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Overcoming the Blood-Brain Barrier with Nanoscale Drug Delivery to the Brain through the Nasal Route: Review

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ABSTRACT:

Nanotechnology has developed as a revolutionary technique for precise drug delivery to the brain via the nasal route, circumventing the blood-brain barrier. This ground-breaking technique provides a non-invasive and incredibly effective way to deliver therapeutic chemicals right to the brain, improving therapy choices for neurological illnesses. Drugs can be encapsulated and tailored to traverse the nasal mucosa and reach the brain tissue with amazing precision by using nanocarriers, such as nanoparticles and liposomes. This ground-breaking use of nanotechnology holds out hope for more effective medications with fewer side effects in the treatment of ailments including Alzheimer's, Parkinson's, and brain cancers.

Introduction:

Various formulation approaches are continuously employed to enhance bioavailability, minimize side effects, and improve patient acceptance in drug delivery systems [1]. A vast array of drugs serves as examples of this ongoing development [2-7]. Targeted drug delivery systems [TDDS] are valuable techniques for administering medications in a manner that concentrates them in the body's target organs, tissues, or cells. This approach enhances treatment efficacy and reduces the side effects associated with the administered drug. TDDS facilitates the precise delivery of necessary medications at lower doses [8].

The brain is a vital organ that controls all bodily systems. Therefore, managing or treating any defects or diseases related to the brain can be extremely challenging due to the presence of the Blood-Brain Barrier [BBB]. Many illnesses of the central nervous system [CNS] cannot be adequately treated with systemically administered drugs because of the BBB, which acts as a strong barrier in the brain. The BBB prevents medications from entering the brain parenchyma and separates blood from the parenchyma. Medicines with high molecular weights or strong polarities cannot cross this barrier, while a small number of tiny molecule medicines can. Given the existence of the BBB, achieving significant pharmacological activity alone is insufficient when developing medications to treat various CNS diseases. The development of brain-targeting drug delivery systems has become the main goal of intense research and development in order to circumvent the BBB and effectively deliver therapeutic medications to the brain [9-12].

Challenges in the brain TDDS

One challenge is that when a drug crosses the BBB, it often does not reach therapeutically relevant concentrations. This could be due to the drug's design, which limits its ability to pass through the BBB, or it may bind to other proteins in the body, making it ineffective in crossing the barrier.Another obstacle is the presence of enzymes in brain tissue that can deactivate the drug [10].

Techniques for brain drug delivery:

Three categories can be used to group the methods frequently used to target the BBB in medication delivery:

I. Invasive methods

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II. Noninvasive methods
III. Miscellaneous methods or alternative routes

Invasive method

This approach encompasses four different types: intracerebral implant/injection [IC], intracerebral ventricular infusion [ICV], convection-enhanced delivery [CED], and BBB disruption. Both IC and ICV routes involve administering various drugs to the brain after creating an opening in the brain through drilling. The implant is then inserted as either a bolus or infusion, depending on the route. This method can accommodate compounds of various sizes [10, 13, 14].

The CED method involves surgically exposing the brain and placing a small-diameter catheter directly into the brain parenchyma. Through this catheter, medicine is continuously injected into the brain over several days until it reaches the interstitial spaces 14-16.

By making the tight connections between the endothelial cells of the brain capillaries permeable, the BBB disruption can make it easier to enter the brain. BBB disruption techniques include laser interstitial thermotherapy, targeted ultrasound, and intra-arterial mannitol infusion [osmotic and ultrasonic disruption][14, 17].

Examples of invasive approaches include IC implantation of many chemotherapy drugs[18, 19] and the local administration of anticancer drugs to intracranial targets [20, 21].However, invasive approaches have their disadvantages [22]:

I. They tend to be expensive.
II. Hospitalization and anesthesia are often required.
III. Successful BBB breakdown through these techniques may enhance tumor spreading.
IV. Neurons may be permanently injured if inappropriate blood components enter the brain.

Noninvasive methods

In general, these methods rely on manipulations of drugs or their characteristics. This approach includes the prodrug approach, nanoparticles, and liposomes.

Prodrug Approach: Using this technique, a prodrug is created by covalently attaching a drug to an inert chemical component. Following administration, the prodrug is digested and transformed inside the brain into the parent drug's active form. Metabolic processes break the bond in the prodrug, leading to the formation of the active drug. This modification aims to enhance the drug's ability to traverse the BBB by improving its lipophilicity [23, 24].

Examples of drugs utilizing the prodrug approach include morphine, levodopa, and valproate [10, 24]. Disadvantages of the Prodrug Approach [22,25]:

This approach can have unfavorable effects on pharmacokinetics because some prodrug molecules may alter the original drug's tissue distribution, efficacy, and toxicity. The increased molecular weight of the drug due to lipidation can be a limitation."

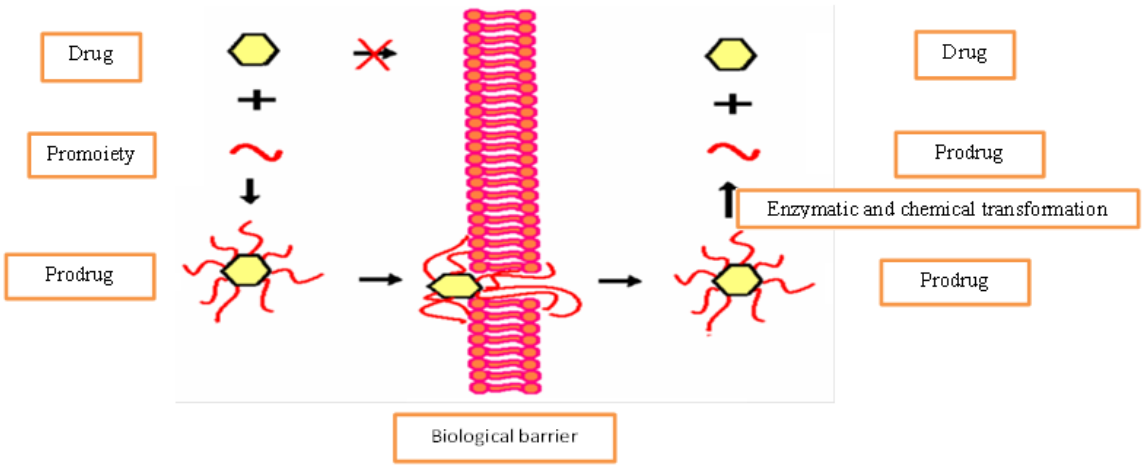

Figure 1: The prodrug approach [25]

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Nanoparticles: Nanoparticles are solid granules or dispersions ranging in size from 1 to 100 nm. In order to dissolve, trap, encapsulate, or bind pharmaceuticals, they use a nanoparticle matrix. Both active and passive drug targeting can be achieved using nanoparticles. However, their small size limits the amount of material they can encapsulate. Nanoparticle systems may simultaneously enhance drug targeting to the BBB and improve its ability to cross it, compared to conventional drugs [26-28]. For these nanoparticles to successfully target the brain, crucial properties including particle size and zeta potential must be present. These nanoparticles can be created from a variety of natural or synthetic materials[29].

Examples of the nanoparticle approach include vaccines, loperamide, and anticancer drugs for metastatic brain tumors [30, 31]. Disadvantages of Nanoparticles [32]:

I. Cost.
II. Low encapsulation efficiency.
III. Water-soluble drugs may quickly leak out in the presence of blood components.
IV. Nanoparticles are difficult to work with in both dry and liquid forms because of their tendency to clump together due to their small size and vast surface area.
V. They may cause allergic reactions and immunological responses.
VI. The preparation process may involve harsh toxic solvents.

Liposomes: Liposomes are aqueous, nano- or micro-sized vesicles enclosed by one or more lipid bilayers on all sides. In the therapy and diagnosis of neurological illnesses, they have undergone substantial research regarding medication, imaging, and gene delivery[33–36]. Different liposomal structures and methods have enhanced medication delivery across the BBB. Therapeutic medications and genes can be effectively transported by cationic liposomes[37–39]. Because of the electrostatic interactions between negatively charged cell membranes and cationic liposomes, which increase nanoparticle uptake by adsorptive-mediated endocytosis, these carriers are thought to be more effective for delivering drugs to the brain than normal, neutral, or anionic liposomes[40-42].

Doxorubicin with quantum dots and apomorphine as liposomal-encapsulated systems for brain therapy and imaging are two examples of the liposome method[43]. It has been discovered that theranostic liposomes can pass through the BBB, providing a cutting-edge method for identifying and treating brain tumors. The term "theranostic" describes nanoparticles that combine diagnostic and therapeutic chemicals in a single system[44, 45]. Disadvantages of Liposomes [46]:

I. Instability or lack of stability.
II. Drug encapsulation issues.
III. Short lifespan.
IV. Batch-to-batch reproducibility challenges.
V. Sterilization difficulties.
VI. Non-specific absorption by peripheral tissues and binding to serum proteins may affect cationic liposomes used for brain delivery, lowering their surface charge and increasing the amount needed to achieve therapeutic efficacy. Therefore, it's imperative to create liposomes that can effectively target parts of the brain that are ill[47].

Spanlastics Nanovesicles

One method is the intranasal route, which travels from the nasal cavity to the central nervous system via the trigeminal pathway without passing via the blood-brain barrier [BBB] or the olfactory region. Medication can be supplied to the brain over the BBB using spanlastic dispersion in order to carry out a specific activity.

By other route, nose to brain drug delivery:

In comparison to IV, per rectum, or oral medication delivery, nasal drug delivery has a number of benefits. These benefits include non-invasive administration, a faster beginning of the therapeutic action, enhanced bioavailability by avoiding hepatic first-pass metabolism, the possibility of greater CNS drug availability by avoiding the BBB, and the absence of the need to change the parent medication for transport to the target[48]. Due to its anatomical and physiological characteristics, particularly its capacity to circumvent the BBB, intranasal administration [IN] offers special advantages for quickly delivering medications directly to the brain. Additionally, it offers a significant, highly vascular absorptive surface right next to the brain and a direct pathway for drug absorption into the bloodstream, reducing systemic side effects[49].

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Nasal administration is an exciting method for treating brain problems since it has the potential to transfer biologics to the brain, such as peptides, proteins, oligonucleotides, and even cells[50]. Various methods exist for IN-administered medications to permeate the olfactory epithelium[51], as illustrated in Figure 2**.**

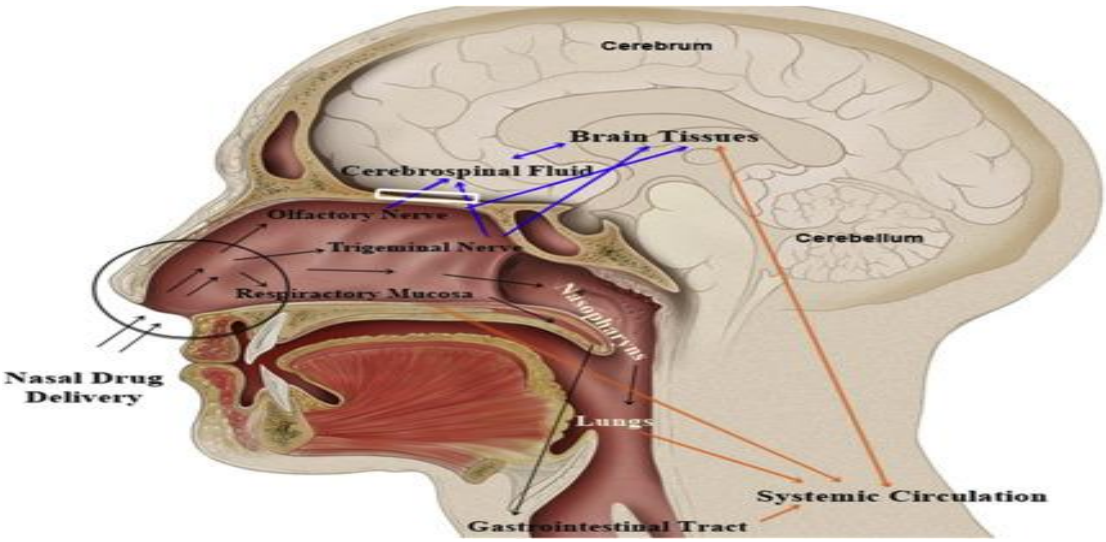

Figure 2: Mechanisms of drug transportation from IN route to brain [52]

Olfactory Neural Pathway: Therapeutic substances delivered orally travel to the olfactory epithelium, where olfactory receptor neurons carry out transduction. Transduction occurs at the cilia located at the tips of these neurons. These substances can enter olfactory receptor neurons via either a paracellular or transcellular route [53]. Drug molecules pass through the cribriform plate, a nerve bundle, and axons on their way to the olfactory bulb, which is located on the surface of the brain. The olfactory nerves allow medications to reach the olfactory bulb and cerebrospinal fluid [CSF][54]. Drugs can enter the brain via combining with interstitial fluid after leaving the CSF. A medication can reach the brain via the olfactory transport from the nasal cavity in just a few minutes. The active moiety may take hours or days to travel through the intra-neuronal pathway to all parts of the brain, but the extra-neuronal pathway, which involves perineural channel trafficking, just needs a few minutes[55–57].

Trigeminal Neural Pathway: The central nervous system [CNS] as well as the respiratory and olfactory epithelium of the nose passages are all innervated by the trigeminal nerve route, the biggest cranial nerve pathway. The nasal cavity, oral cavity, eyelids, and cornea send sensory information to [CNS] via the ocular, maxillary, and mandibular divisions of the trigeminal nerve. The ocular and maxillary nerves are crucial for nose-to-brain delivery because neurons from these branches pass directly through the nasal mucosa. Through this mechanism, drugs can be delivered either by endocytosis or intracellular transport[58].

Systemic Pathway: Compared to the olfactory mucosa, the respiratory mucosa's rich vasculature enables a larger absorption of drugs into the systemic circulation[59]. The respiratory segment consists of both fenestrated and continuous endothelium, enabling the sequential passage of small and large molecules into the bloodstream and across the [BBB] to reach the CNS. Unlike large, hydrophilic molecules, small lipophilic molecules easily enter the bloodstream and traverse the BBB. The active moiety enters the nasal blood arteries and proceeds swiftly from the systemic circulation to the carotid artery, delivering blood to the brain and spinal cord[53].

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Factors Affecting Nasal to Brain Drug Delivery[60]:

Several factors influence intranasal [IN] drug delivery, including:

I. Molecular weight and solubility
II. Osmolality and volume
III. Blood flow and pH
IV. Pharmaceutical dosage forms
V. Mucociliary clearance
VI. Transport mechanisms

Examples of drugs that utilize intranasal delivery include nimodipine, sumatriptan, rizatriptan, and flibanserin [61-64]. Nasal to brain delivery drawbacks [53, 65-67]:

I. Loss of unabsorbed drugs in the respiratory or digestive tract with potential adverse effects.
II. The nasal cavity is only occupied for a brief period of time due to quick physiological clearance mechanisms [mucociliary clearance].
III. Due to the nasal cavity's low permeability to these substances, it is difficult to formulate macromolecules or water-soluble medications.
IV. Molecules with a molecular weight of up to 1000 daltons can normally achieve good bioavailability after nasal medication delivery, while enhancers may increase bioavailability to at least 6000 daltons in terms of molecular weight.
V. Limited administration dose [25–200 µl].
VI. Presence of nasal proteolytic enzymes.

Drug Delivery From Nose to Brain Pharmacokinetics

To assess the efficacy of drug absorption via nose to brain distribution, as opposed to a traditional method for brain delivery [oral, parenteral, and transdermal], particular pharmacokinetic indices are needed.

When a medicine is administered intranasally as opposed to systemically, drug targeting efficiency [DTE], a metric, evaluates how well the drug enters the brain [equation 1]. Changes in drug concentration during the course of the trial are represented by the area under the curve [AUC]68. The values range from 0 to + ∞, and those above 100% show more effective brain targeting through IN than IV, while those below 100% show the opposite.

$$DTE[\%]_{[in]} = \frac{\left(\frac{AUCbrain}{AUCblood}\right)_{IN}}{\left(\frac{AUCbrain}{AUCblood}\right)_{IV}} \times 100 \qquad [1]$$

The drug concentration in the brain was not caused by a particular mechanism, according to DTE. It suggests that intranasal delivery instead of intravenous administration results in increased brain bioavailability.

To measure whether or not intranasal delivery of medications results in the drugs directly reaching the brain, we can employ direct transport percentage [DTP]. DTP is a measurement of the IN dosage to the brain as a percentage of the overall IN dose to the brain [equation 2]. It refers to the part of the drug that was delivered directly to the brain.

$$DTP[\%]_{[in]} = \frac{AUC\ brain\ [IN] - F}{AUC\ brain\ [IN]} \times 100 \qquad [2]$$

F is the systemic circulation's [indirect pathway] percentage of the brain's AUC [equation 3].

$$F = \frac{AUCbrain[IV]}{AUCblood[IV]} \times AUCblood[IN] \qquad [3]$$

DTP values might be between - ∞ and 100%. A high DTP value shows that drug levels are influenced by the direct nasal to brain pathway, whereas a negative or zero value demonstrates that the drug prefers to be delivered to the brain via systemic circulation after IV administration. These quantitative data aid in the development of sophisticated pharmacokinetic-pharmacodynamic models to forecast CNS concentration for delivery from the nose to the brain [68]. High values will be produced by drugs that are poorly permeable to the BBB, albeit this does not always translate into high bioavailability in the brain. One drawback of DTE and DTP is this. B%Brain IN/IV [equation 4] is used to compare the drug accumulation in the brain from IN and IV. Values above 100% indicate better IN injection-induced brain drug accumulation.

$$B\%_{Brain\ IN/IV} = \frac{AUCbrain\ [IN]}{AUC\ brain\ [IV]} \times 100 \qquad [4]$$

Following intranasal administration, Bx [the quantity that reached the brain via systemic transport] is determined using the equation[equation 5][69].

$$Bx = \frac{[AUCblood]IN \times [AUCbrain]IV}{[AUCblood]IV} \qquad [5]$$

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Bioavailability compared to Instead of employing a drug solution, a nanosystem IN is used to assess drug accumulation in the brain [equation 6]. Because many nose to brain delivery techniques use nanocarriers to deliver pharmaceuticals, it could be necessary to compare the effectiveness of the nanosystem to that of a free drug solution.

$$Relative\ bioavailability_{Brain} = \frac{[AUCbrainIN]_{nanosystem}}{[AUCBrainIN]_{solution}} \times 100 \quad [6]$$

Values over 100 indicate that the nanosystem will accumulate drugs more effectively than the drug solution will. Using the relative bioavailability idea, the following equations[equation 7,8][70] can be used to compare the relative DTE and DTP of the nanosystem and drug solution:

$$RDTE\% = \frac{DTE\%_{INnanosystem}}{DTE\%_{INsolution}} \times 100 \quad [7]$$

$$RDTP\% = \frac{DTP\%_{INnanosystem}}{DTP\%_{INsolution}} \times 100 \quad [8]$$

Conclusion

Drug transport to the brain is significantly hampered by the blood-brain barrier [BBB]. Fortunately, there are a number of effective approaches to get over these obstacles and accurately target medications to brain cells. The main benefit of these specialized methods is that they may effectively treat a variety of central nervous system [CNS] illnesses that were previously underserved by traditional medication delivery methods.

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