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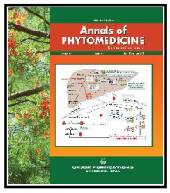

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Nanoparticles for targeting brain *via* intranasal delivery

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Abstract

Barrier between the blood and brain tissue, the blood-brain barrier (BBB) has distinct properties that make medicine distribution to the brain difficult. In order to reach the brain and hit the right spot anatomically, we need to figure out how to get across the BBB. Nanomedicine has considerable promise for resolving this issue, since it allows for the modification of nanoparticles with tactical molecules that can interact with the BBB and drive absorption *via* the brain endothelial cells. This article discusses the feasibility of employing nanomedicines with BBB-crossing nanoparticles to treat neurological disorders. It is difficult to pharmacologically treat central nervous system illnesses because of the blood-brain barrier's (BBB) capacity to block medication entrance into the brain. The advent of nanotechnology offers hope for a solution to this issue. The BBB, the blood-brain tumor barrier (BBTB), and the nose-to-brain barrier (N2B) are only some of the obstacles to brain-targeted medicine delivery that are discussed in this article.

1. Introduction

Schizophrenia, meningitis, migraine, Parkinson's disease, and Alzheimer's disease are all CNS diseases that require medication delivery to the brain for therapy. However, the impermeable nature of the endothelium membrane between the systemic circulation and the central interstitial fluid, the blood-brain barrier (BBB), makes such transport difficult, especially for hydrophilic medicines and big molecular weight medications. Therefore, many therapeutic drugs may have been abandoned because it is not possible to obtain enough drug levels in the brain *via* the systemic circulation (Nishioka, *et al*., 1992). 'Biologics,' which are macromolecules like peptides and proteins, cannot cross the BBB from the systemic circulation without first being broken down by digestive enzymes or liver cytochromes. Patients would prefer a non-invasive treatment for conditions like dementia that require long-term dosage.

The fields of nanoscience and nanotechnology have experienced explosive development in recent years. There is growing hope that the use of nanotechnology to healthcare may lead to major breakthroughs in the prevention, detection, and treatment of disease. Drug administration, *in vitro* and *in vivo* diagnostics, nutraceuticals, and the development of more biocompatible materials are only a few of the potential medical uses of nanotechnology (Zeller *et al*., 1997). One crucial tool for making some of these uses a reality is engineered nanoparticles. Although, the newly suggested and widely accepted definition of a particle size smaller than 100 nm applies to the vast majority of medically relevant particles. It is important to note that this does not apply to all of them. However, this fact need not prevent them from being used in medical settings. These nanoparticles (NPs) are appealing for medical applications because of their crucial and distinctive traits, such as their quantum properties and their capacity to adsorb and transport other chemicals. Their surface to mass ratio is also substantially higher than that of other particles. Nanoparticles (NPs) have a huge (functional) surface area, making them excellent carriers for substances like medicines, probes, and proteins. There are several obstacles that need to be addressed before nanotechnology may be used to increase our understanding of the pathophysiological foundation of illness, provide better diagnostic opportunities, and lead to more effective treatments. However, in other applications, such as drug delivery, larger nanoparticles (those with a size greater than 100 nm) may be required to load a sufficient amount of drug onto the particles. Additionally, the drug itself can be synthesized at the nanoscale and serve as its own "carrier" for drug delivery (Vannicci *et al*., 1997).

Much of the brain's vascular system features a unique physical barrier known as the blood-brain barrier (BBB). It regulates how much ions, chemicals, and cells may go from the bloodstream to the brain and spinal cord. The BBB functions because to the special architecture it was built with, which comprises of a single layer of nonfenestrated endothelial cells surrounded by smooth muscle cells, pericytes, and astrocyte projections. Since the BBB is critical in steady state conditions to protect the brain from dangerous substances, the fact that its great selectivity makes entry difficult for the various pharmaceuticals used to treat many neurological disorders is problematic (Singh *et al*., 2015). Therefore, the challenge

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of crossing the BBB is crucial to the creation of an effective treatment strategy. The use of nanotechnology to create new systems for the efficient delivery of potential therapeutic and diagnostic compounds to specific areas of the brain has the potential to increase therapeutic efficacy, decrease side effects, and increase drug concentration at the site of action (Geldenhuys *et al*., 2011). As a consequence of their potential as a tool for pharmaceutical development, NPs have been receiving a lot of attention in the medical business. Many distinct classes of NPs have been presented as potential solutions for enhancing medication delivery across the blood-brain barrier (BBB). Nanoparticles are used in many different applications, and some examples are included like (Singh *et al*., 2015): liposomes, lipid nanoparticles, polymeric nanoparticles, dendrimers, cyclodextrins, silica nanoparticles, magnetic nanoparticles, gold nanoparticles, quantum dots, and carbon nanotubes. The suitability of a nanodelivery system for brain delivery is contingent on a number of factors, including nanometric size, surface charge, morphology, and-most importantly-the molecular recognition and interaction between a specific ligand conjugated on the nanoparticle surface and the molecule overexpressed on the brain target place (active targeting).

2. Drug delivery using nanoparticles

While it is possible to develop nanoparticle formulations of the drug itself, drug delivery and related pharmaceutical development in the context of nanomedicine should be viewed as the science and technology of nanometer scale complex systems (10-1000 nm) consisting of at least two components, one of which is a pharmaceutically active ingredient. Smart-drugs, also known as theragnostics, are the result of this system and serve a unique purpose in the treatment, prevention, or diagnosis of disease (Zhang *et al*., 2003; Acharya *et al*., 2016; Englert *et al*., 2016).

Nanobiotechnology drug delivery studies aim to achieve the following objectives:

- Improved drug targeting and delivery,
- Decreased toxicity without loss of therapeutic benefits,
- Increased safety and biocompatibility, and
- Accelerated discovery of novel, safe medications.

There are a few fundamental difficulties that must be addressed before any novel materials can be designed, and they all have direct bearing on the search for suitable carriers as drug delivery systems. They include information on: (i) how the medicine is incorporated and released, (ii) how long the formulation will keep for, (iii) how biocompatible it is, (iv) how it will be distributed and where it will go, and (v) how well it will work. The potential for undesirable effects of leftover material after medication administration should also be taken into account when using a carrier as the only method of drug delivery. In this case, it would be best to use biodegradable nanoparticles that only remain in the body for as long as the treatment requires (Neba Jyoti *et al*., 2021; Wang *et al*., 2015; Fuchs *et al*., 2005).

Enhancing transport to or absorption by target cells and/or decreasing the toxicity of the free medication to non-target organs are the goals of entrapping pharmaceuticals in nanoparticles. The therapeutic index, the difference between dosages producing therapeutic efficacy (such as tumor cell death) and levels producing toxicity to other organ systems, will rise in both cases. Making stable, target-specific nanoparticles is essential for these applications (Yilkangas *et al*., 2013).

3. Drug delivery through nanoparticles across the blood-brain barrier

Non-invasive drug delivery approaches that can reduce the high cost and risk aspects of conventional surgery, radiation, and chemotherapy are urgently needed to treat the rising number of patients with neurodegenerative illnesses. Transporting medications or other molecules (such as nucleic acids, proteins, or imaging agents) over the BBB without interfering with normal brain function is a common goal. Nanocarriers are divided into three broad categories: those based on polymers, those based on biomimicry, and those based on inorganic materials.

3.1 Polymer-based nanoparticles

When it comes to getting pharmaceuticals across the BBB, polymeric NPs have numerous benefits. By inhibiting enzymatic and hydrolytic breakdown, they increase medication bioavailability, for instance. Importantly, drug-loaded polymeric nanocarriers can improve brain permeability and increase medication concentrations in the tumor. Common polymer-based transport carriers include poly (lactide-co glycolic-acid) (PLGA), poly (ethylene glycol) (PEG), and poly (lactic acid) (PLA). Low toxicity, great biocompatibility, and tightly regulated drug release are only some of the benefits demonstrated by PLGA NPs. Furthermore, PLGA NPs circumvent the issues of drug solubility and the lack of passive selectivity across the BBB. In order to treat PLGA NPs could be transported across the BBB while maintaining good drug solubility and passage selectivity. In this study, they found that grafting a unique synthetic peptide against somatostatin receptor 2 onto PLGA NPs increased the NPs' ability to deliver their payload. In addition, the data demonstrated that the system was able to successfully incorporate medicines into the glioma and trigger apoptosis. This method of drug delivery can reduce cytotoxicity since PEG and PLA NPs are so biocompatible. In addition, a gatekeeping layer composed of biodegradable PEG and PLA was typically deposited on the surface of NPs to provide regulated medication release. To better medication release under severe oxidative stress, coated mesoporous silica NPs with PLA acts as a ROS-responsive gatekeeper (Banks *et al*., 2012; Mrunal Deshmukh, 2022; Craft, *et al*., 1998).

Since PEG is taken up less efficiently by the reticuloendothelial system, its thick coating on NPs can aid in their passive diffusion in the brain. As a result, the PEGylation technique is utilized to alter polymeric vectors in order to increase their systemic circulation duration, hence, facilitating more efficient brain penetration and accumulation. Researchers took use of these PEG features by coating Au NPs in PEG. Due to their biostability and biocompatibility, they are able to cross the BBB and re-cross it repeatedly under normal circumstances. Because cancer cells are acid-labile, they can disintegrate rapidly in brain tumor cells and concentrate medications where they're needed most.

3.2 Biomimetic nanoparticles

The immune system and the liver and kidneys have little trouble recognizing and eliminating exogenous NPs employed for medication administration. Therefore, biomimetic NPs are gaining popularity in

research and development due to their ability to readily detect and target ligand, to persist in the blood circulation for an extended period of time, and to evade the immune system. Biocompatible, minimally immunogenic, biodegradable, and able to access cellular tight junctions are only few of the reasons why chitosan (CS), produced from chitin by partial deacetylation, is used so frequently as a biomimetic drug carrier. Furthermore, various natural vesicles (formed with membranes) have been explored extensively in the field of brain medication delivery as key biomimetic NPs. These include liposomes, exosomes, red cell membranes, and "Leukolike" coated NPs. Its remarkable biocompatibility can be attributed, not surprisingly, to the presence of a phospholipid bilayer. Here, liposome NPs were coupled with six peptides in order to overcome BBB resistance and deliver glioma chemotherapeutics. IVIS spectra suggest that peptide-modified liposomes can cross the BBB and increase liposome internalization at the tumor location. Biomimetic nanovesicles are also formed using multifunctional or self-assembled proteins like ferritin. As a kind of colloidal system, protein-based nanomaterials have the potential to improve cellular absorption; they are also non-toxic, biodegradable, non-antigengenic, and amenable to surface modification. Because of these characteristics, protein-based nanoparticles may be able to transport medicines over the BBB following intravenous administration. Noninfectious capsid protein based NPs (virus-like NPs, or VLPs) generated from a variety of viral self-assembly methods have been investigated as vaccination and medication delivery possibilities. The capsid protein provides a means of concealing medications or agents within a Trojan horse. Using the Salmonella typhimurium bacteriophage P22 capsid as a precursor, successfully delivered the anal gesic marine snail peptide ziconotide an into *in vitro* BBB model *via* an endocytic strategy, providing an interesting look at engineered VLPs (as a nanocarrier) to transport across BBB (Hoyer *et al*., 2002).

Combinatory activity showcasing both the flexibility of nanomaterials and the functionality and biocompatibility of the biomembrane system is possible when nanoparticles are coated or camouflaged with biological membranes that form core-shell structures. As a result, the stability, retention, and combability of bare NPs may be significantly enhanced by covering with a biomimetic membrane. To avoid unfavorable effects due to the lack of cellular contents, selective use of membrane-targeting dependent mechanisms preserves a variety of bioactivities including recognition, binding, delivery, or cellular modulation. The following components are often used in the production of biomimetic NPs: Stable, inert, or cell-mimetic (*e.g*., size and shape) core nanostructure of synthetic polymers or liposomes; coated biomembrane or membrane-like structure or membrane components (*e.g*., proteins and polysaccharides); assembly strategy for loading and coating separated biological membranes onto nanomaterials. The following is a summary of the most often used NPs coated with biological membranes or membrane components in sepsis treatment at the present time.

3.3 Inorganic-based NPs

Due to high stability and distinct material- and size-dependent physicochemical properties, inorganic NPs have advantages over polymeric and biomimetic NPs in brain drug delivery. Nowadays, versatile inorganic-based NPs with different structures have been widely investigated. It is easy to modify inorganic-based NPs with polymer or specific ligands to facilitate the delivery of therapeutics and macromolecules across the BBB. Silica nanoparticles (Si NPs), as an approved food additive by U.S Food and Drug Administration (FDA), is one of the promising candidates for brain drug delivery due to its relatively low cost, good biocompatibility and manufacturing controllability. In our group, the lactoferrin (Lf) modified Si-NPs have been prepared for investigating the sizedependent transport efficiency of Si-NPs across the BBB model. Polyethylene glycol was conjugated on the surface of Si NPs to reduce protein adsorption. This Lf attached Si-NPs enhanced transport effciency across the BBB compared to bare Si-NPs. Lf modified Si-NPs with different sizes were also studied to evaluate transport efficiency. Experimental results showed that particles with the size of 25 nm diameter have the highest transport efficiency, which is almost 4 times (21.3%) higher than that of bare Si-NPs. Moreover, we also compared the Si-NP transport efficiencies in one-cell (monolayer of endothelial cells) and three-cell (coculture of endothelial cells, pericytes, and astrocytes) BBB models. Mesoporous silica nanoparticles (MSNs), as porous Si-based material, are also popularly used in the drug delivery system. They not only inherit excellent biocompatibility but also own substantial specific surface area for loading drugs or ligands. Au nanomaterials are another inorganic material that offers high potential in drug delivery. As an ideal photothermal therapy (PTT) candidate, some special Au nanomaterials could transfer photo energy into thermal energy under near-infrared (NIR) laser irradiation conditions. Owing to their excellent NIR absorption property. The absence of fibrils network in the transmission electron microscope and atomic force microscope images indicated the effective ability of Au-based NPs for dissociating Ab fibrils upon NIR irradiation. Silver and titanium dioxide NPs have also been used to cross the BBB.

In conclusion, many NPs have their own set of pros and cons. For instance, inorganic NPs cannot be produced without using either costly organic solvents or inorganic reagents. Concerns remain, however, about the toxicity and in vivo clearance of organic NPs (Kianpour Rad *et al*., 2018). However, despite the fact that NPs based on polymers and biomimicry have been shown to have superior biocompatibility, biodegradability, and surface modification, their use in brain drug delivery is constrained by factors such as their enormous size, poor targeting effectiveness, and the complexity of their manufacture.

4. Brain targeting

The blood-brain barrier drugs used to treat NDs are generally unsuccessful in the clinic because they have a hard time crossing the blood-brain barrier. Indeed, one of the greatest difficulties in biomedical techniques is getting therapeutic medicines to the central nervous system. Being weakly permeable and extremely selective to the passage of endogenous and exogenous molecules, including medications, the BBB represents the greatest impediment to the treatment of CNS illnesses. The BBB is a barrier that stops chemicals from freely diffusing from the blood into the extracerebral fluid, which surrounds the brain. Due to its unusual histological structure, the BBB is able to perform its function. This structure consists of non-fenestrated endothelial cells linked by complicated tight junctions, basement membranes, and astrocytic terminal feet. Most drugs, especially those that are big or hydrophilic, cannot cross the BBB at the tight junctions and enter the CNS. Passive and active transport are the two primary pathways for chemical absorption through the BBB (Soumya Singh *et al*. 2022) Hydrophilic and lipophilic substances, respectively, use non-energetic transport channels, such as paracellular and transcellular diffusion.

When the BBB is disrupted, as might happen when local inflammation occurs, tight connections weaken, enabling polar substances to diffuse through the endothelial cells. Small, lipophilic, and low-molecular-weight compounds (400-600 Da) can passively diffuse over the BBB *via* transcellular diffusion. While passive transport relies on diffusion to transfer substances, active transport uses energy-dependent processes to overcome concentration or electrochemical gradients in the body (Abubucker Peer Mohideen, 2021; Reger *et al*., 2006). To get from the blood arteries to the brain's extracellular space, tiny molecules like ions, amino acids, and glucose rely on protein carriers. Specifically, valine, histidine, methionine, tyrosine, and phenylalanine are delivered to the brain *via* the L system, whereas glucose is carried by the glucose transporter 1 (GLUT-1). Alanine, serine, and cysteine are neutral amino acids that can use the alanine-serine-cysteine (ASC) transporter. Endothelial cells in the brain parenchyma contain particular receptors on their luminal side, allowing for the transport of big and/or hydrophilic molecules including hormones and proteins. This process is known as receptor-mediated transcytosis (RMT). A ligand is readily absorbed after binding to its particular receptor. Positively charged peptides and proteins take advantage of a transport mechanism called adsorption-mediated transcytosis (AMT), which entails the endocytosis of vesicles containing the charged molecule. This process shares some similarities with RMT but lacks precision (Reger *et al*., 2008).

Passive transport of chemicals across brain endothelial cells is primarily affected by their lipophilicity and molecular weight. Some medications are naturally lipophilic, yet their reversal in the bloodstream occurs quickly and readily. Efflux pumps such multi specific organic anion transporter (MOAT), P-glycoprotein (Pgp), and multidrug resistance-associated proteins (MRP) play a major role in this phenomenon. In order to get drugs into the central nervous system efficiently, researchers have discovered methods to circumvent the BBB. Biochemical opening, osmotic opening of tight junctions, and intracerebral implants are all examples of such methods. The BBB may usually be breached with a hypertonic solution (including mannitol). Alternately, drugs like angiotensin and bradykinin can be used to trigger the interruption. However, these methods are highly intrusive and may cause permanent harm.

Since lipophilicity plays a crucial role in passive transport across the BBB, many efforts have been made to chemically convert water-soluble molecules into fat-soluble compounds (*e.g*., through the covalent conjugation with lipids such as fatty acids or cholesterol). This is typically done by adding lipophilic functional groups to mask the polar extremity of a selected drug, increasing the drug's chances of crossing the BBB.

5. Using nanotechnology to treat neurodegenerative disorders and access the central nervous system

Nanotechnology provides ideal nanoplatforms on which the medication is loaded and transported, favoring its selective release to the target location, decreasing side effects and systemic exposure, and therefore facilitating efficient CNS delivery. Effective medication transport to the brain has been greatly aided by the vast array of structures made available by nanomedicine. In general, 'nanoparticles' (NPs) refer to materials having a diameter of 200 nm or less, which exhibit more cellular absorption than the bigger microparticles and are readily taken up by Kupffer cells and removed by mononucleus phagocytes. However, smaller NPs (those with a diameter of less than 6 nm) are quickly flushed out of the body by renal filtration. Nanomaterials' key benefits are their size, stability, and low to null systematic toxicity. Their size is equivalent to that of biological macromolecules. The unique physicochemical properties of nanosystems-including their size, shape, charge, hydrophobicity, and surface features-can also be carefully controlled. Because of their large surface area in relation to their volume, NPs can be modified by adding chemically distinct agents to their surface through covalent conjugation, encapsulation, or adsorption, such as ligands for active targeting, polymers, and/or surfactants. Improved medication distribution to the target cells or organs and lower minimum effective doses can be achieved with the use of targeting agents that identify particular brain receptors or transporters. In addition, undesirable NP buildup in other organs or tissues, such the spleen, liver, and kidneys, is reduced by functionalization with appropriate targeted agents.

Numerous nanosystems were developed with the aim of binding to BBB endothelial cell transferrin (Tf) or lactoferrin (Lf) receptors. The transferrin receptor (TfR) is a transmembrane glycoprotein composed of two transferrin-binding subunits of 90 kDa that are linked by a disulfide bridge. In turn, lactoferrin (Lf) is a transferrin (Tf) family member and an iron-binding cationic glycoprotein of 80 kDa. In addition, cell-penetrating peptides (CPPs) have been extensively studied as potential carriers; these are small peptides, often containing less than 30 amino acids. They have the ability to translocate themselves into cells, which allows them to form complexes with certain drugs to improve cellular absorption. Thus, CPPs can enhance the bioavailability of a therapeutic agent of choice without significantly increasing its toxicity. This is accomplished by favoring the drug's intracellular or transcellular release. Aptamers are short oligonucleotides typically chosen from a large random sequence pool using an iterative selection process called systematic evolution of ligands by exponential enrichment (SELEX) (Song *et al*., 2016; Sushnitha *et al*., 2020). These aptamers are functionalized into NPs to promote the efficient and selective brain release of drugs. Several illnesses, including neurodegenerative disorders, have promising aptamers, which have been investigated as targeted ligands. But making the NPs' surface hydrophilic polymers "invisible" to the immune system extends their half-life *in vivo* and decreases their immunogenicity. In reality, the mononuclear phagocyte system is quite good at opsonizing and quickly eliminating unmodified NPs. Polymers and surfactants such as polyethylene oxide, polyethylene glycol (PEG), tween 80 or polysorbate 80 (PS80), poloxamer, and poloxamine can be used to coat NPs and prevent them from sticking together. Specifically, PS80 has been shown to improve NPs' chances of crossing the BBB, most likely due to the adsorption of serum apolipoprotein E and/or B on the PS-coated NPs. To this aim, NPs can imitate low-density lipoproteins and bind to their receptors on the endothelial cells lining the brain's blood vessels. However, NPs' capacity to penetrate the BBB is extremely nuanced and depends on factors such as particle type, size, chemical surface characteristics, and polarity. It is not yet clear how nanoparticles are able to traverse the BBB, however endocytosis through endothelial cells appears to be the most credible method.

6. Neurodegenerative disorders and nanosystems

Stroke, Parkinson's disease, Huntington's disease, Alzheimer's disease, amyotrophic lateral sclerosis (ALS), and spinal muscular

atrophy can all benefit from nanotechnology's ability to enhance sensory motor and cognitive skills. Due to the specific properties of nanomaterials, stem-cell treatment combined with nanoparticles results in more effective cell-based therapy. Both endogenous and foreign neural stem cells (NSCs) can benefit from nanoparticle interactions with proneurogenic elements in the stem-cell niche. Nanotechnology techniques have had a huge impact on stem-cell research, which has resulted in the widespread proliferation of stem cells (Alkhalifa *et al*., 2021; Parodi *et al*., 2017). The expansion of neural cells is a crucial sign that can influence the progress of treatments for neurodegenerative illnesses.

7. Intranasal route for brain drug delivery

7.1 Anatomy and physiology of the nasal cavity

The nasal cavity is made of three components that have various functions: the vestibule, which operates as a baffle system and has the capacity to filter breathed air; the olfatory epithelium, which has metabolic capabilities; and the respiratory region, where medication absorption occurs. Regarding physiology, the nasal cavity essentially performs a protective function, acting as a filter for particles or microorganisms that are entrapped in the nasal vestibule or in the mucus layer that covers the respiratory tract; it is also responsible for mucociliary clearance, the progressive transport of particles to the back of the throat, down the esophagus, and into the gastrointestinal tract. The nasal cavity also avoids the deposition of foreign chemicals in the lower airways, humidifying and warming the inhaled air, and transforming these elements into compounds that are readily removed in the expired air.

In humans and other animal species the principal functions of the nasal cavity are breathing and olfaction. However, it also provides a significant protective action once it filters, heat and humidify the breathed air before reaching the lowest airways. Passage of the nasal cavity which extends from nasal vestibule to nasopharynx has a depth of around 12-14 cm. The overall surface area of the nasal cavity in human adult is around 150 cm^2 and total volume is about 15 ml. Each of two nasal cavities can be separated into several regions: nasal vestibule, inferior turbinate, middle turbinate, superior turbinate, olfactory area, frontal sinus, sphenoidal sinus, and cribriform plate of ethmoid bone. The nasal cavity also contains the nasal associated lymphoid tissue (NALT), which is largely found in the nasopharynx. Nasal cavity is coated with mucus layer and hairs which are engaged in such tasks are trapping inhaled particles and microorganisms. Moreover, mucociliary clearance, immunological activities and metabolism of endogenous chemicals are also crucial roles of nasal structures. The nasal cavity is covered with a mucous membrane which can be divided into two areas; nonolfactory and olfactory epithelium, in this non-olfactory area includes the nasal vestibule which is covered with skin-like stratified squamous epithelium cells, whereas respiratory region, which has a typical airways epithelium covered with numerous microvilli, resulting in a large surface area available for drug absorption and transport. Nasal cavity is split by middle septum into two symmetrical half, each one entering at the face through nostrils and continuing posterior to the nasopharynx. Both symmetrical halves consist of four sections (nasal vestibule, atrium, respiratory region and olfactory region) that are classified according to their anatomic and histological properties.

7.2 Nasal vestibule

Most anterior region of the nasal cavity is nasal vestibule, right inside the nostrils, and provides an area around 0.6 cm^2. Nasal hairs are found in this region, also called vibrissae, which filter the inhaled particles. Histologically, this nasal region is covered by a stratified squamous and keratinized epithelium containing sebaceous glands.

7.3 Atrium

Intermediate portion between nasal vestibule and respiratory region called atrium. Its front part is comprised by a stratified squamous epithelium and the posterior area by psudostratified columnar cells displaying microvilli.

7.4 Respiratory region

Largest section of the nasal cavity is respiratory area, also called conchae, is the cavity and it is split in superior, middle and inferior turbinates which are extruded from the lateral wall. The nasal respiratory mucosa, considered the most essential part for delivering medications systemically, is formed by the epithelium, basement membrane and lamina propria. The nasal respiratory epithelium comprises of pseudostratified columnar epithelial cells, globet cells, basal cells and mucous and serous glands. Many of the epithelial cells are coated on their apical surface with microvilli and the largest part of them also possesses tiny projections, termed cilia.

7.5 Olfactory area

Location of olfactory area located at the top of the nasal cavity and extends a short way down the septum and lateral wall. Its neuro-epithelium is the only portion of the CNS that is directly exposed to the external environment. Similarly to the respiratory epithelium, the olfactory one is likewise pseudostratified but contains specialized olfactory receptor cells crucial for scent perception.

7.6 Mucus membrane of nose and its composition

The nasal mucus layer is just 5 μm thick and it is arranged in two separate layers: an exterior, viscous and dense, and an interior, fluid and serous. Overall, nasal mucus layer comprises of 95% of water, 2.5-3% of mucin and 2% of electrolytes, proteins, lipids, enzymes, antibodies, sloughed epithelial cells and bacterial metabolites. Epithelial cells are generally of two types**:**

i. Provide a physical barrier to the entrance of infectious bacteria and allergenic particles.

ii. Work in combination with mucus glands and cilia to produce and remove mucus and foreign particles from the nasal cavity.

Blood supply to nasal cavity vasculature of the nasal cavity; has an abundant blood supply for carrying out its fundamental thermo-regulatory, humidificatory, olfactory, mucociliary, and immunological tasks. The nasal vascular bed is constructed in a way that facilitates the quick transport of fluid and dissolved excipients between blood vessels and nasal mucosa. It has been found that the capillary flow rate in the nasal mucosa is 0.5 ml/g/min.

7.7 Mechanism of drug absorption from nose

Drugs absorbed *via* the nasal cavity must first traverse the mucus layer; larger or more positively charged particles may have greater trouble doing so. However, this barrier is easily penetrated by tiny, unaltered particles. Paracellular transport involves movement between cells, whereas transcellular transport involves movement across cells, and simple diffusion across the membrane all contribute to absorption through the nasal mucosa.

The water route of transport, also known as the paracellular pathway, is the initial mechanism. This is a very sedentary and slug-gish approach. Drugs with molecular weights above 1000 Daltons had low bioavailability due to the inverse connection between molecular weight and absorption.

Lipophilic medications that exhibit a rate dependency on their lipophilicity are transported through the transcellular process, the second mechanism of transport along a lipoidal pathway. Active drug transport occurs when a carrier mediates the drug's passage across a cell membrane or when tight junctions are opened to allow drug entry. Chitosan, a naturally occurring biopolymer, is one such example; it unlocks tight connections between epithelial cells, allowing drugs to more easily cross the barrier.

7.8 Mechanism of drug distribution

Drug molecules' molecular weight, lipophilicity/hydrophilicity, degree of ionization, and rate of solubilization all interfere with the transepithelial mechanisms of passage and thus affect the drug's transport through the nasal epithelium (Alkhalifa *et al*., 2021; Parodi *et al*., 2017). General CNS pathways for nasal drug distribution are shown in the Figure 1.

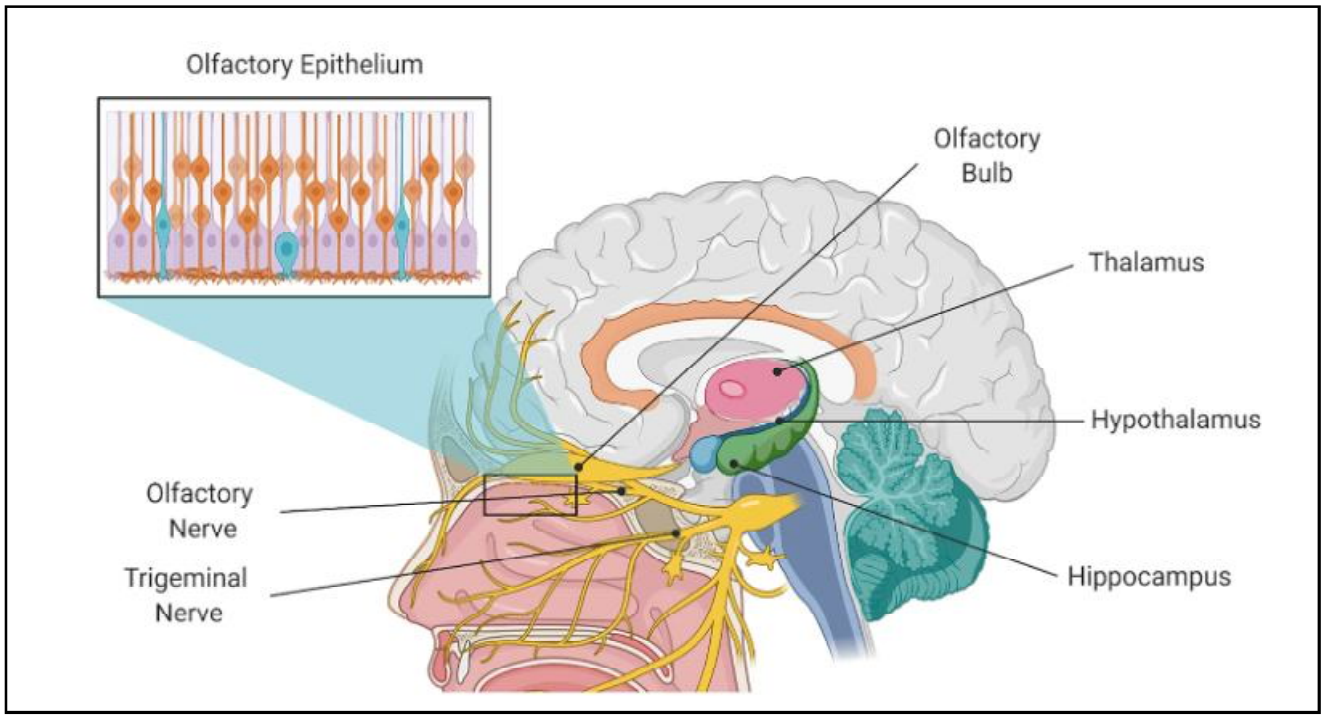

Figure 1: Schematic representation of the olfactory and trigeminal nerve position in the nasal cavity, and pathways to different CNS areas (source: Borrajo *et al*., 2022).

Drugs delivered intranasally have been shown to enter the brain either directly or indirectly via the cribriform plate, but the precise process by which medications are transported to the CNS remains unclear. The medicine enters the bloodstream or lymphatic system, travels throughout the body, and eventually crosses the blood-brain barrier (BBB) enroute to the brain. Several investigations have demonstrated that intranasal delivery of drugs is effective at transporting these substances straight to the central nervous system (CNS) *via* the nerves that go from the nose to the brain and spinal cord. In this respect, the olfactory and trigeminal nerves, the vasculature, the cerebrospinal fluid, and the lymphatic system have been extensively researched as potential delivery routes. One or more routes may be employed for efficient transport to the brain, depending on formulation, drug properties, and delivery method.

7.9 Olfactory nerve pathways

Through the cribriform plate, the olfactory nerve may quickly deliver medicines to the CNS's olfactory bulbs at high concentrations. The positive correlation between olfactory epithelium and bulbar drug concentrations has been demonstrated in a number of studies to be predictive of high CNS drug concentrations.

7.10 Pathways of the trigeminal nerve

The trigeminal nerve travels to the central nervous system and innervates the respiratory and olfactory epithelium. It is responsible for relaying sensations from the nose, mouth, cornea, and eyelids to the central nervous system *via* the ophthalmic division, the maxillary division, and the mandibular division, respectively. A portion of the trigeminal nerve enters the brain through the cribriform plate, which is adjacent to the track of olfactory interactions, making it difficult to know whether a drug administered intranasally reaches the olfactory bulb and other regions of the brain *via* the olfactory pathway, the trigeminal pathway, or both. Some research suggests that the Grueneberg ganglion in the nasal cavity, as well as other sensory structures (such as those innervating the face and head), may represent entry points for intranasally delivered medications that function in the central nervous system.

7.11 Vasculatory pathway

The nasal cavity is a highly vascularized area, receiving blood supply from the carotid artery as well as branches of the maxillary, facial, and ophthalmic arteries. Even though they both get blood, the olfactory epithelium and the respiratory epithelium do so from distinct vessels. The respiratory epithelium is better irrigated than the olfactory epithelium because there are more blood vessels there.

Because of this enhanced vascularization, the respiratory epithelium is the preferred site for absorption of most medicines given intranasally. There are a number of obstacles that inhibit efficient medication entrance and distribution in the brain when using blood circulation to transfer drugs to the CNS. Degradation by plasma proteases, drug clearance by hepatic and renal processes, drug binding to plasma proteins, possible peripheral effects, and the difficulties of getting across the BBB in an intact and active state all contribute to these restrictions.

7.12 Connections between the spinal fluid and the lymphatic system

The subarachnoid space, which includes cerebrospinal fluid (CSF), the perineurial spaces, which contain olfactory nerves, and the nasal lymphatics, which are crucial for CSF outflow, all work together to make it easier for medications supplied intranasally to reach the brain. Furthermore, the CSF and perineurial gaps allow medications given intranasally to reach the CNS without first entering the circulation. Several investigations have shown that medications given through the nasal cavity can enter the cerebral spinal fluid and be disseminated throughout the central nervous system and spinal cord (Reger *et al*., 2006). Direct transport to the brain via this pathway is also possible, albeit its efficacy depends on the drug's molecular weight, lipophilicity, and ionization state.

7.13 Instruments for intranasal dosing

Several strategies have been proposed to enhance both the local and systemic medication distribution *via* the nasal route. Clinical trials have examined several methods of administering medications to the nasal cavity, including the use of droppers, sprays, and needleless syringes. Although powder and suspension formulations and devices are available, liquid formulations account for the vast majority of the pharmaceutical business. Less preservatives are required to guarantee the absence of germs in powders, and the powders are more stable than liquid formulations.

Pipettes and droppers, once common tools for administering liquids via the nasal route, have given way to metered-dose spray pumps. Drug solutions may be delivered with excellent reproducibility of the emitted dose using both squeeze bottles and metered-spray pumps, both of which are utilized in over-the-counter medicines like topical decongestants. In contrast, a number of pharmaceutical firms have created nasal administration systems for powdered drugs. Unidose DPTM, sold by Bespak (UK), consists of a compressed air-filled container that releases the pressure needed to emit a haze of powder. Delivery of an immunoglobulin G (IgG) powder formulation was studied utilizing this apparatus and human MRI. The nasal vestibule was revealed to be the primary location of deposition for the administered IgG. Approximately 30% of the dosage was deposited in the deeper airways, whereas 95% was given in the nasal cavity. Once it is able to direct drugs to the olfactory epithelium, a driven breathing device is a promising candidate for direct delivery of drugs into the CNS, as it allows the administration of both liquid formulations and nasal powders in the nasal cavity and olfactory area, without deposition in the lungs and esophagus. While some factors, such nasal deposition and clearance rates, have been studied, this has slowed its practical use.

8. Intranasal application used for CNS delivery

The most prevalent route of medication administration in humans is through mouth. However, oral administration systems frequently fail to adequately transfer medications to the central nervous system (CNS) for the treatment of neurological illnesses or diseases. The central nervous system (CNS) is shielded from possible dangers by a series of barriers, the most significant of which is the blood-brain barrier (BBB). The BBB is made up of endothelial cells that are joined together by tight junctions (TJs) and adherent junctions (AJs), and serves as a crucial interface between the central nervous system and the rest of the body (Reger *et al*., 2006).

Insulin is a medication that targets the central nervous system (CNS) *via* olfactory-associated pathways, demonstrating the viability of IN use of such pharmaceuticals. Insulin has a crucial role in regulating central nervous system (CNS) energy metabolism. Insulin is transported across the BBB by insulin-sensitive glucose transporters, and insulin receptors are distributed broadly throughout the brain, with the highest concentration in the OB, cerebral cortex, hypothalamus, hippocampus, and cerebellum.

Neurodegenerative illnesses have RNA therapies at its center as a primary target for IN delivery. Since it was demonstrated that siRNAs, for instance, move through the olfactory nerve following IN administration, there has been a rise in the number of articles in the recent decade exploring the potential of siRNA and anti-senseoligonucleotides for such techniques (Claxton *et al*., 2015; Craft *et al*., 2017; Malhotra *et al*., 2013; Abdul Sayeed Khan *et al*., 2022; Asha Aurora *et al*., 2022). Stem cell transfer *via* the olfactory canal to the central nervous system is another fascinating novel use for IN technology. Fuorescently labeled rat mesenchymal stem cells (MSCs) and human glioma cells intranasally given to naïve mice and rats in 2009 revealed that these cells use the olfactory-associated neuronal pathways to reach different parts of the central nervous system. There is a growing body of pre-clinical research looking at the therapeutic potential of neuronal stem cells, progenitor cells, and mesenchymal stem cells for the treatment of brain tumors and neurological disorders. These methods appear to be a viable alternative to invasive procedures like intravenous injection.

9. Conclusion

When trying to transfer drugs to the brain to treat cancer or neurodegenerative diseases, the blood-brain barrier (BBB) is a major roadblock. The successes made thus far in developing NP-based drug carriers for effective drug delivery strategies across BBB are summarized in this study. In our quest for the most effective drug delivery methods, we reviewed the many features of NPs in order to shed light on the influencing elements for increased penetration effectiveness. We do want to stress that several factors affect NP transport across the BBB. Most notably, there are dimensions, shapes, ligand densities, surface charges, and approaches to drug loading. Despite extensive use of NPs-based systems to provide a synthetic platform for brain medication delivery because to their unique features, certain crucial problems have not been adequately investigated.

Development of nano-carriers to deliver medications to specific places is made possible by advances in nanotechnology. Multifunctional theranostic nanoplatforms, such as NP-based magnetic resonance imaging, computerized tomography, and photoacoustic imaging, are

being developed right now with particular nanocarriers that can pass the blood-brain barrier. Preclinical data have been encouraging for ligand conjugated NPs, which demonstrate the highest performance in carrying medicines through BBB. With further study, we anticipate that NP-based medication delivery into the brain will be a promising future avenue for the treatment of neurological disorders.

New medicines that can be taken by nose are likely to be the most interesting area of study in the future. So far, many possible new drugs have been talked about, such as oxytocin, IGF-1, insulin, glutathione, and many more. As the exact way more brain diseases work is figured out, more drug targets will be found. Even diseases that are not usually thought of as brain can have promise, like the weight loss drug leptin. This list will only keep growing as more experts learn about this new process.

Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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