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NASAL TO BRAIN DRUG DELIVERY SYSTEM: AN OVERVIEW

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Abstract:

Delivery from the nose to the brain is a significant difficulty. Numerous neurological conditions really call for treatments where the medication must enter the brain without encountering the blood-brain barrier (BBB) or issues related to systemic administration, such drug bioavailability, and adverse effects. Compared to oral administration, which can lead to unacceptable low drug bioavailability, or parenteral administration, which can occasionally be unpleasant, intra-nasal delivery of medications offers an intriguing alternative for attaining systemic therapeutic benefits. Therefore, it is critical to comprehend the advantages and disadvantages of different nasal medication delivery systems. However, nasal administration also has some limitations, such as its low bioavailability due to metabolism on the mucosal surface, and irreversible damage to the nasal mucosa due to the ingredients added into the formula. Moreover, the method of nasal administration is not applicable to all drugs. The present paper discussed the nasal anatomy, history of nasal to brain drug delivery systems, and its mechanism. Nevertheless, nasal administration of drugs in order to bypass the BBB and facilitate direct entry of a drug into the CSF or brain tissue is still a safe, convenient, and non-destructive method of targeted drug delivery to the CNS.

Key words: *Nasal to brain, central nervous system, respiratory region, Traditional Chinese Medicine, columnar epithelium.*

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INTRODUCTION:

The delivery of therapeutic agents to the brain remains one of the greatest challenges in modern pharmacology due to the presence of the blood–brain barrier (BBB), which restricts the entry of most drugs into the central nervous system (CNS). Traditional routes of administration, such as oral or parenteral delivery, often fail to achieve effective drug concentrations in the brain, limiting their therapeutic efficacy in treating neurodegenerative and neuropsychiatric disorders. In recent years, nasal-to-brain drug delivery has emerged as a promising non-invasive approach to bypass the BBB and directly transport drugs to the brain. The unique anatomy and physiology of the nasal cavity, particularly the olfactory and trigeminal neural pathways, provide a direct connection between the nasal mucosa and the CNS. This enables rapid onset of action, improved bioavailability, and reduced systemic side effects.

Nasal delivery is particularly advantageous for drugs with poor oral absorption, short half-life, or those susceptible to degradation in the gastrointestinal tract and first-pass metabolism. Various drug carriers and formulations, such as nanoparticles, liposomes, dendrimers, gels, and in-situ gelling systems, are being explored to enhance drug retention, permeation, and stability within the nasal cavity. Thus, nasal-to-brain delivery holds significant potential for the treatment of neurological and psychiatric disorders such as Alzheimer's disease, Parkinson's disease, epilepsy, schizophrenia, depression, and brain tumours, offering a patient-friendly and efficient alternative to conventional drug delivery methods [1-3].

History of Nasal-to-Brain Drug Delivery

The concept of nasal administration of therapeutic agents is not new. Traditional systems of medicine, including Ayurveda, Unani, and Traditional Chinese Medicine, have used intranasal routes for centuries to treat neurological disorders, headaches, migraines, and sleep disturbances. The practice of "Nasya" in Ayurveda, where herbal oils, powders, or medicated preparations are administered through the nose, is one of the earliest documented examples of targeting the brain through the nasal cavity.

In modern medicine, nasal administration initially gained attention for its role in providing systemic drug delivery (e.g., peptides, hormones, and vaccines), since it avoids gastrointestinal degradation and hepatic first-pass metabolism. However, its potential for direct nose-to-brain delivery was recognized later in the 1980s, when researchers demonstrated that certain substances administered intranasally could bypass the blood–brain barrier and reach the central nervous system via the olfactory and trigeminal pathways. Since the 1990s, advancements in drug delivery systems, such as nanoparticles, liposomes, dendrimers, and hydrogels, have significantly enhanced interest in nasal-to-brain targeting. These carriers improved drug stability, retention time, and penetration across the nasal mucosa. The development of imaging techniques and pharmacokinetic studies further confirmed that drugs delivered intranasally could rapidly reach the brain in therapeutically relevant concentrations.

In recent decades, the nasal route has gained increasing importance for the treatment of neurological and psychiatric disorders, including Alzheimer's disease, Parkinson's disease, depression, epilepsy, and brain tumours. Regulatory approvals of some intranasal products for systemic and CNS effects (e.g., intranasal sumatriptan for migraine, intranasal esketamine for depression) have validated this approach, paving the way for more research and clinical applications. Thus, from ancient practices of intranasal herbal remedies to cutting-edge nanotechnology-based formulations, the evolution of nasal-to-brain drug delivery highlights its growing potential as a non-invasive, effective, and patient-friendly strategy for targeting the brain.

The amount of drug that reaches the target brain region is limited by the low diffusion coefficient of the blood-brain barrier (BBB), which reduces the therapeutic effect. Currently, the oral route is exposed to first-pass hepatic metabolism and requires frequent administrations to ensure the constant presence of the drug at the site of action. The rising incidence of CNS illnesses has led to an increase in the need for safer, faster, and more effective treatments. An accessible and usually well-tolerated route is the nasal cavity. The nasal mucosa's profusion of blood vessels aids in medication absorption, which in certain cases is nearly identical to intravenous injections. Both local and systemic medication administration are possible using the nasal route. For example, nasal cavity disorders such congestion, rhinitis, sinusitis, and associated allergy diseases are typically treated with localised nasal medication administration. Local administration of a wide variety of medications is possible, including corticosteroids, antihistamines, anticholinergic, and vasoconstrictors. The use of the nose as the body's entrance point to achieve a systemic pharmacological effect has drawn more interest in recent years.

Systemic pharmacological effects can be achieved using a variety of pharmaceutical dosage forms, such as solutions, gels, suspensions, emulsions, liposomes, and microparticles. The main purpose of these dosage forms is to take advantage of the quick start of effect that comes with nasal administration.

For instance, intra-nasal administration of morphine and ketamine can produce quick analgesic effects. Furthermore, certain vaccinations, including those for influenza, can be given through the nose [1,4-8].

Nose

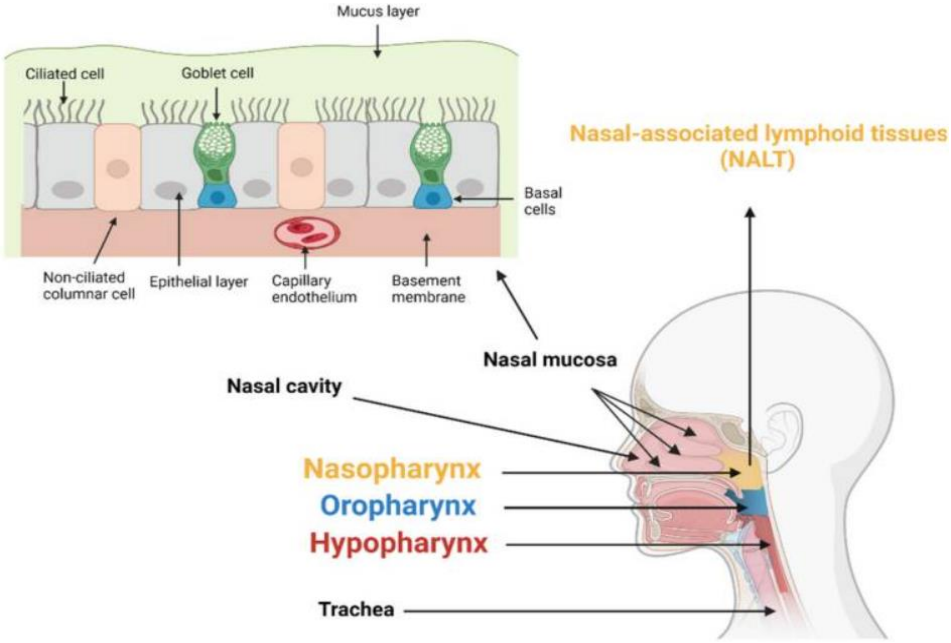

Figure 1: Diagram of the nose, including the main cell types, characteristic absorption barriers

The main entry to the respiratory system, which lets air into the body for breathing, is the nose. The nasal septum, a cartilaginous wall, separates the nasal cavity, which is 120–140 mm deep and extends from the nasal vestibule to the nasopharynx. The nose's overall capacity is around 16–19 ml, and its surface area is approximately 160 cm^2. Warm, humidified air is delivered to the lungs through the nose. As the main organ for removing particles from inspired air, it also acts as a first line of defence for the immune system by bringing the inspired air into touch with the mucous membrane.

The vestibular, turbinate, and olfactory areas are the three primary parts of the nose. The nasal cavity's smallest section is the vestibular area, which is located in front of the nose. Most of this region is covered by vibrissae, which allows it to filter out airborne particles larger than 10 µm in aerodynamic size. A stratified squamous epithelium replaces the skin that lined the vestibular area at the beginning of the passage. A significant vascular component of the nose, the turbinate region is separated into superior, middle, and inferior regions.

It is lined with a pseudostratified columnar epithelium. It is composed of mucus secreting, ciliated, non-ciliated and basal cells. The ciliated and non-ciliated cells are covered with non-motile microvilli, which are responsible for increasing the surface area, thus, this is the region where the drug absorption is optimal. Ciliated cells are covered with approximately 100 motile cilia which are responsible for mucus transport so mucociliary clearance prevails. Once drug (as particles or in solution) find their way to the mucociliary area, they will be cleared from nasal cavity and then have limited access to the absorption site. The pH of the nasal secretion's ranges from 5.0 to 6.5 [9-13].

Mechanism of drug absorption

The principal step in the absorption of a drug from the nasal cavity is the passage through the mucus. Fine particles easily pass through the mucus layer; however, large particles may find some difficulties. Mucus contains mucin, a protein with the potential to bind with solutes and thus affect the diffusion process. Structural changes can occur within the mucus layer as a result of environmental or physiological changes. Subsequent to a drug's passage through the mucus, there are numerous mechanisms for absorption through the mucosa. These include transcellular or simple diffusion across the membrane, paracellular transport via movement between cell and transcytosis by vesicle carriers. Several mechanisms have been proposed, but paracellular and transcellular routes dominate. Paracellular transport is slow and passive. There is an inverse correlation between intranasal absorption and the molecular weight of water-soluble compounds. Poor bioavailability was reported for drugs with a molecular weight greater than 1000 Daltons.

The second mechanism involves transport through a lipoidal route that is also known as the transcellular process and is responsible for the transport of lipophilic drugs that show a rate dependency on their lipophilicity. Drugs also cross cell membranes by an active transport route via carrier-mediated means or transport through the opening of tight junctions. Obstacles to drug absorption are potential metabolism before reaching the systemic circulation and inadequate residence time in the nasal cavity [14-20].

Table 1: Advantages and disadvantages of nasal drug delivery system

Advantages	Disadvantages
Rapid onset of action	Drug elimination
Less drug degradation	Low bioavailability
High rate of absorption	Irreversible damage of nasal mucosa
High patient compliance	Drug dose loss due to improper use
Self-administration by patients	The state of the nasal cavity affects the absorption of drugs
Direct nose-to-brain delivery	Unclear mechanism
Non-invasive drug delivery	Limited dose

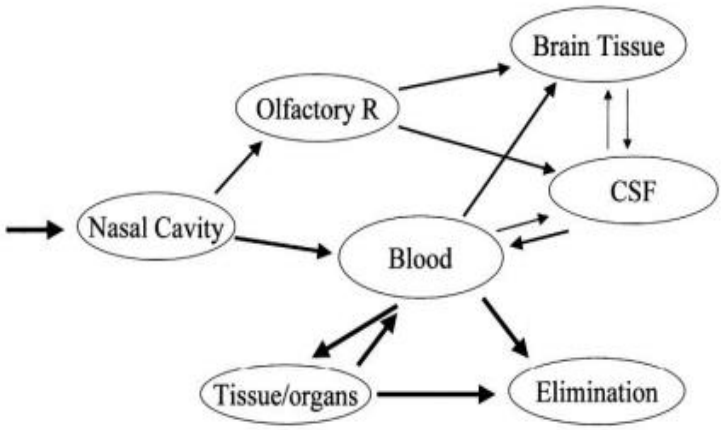

Figure 2: Connectivity of nasal cavity to other organs

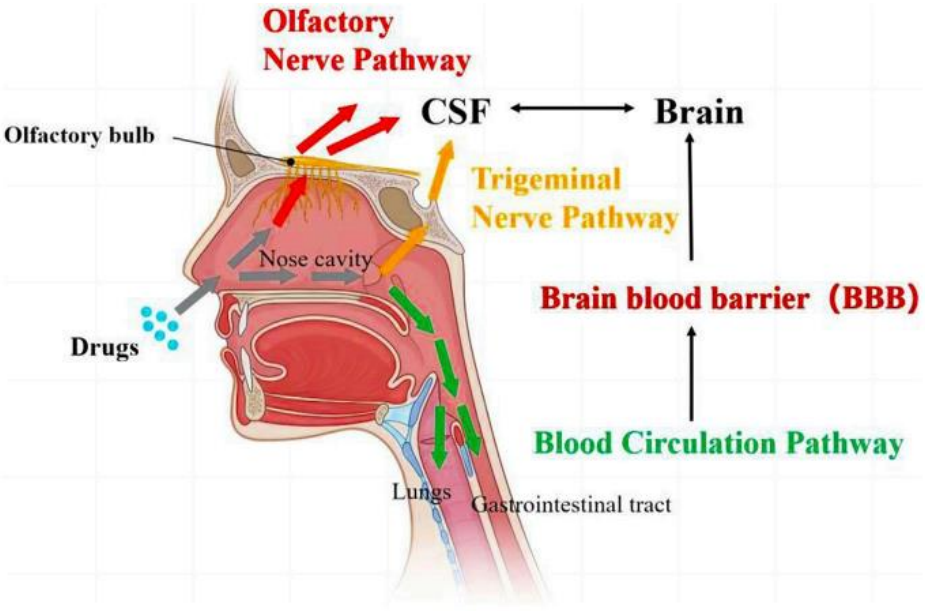

Figure 3: Transport of drugs from nose to brain

CONCLUSION:

The nasal cavity has emerged as a potentially effective and adaptable drug delivery method within the past ten years. Its special capacity to prolong medication release by bypassing the liver's first-pass metabolism and delivering pharmaceuticals directly to the brain is very promising for the field of drug delivery. An

increasing amount of research on nasal drug administration points to the possibility that it could be applied to difficult medications, helping to overcome the difficulties associated with pharmaceutical manufacture and drug delivery. Their review paper has covered a variety of pharmacological dosage forms and their possible applications for systemic or local drug administration. For high molecular weight medications like peptides and proteins, nasal to brain delivery can be used; however, the presence of permeation enhancers significantly affects systemic bioavailability. The administration of nasal to brain delivery may be especially appealing for treatments that call for long-term dosage. For many medications, nasal administration to the brain offers a good substitute for oral delivery, which may have issues including low bioavailability and the possibility of GI-related adverse effects, as well as the invasiveness of injections.

Nasal to brain delivery can be utilized for high molecular weight drugs such as peptides and proteins, however, systemic bioavailability is dramatically dependent upon the presence of permeation enhancers. Nasal to brain delivery administration may be particularly attractive for therapies requiring chronic dosing. For many drugs, Nasal to brain delivery administration provides a good alternative to the invasiveness of injections and to oral delivery, which may be associated with problems such as poor bioavailability and the potential for GI related side-effects. When determining nasal to brain delivery dosage for novel chemical entities and for prolonging the life of products, the formulation scientist should take these features into account. Compared to parenteral drug administration, intranasal drug delivery offers advantages in terms of increased patient acceptability and compliance, making it a viable alternative method of administration for a number of systemically acting medications with low bioavailability.

Conflicts of interest
None declared.

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