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RECENT ADVANCEMENT IN NOSE TO BRAIN DRUG DELIVERY

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Abstract:

The number of small and large molecules that have been discovered recently as possible therapies for illnesses affecting the central nervous system (CNS) has grown.One possible way to directly deliver materials from the nasal cavity to various brain regions is through nasal-to-brain transfer. In the context of CNS illnesses, intrathecal administration is a noninvasive way to quickly deliver therapeutic drugs to the brain, spinal cord, lymphatics, and walls of cerebrovascular veins while avoiding the blood-brain barrier. The report also discusses the primary benefits of nasal delivery as a potential medication delivery substitutes, along with any related routes or processes. Many drugs have been developed to treat the different CNS disorders that people experience, like Parkinson's disease, Alzheimer's disease, and multiple sclerosis, but they haven't been able to demonstrate the level of focus required for effective treatment. On the other hand, when a drug is administered by the nose to the brain, it goes straight into the brain. This article aims to present an overview of the nose from a physiological, anatomical, and medication delivery perspective, as well as its advantages from a physicochemical and biological standpoint.

Keywords: Brain targeting, intranasal drug delivery, and obstacles to intranasal delivery.

I. Intranasal drug delivery:

A number of invasive techniques include intrathecal, intraventricular, and intraparenchymal delivery; have been investigated to show the direct transport of drug molecules to the brain.[1] These treatments may not be suitable for people with long-term care needs who have chronic diseases, though, due to the discomfort involved and the possibility of reduced medication effectiveness When administered via the IN route, drug molecules can reach the central nervous system (CNS) swiftly, painlessly, and non-invasively.[2] Rapid drug onset and absorption can be facilitated by the nasal cavity's large surface area and highly vascularized mucosa.[3] The IN pathway also gets over the severe surroundings of the GI tract and first-pass metabolism. Additionally, because it provides the rare opportunity to directly target drugs to the brain by utilizing the nerve routes following nasal administration, it is an especially alluring choice for the delivery of sensitive bio therapeutics. [3]The basis for IN drug administration is the unique physiology of the nasal canal, which provides a direct channel between the external environment and the central nervous system. A basic graphic illustrating the anatomy of the human nasal cavity may be found in Figure 1. The complexities of nasal physiology have been extensively covered in a number of papers. [5, 6]

The highly vascularized and permeable mucosal lining of the nasal cavity, which promotes rapid and efficient drug absorption, and the accessibility of the olfactory and trigeminal nerve pathways are important features to highlight in this context. The olfactory bulb and other parts of the brain are connected to the olfactory area by olfactory nerves. Trigeminal sensory neurons and blood vessels also supply the respiratory area. [7] Drugs have the ability to pass the blood-brain barrier and enter distinct brain regions through direct neural pathways. While the precise process by which drugs are transported from the nasal cavity to the brain is still unclear, some writers argue that transporters are present in the nasal cavity's olfactory bulb and respiratory mucosa, and that these transporters may play a significant role. [8,9]

II. Advantages of intranasal drug delivery:

- Fast drug absorption through a highly vascularized mucosa; non-invasive delivery; enhanced bioavailability.
- Using an absorption enhancer or some other technique
- Large surface area of the nasal mucosa for absorption of dosage.

- Avoiding the gastrointestinal tract and first-pass metabolism.
- Improving convenience and adherence.
- Rapid onset of action and minimum side effects.
- Convenient method for long-term therapy as compared to parenteral route; medications that are not absorbed orally can be given to the systemic circulation.
- Greater bioavailability of bigger drug molecules can be accomplished by utilizing an absorption enhancer or other means.

III. Disadvantages of intranasal drug delivery:

- Certain medications may irritate the mucosa in the nose.
- Distribution via a nasal medication delivery mechanism.
- Allergies or cold-induced nasal congestion may impede medication absorption.
- It is anticipated that when molecular weight increases, drug delivery will decrease. Damage to the mucosa results from frequent use of this pathway.
- The amount of each medication that reaches various areas of the brain and spinal cord varies.[10]

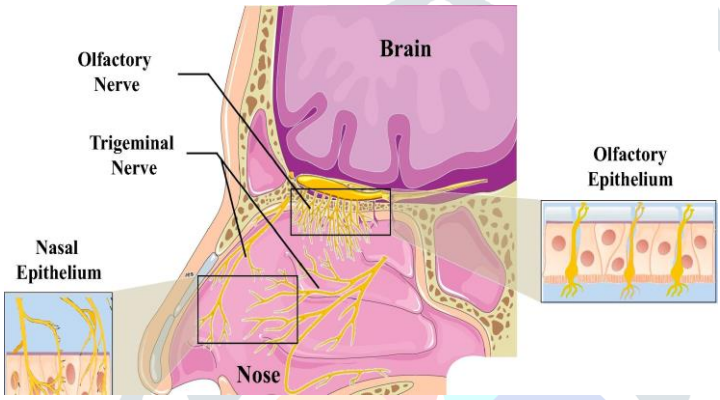

Figure: An illustration of the nasal cavity's architecture in humans is shown above

IV. The physiology and anatomy of the nose: [11]

The hair and secretory layer lining the nasal cavity gather inhaled particles and microorganisms. An adult's nasal cavity has a surface area of 150 cm^2 and a volume of 15 to 20 ml. Four places are provided by the nasal halves with them and they are named as follow,

1. Vestibule in the nose 2. The Atrium 3. The respiratory system 4. Olfactory area

1. Nasal vestibule: The air that is inhaled is filtered by the vibrissae, or nasal hairs, in this area of the nasal cavity. The intriguing properties of nasal proprioception allow for a high level of resistance against lethal environmental toxins, but they also significantly hinder the absorption of medications in the affected area.
2. Atrium: the atrium is the area that is in between the respiratory region and the nasal vestibule. They are recognized by the presence of pseudostratified columnar cells with microvilli in the posterior region and stratified squamous epithelial tissue in the anterior section.

3. Respiratory region: The respiratory region extends from the lateral wall and is made up of the superior, middle, and inferior turbinate. The main functions of these specialized structures are to regulate the temperature and humidity of the air that is inhaled. The spaces between are called passageways; they are routes where airflow is generated, and they serve to guarantee that the inhaled air contacts the respiratory mucosal surface at a depth. The nasal cavity is surrounded by air-filled chambers termed the paranasal sinuses and nasolacrimal ducts, which are found inside the bones of the face and supply air to the inferior and middle meatus called the nasolacrimal ducts and paranasal sinuses, are received by the inferior and middle meatus. The nasal respiratory mucosa is believed to be the most important area for the distribution of systemic medicine, and it is identified by the basement membrane, lamina propria, and epithelium. Nasal mucus is essential for several physiological processes, such as warming and humidifying the air that is inhaled.

Additionally, it gives the nasal epithelium physical and enzymatic protection against a range of external chemicals, including drugs. They may be trapped by the mucin that makes up the nasal mucus layer, which contains large molecular weight medications like peptides and proteins. Beneath it lies the lamina propria, which is crammed with fenestrated capillaries, neurons, glands, immune cells, and blood arteries. It is also very permeable. The final group produces immunoglobulin, an antibody that provides immune defense against pathogens and viruses.

4. Olfactory region: The olfactory area travels a short distance down the septum and lateral wall from its location in the nasal cavity's roof. The neuroepithelium is the only area of the central nervous system that has direct touch with the outside world. Similar to the respiratory area, the olfactory region is pseudostratified and contains specific olfactory receptor cells that are necessary for the sense of smell.

V. Mechanism of nasal absorption: [12]

Drugs must first pass through the mucous layer in order to begin to be absorbed from the nasal cavity. This barrier is difficult for large charged drugs to pass through, but it is easy for small, unchanged compounds to do so. The primary protein in mucus, mucin, has a tendency to adhere to solutes and impede diffusion. Moreover, changes in the environment (pH, temperature, etc.) can lead to structural changes in the

mucus layer (Illum L et al., 1999). Although more absorption mechanisms have been identified in the past, only two have been widely used, including

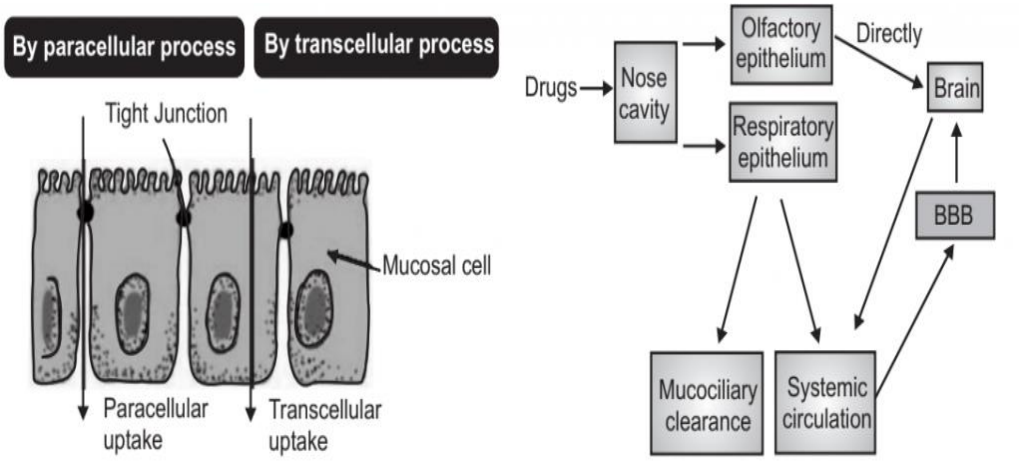

Figure: Mechanism of nasal absorption

A. The first process is the paracellular route, a passive, sluggish water transport system. There is an inverse relationship between intranasal absorption and the molecular weight of water-soluble substances. Medications with molecular weights larger than 1000 Daltons have low absorption, according to Aurora J et al. (2002).
B. The second method, commonly referred to as the transcellular procedure, involves transfer through a lipoidal channel. It is in charge of transferring lipophilic medications, whose nature dictates the most effective method of transportation. Furthermore, drugs can actively pass through cell membranes by utilizing carrier-mediated transport or by triggering tight junctions (Aurora J et al., 2002).

VI. Routes for Nose-to-Brain Delivery:

Studies have looked into the possibility of using the olfactory mucosa to carry drugs to the brain in order to treat disorders of the central nervous system. Its main advantage, as mentioned before, is that it avoids the BBB and lowers systemic exposure. A number of recent studies have made some important ideas, although the exact pathways that enable N2B dispersion remain unclear. Direct drug delivery to the brain via neural pathways like the trigeminal or olfactory nerves is one method. The alternative method gets beyond the blood-brain barrier by indirectly transporting medications through the lymphatic and vascular systems. [13] Rather than just one pathway, there may be several regulating drug absorptions from the nose to the brain.

Olfactory pathway:

The paracellular, transcellular, extracellular, and intraneuronal pathways are the four primary types of drug transport channels originating from the olfactory system.[14,15,16] In the N2B delivery pathway, olfactory neurons are important. Via intracellular axonal transport, therapeutic components that are endocytosed by OSN and form vesicles can be delivered to the olfactory bulb, neurons, and cribriform plate. They will be dispersed throughout the central nervous system (CNS) after exocytosis in the brain. [17] With a diameter of 0.1–0.7 µm, the human olfactory axon is among the smallest in the central nervous system. [18] This minuscule dimension indicates that only small molecules can be transported within this region by the intrinsic axonal transport mechanism. Another disadvantage of intracellular axonal transport is its delayed-release feature. The average axonal transit speed is 25 mm per day, which means that active moieties may take hours or days to reach the brain.[19] There is a chance that this route is not the primary one because of several studies showing the rapid transport of molecules through intranasal administration. [20, 21] Between the OSN and SUS, in the epithelium layer, molecules enter an extra-neuronal pathway. Subsequently, they penetrate the fissure and arrive at the lamina propria, situated between the axons and OECs. [22] Neuronal turnover in the olfactory epithelium results in a gap in the tight epithelial junction that the active chemicals need to cross in order to reach the cleft. Even for bigger moieties, drug transport is made possible by this gap. [23, 24] Through the hole along the SUS, a paracellular pathway is generated by passing through the olfactory epithelium and the basement membrane. Therapeutic molecules have the ability to cross the blood-CSF barrier, penetrate the subarachnoid space, and ultimately make their way to the brain. Drug binders are not necessary for this pathway, which works best for tiny and hydrophilic molecules to bind to receptors. [25, 26] Either passive particle diffusion or receptor-mediated endocytosis creates a transcellular route.

Trigeminal Pathway:

The trigeminal nerve, the biggest and fifth cranial nerve, innervates both the olfactory system and the respiratory mucosa. It is responsible for transmitting sensory and motor information from these areas to the medulla, pons, and spinal cord. The ophthalmic, maxillary, and mandibular nerves are its three branches. [28, 21, 29] Among those branches, N2B delivery involves the maxillary and ophthalmic branches. While the ophthalmic branches enter through both the front part of the nose and the dorsal wall of the nasal mucosa, the maxillary branches pass through the nasal mucosa's lateral wall. [14, 25] Similar to the olfactory nerve system, the trigeminal nerve facilitates drug transfer through a variety of routes. Once drug molecules have reached the branches of the trigeminal nerve, they will mix in the trigeminal ganglion and enter the brain near the pons. Furthermore, because portions of the trigeminal nerve are situated in close proximity to olfactory bulbs, drug molecules have the ability to cross the cribriform plate and enter the caudal and rostral areas of the brain. [14, 30]

VII. Applications of nose to brain drug delivery:

1. Medication delivery for schizophrenia and epilepsy:

Numerous researches have been done on the administration of medication for various illnesses via the nose. Shende et al. developed lamotrigine as a microemulsion to facilitate its transfer from the nose to the brain. Intranasal administration of medication is a more effective technique to deliver a targeted medication to the brain in the event of an epileptic emergency because it can cross the blood-brain barrier and reach the brain faster.[31] An antiepileptic drug called clonazepam has been added to a mucoadhesive microemulsion.[32] The objective was to rapidly administer the drug to the rat brain. Up to eight hours after clonazepam mucoadhesive microemulsion was given intranasally as opposed to intravenously, the brain/blood ratio was found to be two times higher at all sampling sites, suggesting a greater degree of drug dispersion in the brain. The fractional diffusion efficiency and cerebral bioavailability of the valproic acid microemulsion were enhanced.[33] Thus, using microemulsions to administer valproic acid for the treatment of epilepsy appears to be the most promising approach. The average time for clobazam microemulsion formulations to cause seizures in mice administered phenylene tetrazole was also assessed. This study showed that the produced clobazam microemulsion had a high brain targeting efficacy and that intraperitoneally treated mice showed a delayed onset of seizures. After that, the mice were given phenylene tetrazole to induce convulsions.[34] Further clinical testing of the developed formulation may result in a product that can be used to treat acute seizures caused by status epileptics as well as patients with medication tolerance and hepatic impairment on long-term usage in the treatment of epileptics, schizophrenia, and anxiety.

2. Antidepressant administration:

A eucalyptus oil micro emulsion has been created for intranasal delivery to the brain.[35] The eucalyptus oil microemulsion has been demonstrated to have an immediate relaxing stimulant and antidepressant impact. It was also fairly priced.

3. Amnesia and Alzheimer's disease treatment

In both micro emulsion and mucoadhesive micro emulsion formulations, tacrine's pharmacokinetic-pharmacodynamics performances for brain targeting and memory augmentation in scopolamine-induced amnesic mice were assessed.[36] The findings demonstrated that mice with scopolamine-induced amnesia regained their memory loss more quickly and completely following the treatment of intranasal microemulsion.

Liposomes containing rivastigmine have been produced for Alzheimer's disease. When given orally, acetyl cholinesterase, such as rivastigmine, are rapidly absorbed, despite being heavily degraded by other cholinesterase. Liposomes may be used to administer the medication through the nasal route to the central nervous system (CNS). A comparison study comparing intranasal liposome and oral free medicine revealed that liposomal formulation may provide ten times higher Cmax, systemic AUC, and brain concentration than oral delivery. Compared to the free drug, the liposomal formulation demonstrated better brain absorption when intranasally delivered. This may be the consequence of the drug traveling straight from the nasal mucosa to the brain through the olfactory pathway.[37]

4. The management of migraine:

Although the medical profession has made strides in treating migraines, opinions on whether the illness is primarily caused by vascular or neurological dysfunction remain mixed.[38] Following oral treatment, sumatriptan undergoes first-pass metabolism and is rapidly absorbed but insufficiently metabolized, resulting in a low absolute bioavailability of 14% in humans. Very little of the blood-brain barrier (BBB) is crossed by sumatriptan.[39] Based on research, intranasal drug administration appears to be a feasible, non-invasive method of brain delivery.

5. Management of neurological deficit and angina pectoris:

Nimodipine's brain absorption and solubility were enhanced via the creation of a microemulsion, enabling intranasal delivery. Nimodipine was absorbed in the olfactory bulb three times more readily through the nasal route than it was through the intravenous (IV) route. The ratios of AUC in brain tissues and cerebrospinal fluid to those in plasma were much higher after nasal injection than they were after intravenous therapy. These results suggest that nicodipine can be administered intranasally using the microemulsion technique as a means of treating and preventing neurodegenerative diseases. [40]

6. The transfer of genes

The limitations of currently available vectors provide a major clinical barrier to gene delivery to the central nervous system. Most viral vectors have to be injected directly into brain tissue because they are too big. Nasal administration is gaining popularity as an alternative method of administering plasmid DNA carrying therapeutic or antigenic genes since it is non-invasive. One study looked at the potent vasodilator calcitonin gene-related peptide (CGRP) administered intravenously to the brain. The study found that intranasal CGRP improved cerebral blood flow, reduced vasospasm, and markedly reduced cortical and endothelial cell death. The intranasal route has proven to be an effective means of administering CGRP for brain targeting.[41] The recombinant plasmid-encoded beta-galactosidase protein was significantly overexpressed in brain tissues following intraperitoneal injection. Over the duration of an hour following dosage, plasmid DNA administered intravenously consistently showed lower brain targeting efficacy than plasmid DNA administered intranasally.

The researchers concluded that nasal delivery might be an alternative method of delivering plasmid DNA to the brain, and that intravenous delivery of the DNA might go straight to the brain, possibly through the olfactory bulb.[42] One benefit of the herpes simplex virus-based vectors is their neurotropic nature. Nevertheless, earlier studies have demonstrated that vectors derived from the type 1 herpes simplex virus (HSV-1) led to the death of CNS neurons in immunocompetent individuals, causing a severe and usually fatal encephalitis.[43]However, vectors based on the herpes simplex type 2 virus, ΔRR, are less harmful to the central nervous system and do not induce apoptosis in CNS neurons as compared to HSV-1.[44]A study found that rats and mice given ΔRR orally were protected against convulsions and death of neurons, therefore offering a potentially useful therapeutic platform for the treatment of chronic neurodegenerative diseases.

7. Delivery of proteins and peptides

Because of gastrointestinal enzyme breakdown and hepatic first-pass effects, oral peptide administration is not practical. An increasing amount of evidence suggests that administering certain drugs by intranasal route may be a desired and useful option for delivering them to the brain. In fact, some peptides, such as oxytocin, calcitonin, vasopressin, and luteinizing hormone-releasing hormone, are frequently administered intranasally in therapeutic settings. Currently under investigation are additional peptides such somatostatin, insulin, glucagon, growth hormone, and growth hormone-releasing hormone. [44]

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