Agents:

Different polymers, such as chitosan, carbomer, polyacryl acid, pectin, etc., with mucoadhesive qualities are used as formulation excipients.It is predicated on

how mucoadhesive functions in conjunction with mucous and lengthen the medication's duration of residence within the nasal cavity. Additionally, it improves permeability and aids in the mucosal membrane's fluidization. Since mucoadhesive drugs do not preferentially adhere to olfactory epithelium, a combination of mucoadhesive with an appropriate targeting ligand is more effective. Typically, mucoadhesive compounds are found in powder forms. Chitosan-poloxamer 188 has been utilized in fentanyl nasal spray [31,32].

Transporter interactions [37-41].:

Because therapeutic medicines have a limited brain penetration rate, CNS illnesses remain challenging to treat. The blood-brain barrier is the main factor preventing these drugs from being absorbed (BBB). The polarized endothelial cells that make up the BBB are joined by tight junctions, which restrict paracellular permeability. Numerous strategies have been investigated to enhance BBB penetration and hence boost brain absorption. Increasing substrate lipophilicity (to increase passive permeability), conjugating with a substrate of an endogenous uptake transporter to increase carrier-mediated transport across the blood-brain barrier, and reducing efflux through transport inhibition or substrate modification are a few of these techniques. Furthermore, the transport of substrates to the central nervous system via the nose has been investigated. Previous research has shown that nasal delivery of suitable transporter inhibitors may reverse the attenuation of efflux transporters, which reduce brain absorption of substrates. These findings appear to point to the presence of efflux and absorption transport mechanisms at this location [33,34].

The effectiveness of medication distribution and treatment may be improved by targeted nano-drug delivery systems conjugated with certain ligands to target particular cell-surface receptors or transporters. Various cell types express various transporters on their cell surfaces, and in pathological situations, some transporters are expressed at greater levels than normal in a subset of cell types. The effectiveness of medication delivery may be improved by targeted nano-drug delivery systems coupled with certain ligands. The majority of transporters express themselves at specific sites, making them perfect targets for drug delivery that aims to improve penetration across biological barriers like the blood–brain barrier or boost absorption at a particular place [35,36]. The ligands for the receptors are much more selective, whereas transporters often have wide substrate selectivity. Since there are many options for ligands to modify the surface of the nanoparticles in order to target the transporters, these differences may actually be advantageous when choosing cell-surface transporters for nano-drug delivery systems. Another benefit of such ligands is their lack of immunogenicity

CONCLUSION:

In this review paper basically studied about nasal drug delivery to the brain has primarily focused on overcoming the blood-brain barrier. One promising method is the nose-to-brain route, utilizing the trigeminal or olfactory nerves. This pathway allows direct access to the brain parenchyma, crucial for treating neurodegenerative diseases. Medications can enter through various routes, including transcellular or intercellular pathways in the nasal cavity. Efflux transporters pose challenges, but inhibitors may enhance drug efficacy. As our understanding of the brain expands, optimizing these delivery routes remains crucial for targeted CNS treatment. The authors discuss the methods to enhance nasal drug delivery through the nasal epithelial route and elaborate *in vitro, ex vivo*, and in *vivo models* for studying intranasal drug delivery, which are based on the most recent research in the area.

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