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A Review of Nasal Drug Delivery: A Gateway to the Brain for Treating Neurological Disorders

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ABSTRACT: The blood-brain obstruction is a profoundly particular film that shield the brain from destructive substance but moreover confines the selection of helpful specialists making challenge in treating neurological disarranges. This audit investigates how nanotechnology can address these challenges by empowering focused on sedate conveyance over the BBB. Nanoparticle display a promising approach as they can be designed to cross the BBB and provide drugs straight forwardly to particular brain locales subsequently expanding treatment viability whereas minimizing side impacts. Diverse sorts of NPs such as liposomes ,polymers and metal based particle can be custom fitted with particular properties like measure surface charge and ligand connection to help BBB crossing through instrument such as receptor-mediated transport. The audit too looks at the BBB's physiology complex boundary. In addition, intranasal organization is highlighted as a non-invasive sedate conveyance strategy that bypasses liver and intestinal debasement utilizing the olfactory and trigeminal nerve pathway for coordinate brain transport. In conclusion, NP-based conveyance framework, when optimized for biocompatibility and steadiness have the potential to change medicine brain disarranges. Proceeded inquire about into NP-BBB intelligent is basic to development neurotherapies and move forward result for condition like brain tumors and Alzheimer's malady.

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INTRODUCTION:

The blood-brain barrier (BBB) is like a protective shield of the brain, made up of special cells that tightly control what substances can pass from the blood into brain. When this barrier is crucial for keeping harmful agent out of the brain, but it also poses a challenge for delivering drugs to treat brain disorders because it blocks many substances from entering [1].

To the overcome of these challenges, scientists are turning to nanotechnology; they involve manipulating mite particle at nanoparticle scale. Nanoparticles (NPs) offer promising solutions because they can engineered to carry drugs directly to specific areas of the brain, reducing side effects and increasing effectiveness [1,2].

There are many types of NPs, such as liposome, polymers, and metal nanoparticle, each with unique properties that can help them bypass BBB. For example, their small size and surface charge can all influence how well they can penetrate the barrier and deliver drugs to the brain.

When by attaching specific molecules surface of NPs, called ligands, scientists can enhance their ability to target and bind to receptors in brain cells, a process known the active targeting. This molecular recognition helps to ensure the drugs carried by the NPs reach their intended destination in the brain.

Fig 1. Graphical abstract of Brain Targeting drug delivery system.

Before these NPs can be used in therapy, it is crucial to understand their characteristics, such as size, surface charge, and how efficiently they can encapsulate drugs. These factors ultimately determine their effectiveness in delivering drugs across the BBB and treating brain disorders. The nanoscale is critical because it allows nanoparticles to interact with cells, triggering a cellular response. This means that are manipulating the size and composition of nanosystems, we can create particles that ability to traverse the blood-brain barrier (BBB). Most research suggests that nanoparticles ranging 100 to 300 nm are ideal for transporting drugs across the BBB. Furthermore, it is essential to ensure that these nanoparticles are both biocompatible and biodegradable to minimize any potential toxicity when used in living organisms [1,2].

Nanosystems play a major role in reducing the unintended spread of drugs throughout the body, thus minimizing adverse effects. By concentrating drugs specifically at their intended target sites within the brain, nanosystems enhance therapeutic effectiveness [2].

Objective [2,3]:

- Examine the physiology and intricate structure of the blood-brain Barrier (BBB).Investigate the different type of Nanoparticles and their modification, including size, surface charge, and ligand, interaction, to facilitate BBB penetration.
- Highlight intranasal drug delivery as a non-invasive method for targeted brain transport via the olfactory and trigeminal nerve pathways.
- Evaluate the biocompatibility, stability, and therapeutic potential of nanoparticle-based drug delivery systems for neurological disorders such as Alzheimer disease and brain tumors.
- Identify future research opportunities to optimize nanoparticle-BBB interaction for the development of advanced neuro therapies.

Blood-brain barrier physiology:

The connection between the bloodstream and brain tissue is maintained by microvascular network extent from arterioles to capillaries and venules. The health and proper functioning of the blood-brain barrier (BBB) are major for normal brain hemostasis. The key elements that contribute to barriers effectiveness to include [3,4].

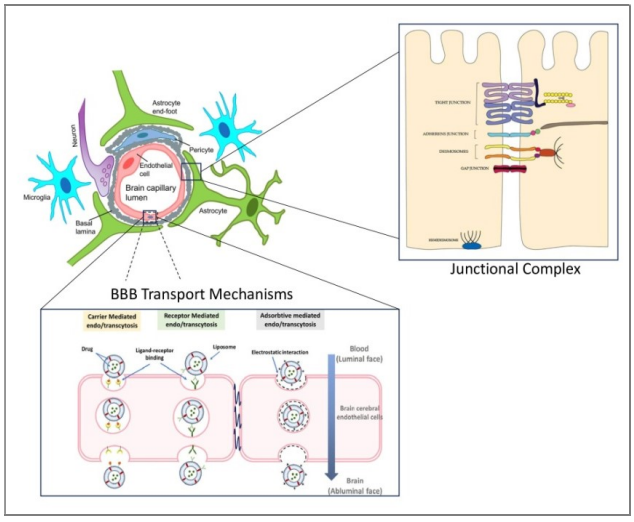

Fig 2. Physiology of Blood Brain Barrier [5,6].

Expression of junctional adhesion molecules (JAMs) and tight junction proteins (TJPs):

These molecules prevent substances from passing through cells and maintain the integrity of the barrier.

Inhibition of pinocytic vesicle and fenestrae:

These structures restrict the movement of substances across cells.

Presence of efflux pumps:

This pump actively expel substances from brain endothelial cell membranes, preventing them from entering the brain [7].

Expression of enzymes:

These enzymes break down compounds before they can reach the brain [7,8].

Structural components of BBB [8,9]:

The blood-brain barrier primarily serves to protect the brain tissue from pathogens and harmful substances. This selectively permeable barrier allows small, lipid-soluble molecules such as alcohol and anesthetics to diffuse across it. Proteins are mainly transported through tight junction solute carriers, which utilize electrochemical or concentration gradients for movement.

Moreover, smaller molecules like amino acids, ketones, glucose, nucleotides, and ions can be absorbed through receptor-mediated transport. The BBB relies on a complex interplay of both cellular and non-cellular components to maintain its integrity and function. These include brain microvascular endothelial cells, pericytes, and the end feet of astrocytes, which all play vital roles in forming and sustaining the BBB.

Endothelial cells:

Blood-brain barrier is firstly composed of the brain microvascular endothelial cells (BMECs), which are distinct from other endothelial cells due to having more mitochondria and lacking fenestration. They are express tight junctions (TJPs), creating a barrier that prevents most molecules from passing through, except for smaller and lipophilic molecules [10,11].

In addition to passive diffusion, efflux, and receptor-mediated transport are commonly used mechanisms for material exchange across the BBB. BMECs contain efflux transporters such as P-glycoprotein, including multiple drug resistance 1 and breast cancer resistance protein, which involved the activity transporting substance across the BBB.

Transport protein on BMECs selectively recognize and move essential substances like glucose, amino acids, purine bases the brain, and nucleosides from the bloodstream into the brain using RMT. This is crucial for supplying the brain with necessary nutrients and components [11,12].

Pericytes:

Pericytes are cells that surround and support endothelial cells along the walls of capillaries. They play a crucial role in the metabolism of the blood-brain barrier by facilitating the exchange of ions and metabolites between ECs. Both pericytes and ECs are separated by a continuous basal membrane and contribute to the tight junctions that ensure the impermeability of the BBB. The ability of the BBB to prevent the passage of substances is not solely attributed to ECs but is also enhanced by pericytes.

Pericytes contribute to the maintenance of specific proteins involved in TJ formation on ECs, such as Claudin-5 Occludin, and Zonula Occludens-1, which are essential for maintaining BBB integrity and function. Studies have shown that mice lacking viable pericytes exhibit significantly increased BBB permeability to water and various molecules, underscoring the importance of pericytes in BBB function. Pericytes influence EC tight junction proteins through chemical signaling and interactions with astrocyte end feet. Additionally, pericytes possess stem cell-like properties that contribute to repairing cerebral blood vessels and promoting new blood vessel formation (angiogenesis). Pericyte networks also play a role in controlling blood flow within capillaries through signal propagation along the vascular network [12].

Microglia in BBB:

Microglia, the resident macrophages in the central nervous system (CNS), play a critical role in maintaining the blood-brain barrier (BBB) integrity. These cells can be categorized into cytotoxic and neuroprotective types depending on the inflammatory conditions in the CNS. During inflammation, microglia migrate towards and accumulate around brain arteries. Surprisingly, this initial interaction with cerebral blood vessels actually serves to protect BBB integrity. However, chronic inflammation triggers a shift towards a more active microglial phenotype, leading to the phagocytosis of astrocytic end feet and subsequent loss of BBB integrity. The study employed Cx3cr1-GFP mice, which express a green fluorescent protein (GFP) specifically in microglia cells, to observe these dynamics. Administering lipopolysaccharides (LPS) resulted in a significant increase in the permeability of normally impermeable substances like dextran following microglial contact with the arteries. This research suggests potential strategies for manipulating BBB

integrity by targeting microglial cells in specific inflammatory conditions [13,14].

Basement membrane:

The basement membrane (BM) is an important part of the blood-brain barrier serving as a dynamic extracellular matrix that regulates interactions between cells and the matrix to maintain BBB structure and function. Within the BBB, there are two main types of basement membranes: the endothelial BM and the parenchymal BM. The endothelial BM, which lines the capillaries, is composed of collagen IV, fibronectin, and laminins. Pericytes are embedded within this basement membrane, contributing to its structure and function. On the other hand, the parenchymal BM consists of ECM components like laminin, along with astrocyte and neuron end foot processes. This layer surrounds the perivascular space and helps prevent the invasion of leukocytes into the central nervous system during inflammatory events.

Overall, the basement membranes within the BBB play a critical role in maintaining the integrity of the barrier by providing structural support and regulating immune cell infiltration into the CNS [15].

Blood CSF barrier at the choroid plexus:

The choroid plexus is a highly vascularized epithelial tissue located within the lateral, third, and fourth ventricles of the brain. Its primary function is to produce and release cerebrospinal fluid. The blood-cerebrospinal fluid barrier is formed by the epithelial cells of the choroid plexus, which separate the blood from the CSF and brain tissue. Unlike the blood-brain barrier, which is found in the brain's microvasculature, the BCSFB at the choroid plexus has unique structural features that allow for the transport of various substances. The choroidal capillaries are highly permeable and are not surrounded by astrocytes and pericytes as seen in the BBB. This unique arrangement includes fenestrated endothelial cells that facilitate the transport of water, lipophilic molecules, and gases. Microvilli present on the surface of CP epithelial cells facing the CSF contain Na+/K+ ATPase channels, creating an electrochemical gradient that allows sodium ions (Na+) to enter the CSF. These microvilli also increase the surface area, aiding in fluid secretion. The stroma surrounding the CP consists of collagen bundles and is lined by leptomeningeal cells.

The endothelial cells forming the choroid plexus still maintain tight junctions, but the electrical resistance observed here is lower compared to the BBB, making the CP membrane relatively leaky. This leakiness allows for easier movement of substances, including pathogens, into the brain. Therefore, the choroid plexus represents an important gateway for drug delivery to the brain due to its permeable nature and unique transport capabilities [14,15].

Circumventricular organ barrier:

Circumventricular organs are specialized regions in the brain characterized by fenestrated and highly vascularized blood vessels that allow for direct communication between neurons and the bloodstream, facilitating the detection of hormones and other substances in the blood. CVOs serve two main functions: sensory and secretory. Sensory CVOs, including the organum vasculosum of the lamina terminalis, the subfornical organ, and the area postrema, enable the brain to sense and respond to hormonal signals from the blood. Secretory CVOs, such as the intermediate lobe of the pituitary gland, pineal gland, median eminence (ME), and neurohypophysis, are involved in secreting hormones or other substances into the bloodstream. The lining of CVOs is composed of ependymal cells that form the ventricular walls and are bordered by astroglial cells. The epithelium lining the brain's ventricles expresses tight junction proteins similar to those found in endothelial cells of blood vessels. The capillaries within secretory CVOs, like the median eminence, are rich in fenestrae (small openings), allowing for a more liberal exchange of substances between blood vessels and the CVOs.

That suggests the ependymal cells at the ventral interface may facilitate the transport of larger molecules, such as leptin, between the cerebrospinal fluid and blood. This unique architecture and function of CVOs play a crucial role in the brain's ability to sense and respond to systemic signals from the bloodstream [30,31].

NANOMEDICINE FOR BRAIN DELIVER:

Nanoparticles are a captivating instrument with the potential to improve medicate transport over the blood-brain boundary or blood-tumor obstruction (BTB). NPs can be customized to offer different functionalities and carry assorted payloads. They can offer assistance in sidestepping sedate efflux transport, ensure against the digestion system, and explore tight intersections to provide typified drugs effectively. The flexibility of NPs in brain medication may encourage a more exact focus on the BBB and upgrade penetrability. When drugs are typified inside NPs, their penetrability over the BBB is

decided by the physicochemical and natural properties of the NPs or maybe exclusively by the drug's chemical structure. The biodistribution of NPs is incredibly affected by their physical characteristics, such as molecule measure, shape, surface charge, and utilitarian groups [16,18,20].

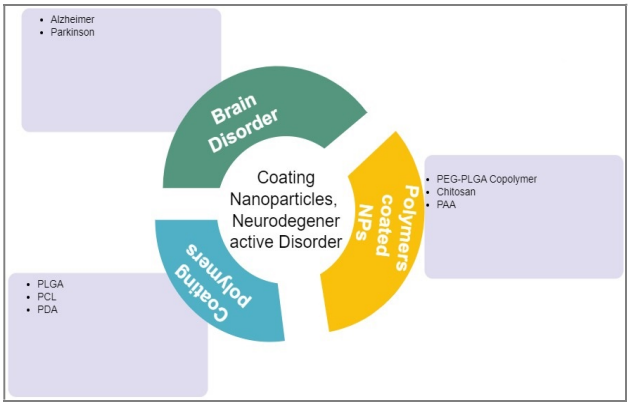

Fig 3. Nanomedicine for brain delivery [17].

To move forward with transport of NPs over the BBB and upgrade cellular take-up in brain tumor cells, analysts have investigated brightening NPs by focusing on ligands such as antibodies, peptides, little compounds, and aptamers. Peptides are especially emphasized as focusing on ligands due to their cost-effectiveness, lower immunogenicity, and more prominent chemical differences compared to bigger proteins like Trojan horse antibodies. Different instruments through which little particles and NPs enter the BBB have been investigated [21,22].

INTRANASAL ORGANIZATION FOR BRAIN-TARGETING DELIVERY:

Traditional strategies of regulating drugs to target the brain, such as verbal and parenteral courses, include conveying drugs into the brain through the circulation system. Be that as it may, numerous drugs managed this way battle to enter the blood-brain boundary, driving to moo brain bioavailability. Huge particles and most low-molecular-weight drugs confront critical challenges crossing the BBB. The Verbal organization regularly comes about in the liver digestion system and intestinal debasement sometime recently comes to the brain. Parenteral strategies like intrathecal conveyance can lead to complications such as cerebrospinal liquid spillage and meningeal issues [23,24,26].

In differentiate receptor-mediated approaches point to improving brain-targeting capabilities without disturbing the BBB but carry the chance of sedate carriers amassing in unintended destinations like the liver.

In 1989, William H. Frey II presented intranasal organization as a non-invasive strategy for nose-to-brain sedate conveyance. This approach takes advantage of coordinate associations between the olfactory nerve and the brain's frontal locale, encouraged by the olfactory bulb, as well as the trigeminal nerve's section through the trigeminal ganglion and pons. These associations permit drugs to bypass the BBB, maintain a strategic distance from the hepatic digestion system, and anticipate debasement by intestinal chemicals. Intranasal conveyance offers tall quiet compliance, and reasonableness, and dispenses with the requirement for complex restorative interventions [25-27].

Pathway of Intranasal Transport to the Brain:

The improvement of intranasal sedate organization is driven by the requirement to convey drugs to the brain while circumventing the Blood-Brain Boundary. In intranasal organization, drugs can utilize two essential pathways the olfactory and trigeminal nerve pathways that offer coordinated courses to the brain. In the olfactory nerve pathway, drugs are ingested by olfactory receptors in the olfactory epithelium through endocytosis or detached dissemination. They are at that point transported along olfactory nerve axons by means of intracellular axonal transport. Small-molecule drugs beneath 200 nm are especially compelling in this pathway due to the estimate of olfactory nerve axons. The interesting structure of these axons, encompassed by olfactory ensheathing cells and amplifying to the olfactory bulb through the cribriform plate, permits for medicate conveyance from the fringe anxious framework (olfactory epithelium) to the central anxious framework (brain). From the lamina propria of the olfactory epithelium, drugs can reach the perineural space containing cerebrospinal liquid, which interfaces with the subarachnoid region [27,28,32].

This nerve has branches innervated with ophthalmic, maxillary, and mandibular nerves, focalizing in the trigeminal ganglion. Beginning from the pons of the brainstem, the trigeminal nerve serves as a potential course for calm transport to the central anxious system (CNS). Drugs ingested in the maxillary and ophthalmic nerve branches can be passed on to the brainstem by implies of the pons, empowering brain-targeted movement.

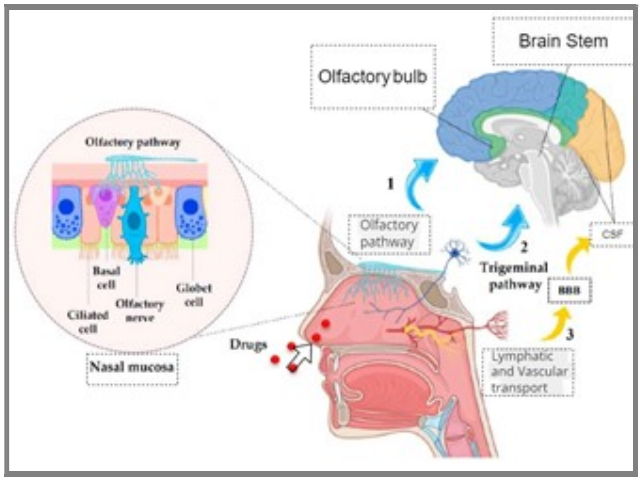

Fig 4. Intranasal mechanism of nose-to-brain delivery [29,30].

The trigeminal nerve pathway enables nose-to-brain transport through both intracellular axonal transport and extracellular rebellious, related to those observed in the olfactory nerve pathway. Be that as it may, the intracellular transportation rate in the trigeminal nerve pathway is slower compared to the olfactory nerve pathway [28,29,33].

DISCUSSION:

Nanotechnology offers promising solutions for overcoming the challenges of delivering drugs across the blood-brain barrier (BBB). By leveraging nanoparticles (NPs), scientists can design targeted delivery systems that enhance the efficacy and reduce the side effects of treatments for brain disorders.

Key Challenges and Innovations:

The BBB's selective permeability, maintained by tight junctions, efflux pumps, and metabolic enzymes, poses a significant challenge for drug delivery. NPs, due to their small size and customizable surface properties, can bypass these barriers by mimicking natural transport mechanisms such as receptor-mediated transport (RMT). Attaching specific ligands to NPs enhances their ability to target and bind to brain endothelial cells, improving delivery precision and minimizing off-target effects.

Critical NP Characteristics:

The effectiveness of NPs in crossing the BBB depends on their size, surface charge, and biocompatibility. NPs within the 100-300 nm range are optimal for BBB penetration, and surface charge influences their interaction with cell membranes. Ensuring NPs are biocompatible and biodegradable is crucial for their safe application in clinical settings.

Clinical Implications:

NP-based drug delivery systems have the potential to revolutionize the treatment of neurological disorders by enabling targeted delivery of therapeutics to the brain. This could significantly improve outcomes for conditions like brain tumors, Alzheimer's disease, and Parkinson's disease. Future research should focus on optimizing NP formulations for specific applications and advancing our understanding of NP interactions with BBB components.

In summary, nanotechnology holds great promise for advancing drug delivery across the BBB. Continued research and interdisciplinary collaboration are essential to translate these innovations into clinical practice, ultimately improving patient care and treatment outcomes.

CONCLUSION:

In conclusion, nanotechnology presents promising avenues for drug delivery across the blood-brain barrier (BBB). Utilizing nanoparticles (NPs), tailored delivery systems can be crafted to improve treatment effectiveness for brain disorders, while also reducing adverse effects. Key NP features including size, surface charge, and biocompatibility play crucial roles in navigating the BBB. While NP-based drug delivery systems hold transformative potential for neurological treatments, ongoing research, and collaborative efforts are essential to refine formulations and comprehend NP interactions within the BBB. Ultimately, nanotechnology stands poised to significantly enhance patient care and treatment outcomes in the field of neurology.

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