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NASAL DRUG DELIVERY: A PROMISING WAY FOR BRAIN TARGETING

Azhar Danish Khan*[1], Lubhan Singh[1]

1. Ram-Eesh Institute of Vocational and Technical Education Greater Noida U.P.

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Corresponding author:
Azhar Danish Khan
Assistant Professor
Ram-Eesh Institute of Vocational and Technical Education
Plot No. 3, Knowledge Park-I
Greater Noida,
Uttar Pradesh- 201310

ABSTRACT

The nasal route is especially advantageous as an alternative route of drug administration for the delivery of drugs that undergo extensive first-pass metabolism or are sensitive to gastrointestinal degradation. The nasal delivery seems to be a favourable way to circumvent the obstacles for blood brain barrier (BBB) allowing the direct drug delivery in the biophase of central nervous system (CNS)-active compounds**.** It is the only site in the human body where the nervous system is in direct contact with the mucus linings and surrounding blood capillaries. The nasal route, therefore, offers a potential route for drugs targeting the brain providing more opportunities to enter the CNS to treat CNS disorders. This review highlights vast applications for nose to brain drug delivery.

INTRODUCTION

The nasal administration of various drugs, namely numerous compounds, peptide and protein drugs, for systemic administration has been widely investigated in recent years. Recently many researchers have also attempted delivery of drugs to the CNS through the nose. A lot of research is going on in brain and central nervous system disorders like schizophrenia, meningitis, migraine, Parkinson‘s disease and Alzheimer‘s disease still remains the world's leading cause of disability, and responsible for more hospitalizations cases and prolonged care than all other diseases combined. The major concern in drug delivery to brain is the presence of the BBB[1]. Brain is tightly separated from the circulating blood by a membranous barrier called the Blood Brain Barrier (BBB) [2, 3]. The major challenge in CNS drug delivery is the blood-brain barrier (BBB), which limits the access of most drugs to the brain. Advances in knowledge of the cell biology

of the BBB have made new avenues and possibilities for improved drug delivery to the CNS. It is well established that the BBB is a membranous barrier that segregates the brain from the circulating blood [4].

The second barrier that a systemically administered drug molecule encounters before entering the CNS is the blood-cerebrospinal fluid barrier (BCB). As the CSF has the ability to exchange molecules with the interstitial fluid of the brain parenchyma, the passage of blood-borne molecules into the CSF are also carefully controlled by the BCB[5]. The BCB is found in the epithelium of the choroids plexus, and is arranged in such a manner that it limits the passage of molecules and cells into the CSF[6].

Nasal route has been explored as the conventional route, for the local delivery of drugs for treatment of local diseases like nasal allergy, nasal infections, rhinitis and nasal congestion. Since last few decades, nasal route had attracted a wide attention for researchers as an acceptable, reliable and a safe route to achieve faster and higher levels of drug absorption[7]. Most of the therapeutic agents have been abandoned because sufficient amount of drug levels in the brain have not been achieved by the drugs via the systemic circulation. Macromolecular drugs like peptides and proteins, termed as “biologics” are too large and too hydrophilic to penetrate the BBB from the systemic circulation. The major disadvantage associated with them is that they would be rapidly degraded by gastrointestinal enzymes or by the liver cytochromes, if taken orally. A non-invasive therapy seems to be desirable for the patients particularly for diseases that require chronic dosing in case of dementia. It has been proved theoretically in the animal and human investigations that transport of exogenous materials directly from nose-to-brain is a potential route for by-passing the BBB[8].

The prevailing interest in intranasal route for therapeutic purposes other than the topically nasal drug delivery arises from the particular anatomical, physiological and histological aspects of the nasal cavity, which provides potential for rapid systemic drug absorption and quick onset of action. Further intranasal absorption avoids the gastrointestinal and hepatic pre systemic metabolism, thus enhancing drug bioavailability in comparison with that obtained after gastrointestinal absorption [9, 10]

CONVENTIONAL BRAIN TARGETING STRATEGIES:

INVASIVE STRATEGIES:

DISRUPTION OF THE BLOOD BRAIN BARRIER:

In this technique mannitol solution is injected into arteries in the neck thus

causing shrinkage of BBB instantly. The resulting high sugar concentration in brain causes the capillaries to take up water out of the endothelial cells which leads to shrinkage of endothelial cells and leads opening tight junction. The effect lasts for 20 to 30 minutes, which is sufficient for the drugs to diffuse freely, that might not normally cross the BBB[11]. Apart from opening of junction complexes and formation of inter endothelial gaps, trans-endothelial opening and tracer passage through the cytoplasm of injured endothelial cells were also observed in response to the hypertonic barrier disruption[12].

INTRACEREBRAL IMPLANTS:

Intracerebral chemotherapeutic implants are the controlled release systems. Small pellets of testosterone (T) or estradiol (E_2), but not cholesterol (CH), when implanted into the brain of neonatal female rats on day 2 or day 5 of life, produce masculinization of the adult regulation of gonadotropic hormone (GTH) release, female sexual behavior or masculine sexual behavior, specific to the site and time of implantation and the hormone implanted. Ovariectomized female rats were estrogen-primed by subcutaneous injection and two days later were tested for sexual receptivity 6 h following bilateral implants of crystalline progesterone or cholesterol combined with a subthreshold injection of progesterone administered systemically. Cannulae were located in either the medial basal hypothalamus (MBH) or the mesencephalic reticular formation (MRF) in different groups of females [13-14].

INTRAVENTRICULAR DELIVERY:

Intraventricular route is best suited for meningioma treatment and metastatic cells of CSF as it distribute drugs mainly into ventricles and subarachnoidal area of brain[20]. Thus it act as an approach to bypass BBB by neurosurgical means where therapeutic agents are instilled directly into cerebral ventricle. Due to lack of interconnection with interstitial fluid of brain unlike intracerebral delivery, this is a very promising approach. Thus the drug achieves higher concentration in brain in comparison to that of its extravascular distribution[21]. But the major disadvantages are the chance of causing subependymal astrogliatic reaction due to high drug exposure at the ependymal surface of brain[15].

INTRATHECAL DELIVERY (INTRA-CSF DRUG DELIVERY):

Intrathecal route involves delivery of neurotherapeutic agents to brain by direct administration of drugs through intrathecal route into cisterna magna of brain. Intrathecal infusion is currently used clinically to deliver analgesics for chronic

pain and antispasticity drugs for severe spasticity[16, 17, 18]. Although intrathecal delivery with an infusion pump provides reliable, continuous administration of agents, cath-eterization of the SAS is an invasive technique, which may require a hemilaminectomy for exposure of the vertebral interspace. Also, implantation of the catheter can cause adverse reactions, namely chronic inflammation and dural fibrosis, or result in spinal compression or infection, as reported in rodents and dogs [19, 20].

PHYSIOLOGICAL STRATEGIES:

Pseudo nutrient Approach:

Pseudo nutrient Approach Peptide drug design incorporates a specific molecular characteristic that facilitates the drug to be transported by one or more of the inwardly directed nutrient carriers. The BBB conveys several systems for the transport of nutrients and endogenous compounds**.** Peptides and small endogenous molecules are forming the drug carrier system that are transported via definite transporters which is present on endothelial cells .BBB have the several transporters system which deliver a drug at controlled manner in to the brain. Pseudo nutrient should show similarity with the molecular structure to the drugs. Amino acid and hexose molecular carrier system have good capacity for deliver a drug in to the brain. These are called carrier-mediated transport system. Small drug molecules directly conjugate with antibodies and target to the brain by overcome of BBB restriction. For example, to deliver of dopamine by antibodies conjugation in Parkinson's disease. Choline transporters, amino acid transporters are the use of BBB transport [21]

Ligand Binding Proteins:

Protein ligands possesses various properties such as high affinity to receptors and selectivity for targeting, which facilitates the interest towards the use of proteins as a delivery tool for targeting drugs to the brain. Central ligand binding component such as lectins act as a ligand binding protein for brain targeting of glucose triggered glycosylated insulin and bispecific antibodies. Cationized albumin appears to be useful for the delivery of the active agents across the BBB to the brain. Other classes of ligand binding protein include biotin-binding proteins, lipid binding proteins and avidin binding proteins. The way avidin biotin conjugates, similarly immonoglobins occupy a special place in the field of ligand binding proteins because of their ability to recognize almost infinite number of ligand molecules[22].

Chimeric Peptides:

Synthesized chimeric peptides are another possibility for the drug delivery to the brain. Chimeric peptides are generated by linking of a drug which lacks transport at

BBB to a vector at the luminal membrane of brain capillary endothelial cells. The vector initiates receptor - mediated or adsorption - mediated trancytosis[23].

PHARMACOLOGICAL STRATEGIES:

Pro-drug Based Brain Targeting:

Naproxen (Nap) is an NSAID used as a neuroprotective agent to treat several neurodegenerative diseases. The noticed limited brain bioavailability of the drug prompted the design of several chemical delivery systems. It was found that the synthesis and preliminary in vitro and in vivo investigations of Nap prodrugs with dihydropyridine (I) and ascorbic acid (II) through an ester spacer to target specific brain delivery of Naproxen. The aim of this study was to determine the brain bioavailability of Nap after oral administration of the prodrugs in rats. The results conclude moderate oral bioavailability of prodrugs (AUC = 53-94 h · μg/mL) in rats compared with parent Nap (AUC = 155 h · μg/mL) at equimolar doses. Whereas, there was a twofold increase in Nap levels in the brain with the prodrugs compared to parent Naproxen. The increased brain bioavailability may be attributed to the specific carrier system in addition to the reduced percentage of plasma protein binding of Nap. The binding of the tested prodrugs with plasma proteins was investigated in vitro using equilibrium dialysis. The amount in percentage of plasma free fraction of prodrugs (9-15%) was significantly greater than that of Nap (about 5%) when tested at 20 μM, showing more available prodrug to cross the blood brain barrier. A convincing decrease in gastric ulcerogenicity of the prodrugs compared with parent Nap was also noted. therefore, oral dihydropyridine and ascorbate prodrugs for brain site-specific delivery of Nap may be promising candidates for safe and chronic use of NSAIDs for the treatment of neurodegenerative diseases[24].

Nanoparticles :

Nanomedicine is certainly one of the scientific and technological challenges of the future. In common, biodegradable nanoparticles formulated from poly (D, L-lactide-co-glycolide) (PLGA) have been largely investigated for sustained and targeted delivery of various agents, namely recombinant proteins, DNA plasmids, and low molecular weight agents. PLGA NPs show some very attractive properties such as biodegradability and biocompatibility, protection of drug from being degraded, sustained release property, and the surface modifying properties to target nanoparticles to specific organs or cells. Moreover, PLGA NPs have been approved by the FDA and European Medicine Agency in drug delivery systems for parenteral application, thus shortening the time for human clinical applications. Some

reports deals on surface modification of PLGA NPs and their possibility of clinical applications, including cure for brain pathologies such as brain tumors and Lysosomal Storage Disorders with neurological consideration. As large number of pharmacologically active compounds are not able to cross the Blood-Brain Barrier (BBB) and reach the Central Nervous System (CNS), new brain targeted polymeric PLGA NPs modified with glycopeptides (g7- NPs) have been recently formed. Several in vivo biodistribution studies and pharmacological proof-of evidence of brain delivery of model drugs are reported, demonstrating the ability of g7-NPs to create BBB interaction and trigger an efficacious BBB crossing. Another relevant development of NPs surface engineering was achieved by conjugating to the surface of g7-NPs, some specific and selective antibodies to drive NPs directly to a specific cell type once inside the CNS parenchyma.[25]

Liposomes

Nanoformulations such as liposomes consists of bilayer phospholipid systems in which water-soluble drugs could reside inthe aqueous phase enveloped by phospholipid bilayer and the lipophilic drugs, could directly integrate into the membrane30.Researchers are actively investigating on several advanced versions of liposomes such as long-circulating (PEGylated)liposomes, triggered release liposomes, liposomes containingnucleic acid polymers, ligand-targeted liposomes and liposomes containing combinations of drugs in order to achieve better drugdelivery. These advances have led tonumerous clinical trials of anticancerdrugs, anti-fungal drugs, antibiotics, gene medicines[26].

Nanoconjugates

These are low molecular weight conjugates of a small drug or toxin and targeting the ligands, coupled through a cleavable linker group. It consists of three functional areas, the targeting groups, linker and an active drug/agent. The drug movement and distribution in the interstitium depends on convection and diffusion[27].

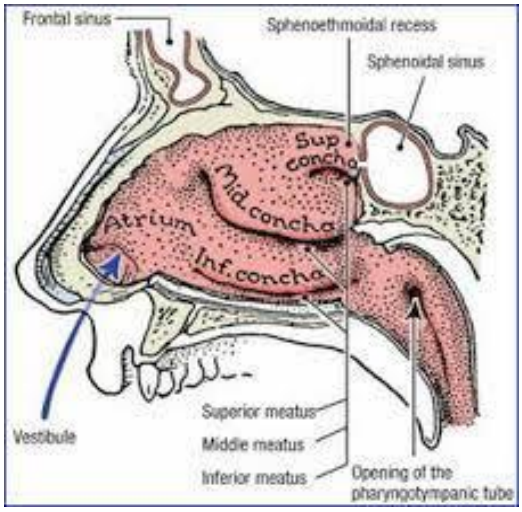
Cyclodextrins

The blood-brain barrier (BBB) restricts the transfer and delivery of most drug substances to brain. A novel nano-drug delivery system for brain-targeting was developed and investigated in vitro and in vivo. Lactoferrin (Lf) was selected as a brain-targeting ligand and conjugated to β-cyclodextrin (β-CD) via the heterobifunctional polyethyleneglycol (PEG) linker NHS-PEG-MAL, yielding Lf conjugated β-cyclodextrin (Lf-CD). UV-vis, FTIR, NMR and transmission electron microscopy (TEM) techniques clearly demonstrated the successful synthesis of

Lf-CD nanoparticles with the average diameter of 92.9 ± 16.5 nm. Using near-infrared fluorescent dye IR-775 chloride (IR) as a model compound of poorly water-soluble drugs, IR-loaded Lf-CD nanoparticles (Lf-CD/IR) were successfully prepared with a high entrapment efficiency of 98.1 ± 4.8%. Biodistribution and pharmacokinetics of Lf-CD/IR were evaluated in KM mice after intravenous administration. The tissue distribution studies revealed that Lf-CD/IR treatment showed greatly improved BBB's efficiency of transportation. Further, AUC0-2h of IR in brain after Lf-CD/IR treatment was seven fold higher compared with that of IR treatment without Lf-CD nano-carriers, showing that the introduction of Lf-CD drug-delivery system positively resulted in a higher AUC located in brain tissue. These results prove that Lf-CD nanoparticles could be exploited as a potential brain-targeting drug delivery system for hydrophobic drugs and diagnostic reagents which normally fail to pass through the BBB[28].

NASAL CAVITY ANATOMY, PHYSIOLOGY & HISTOLOGY:

The major functions of the nasal cavity are breathing and olfaction. It also affords an important protective activity once it filters, heat and humidity the inhaled air before reaching the lowest airways. Nasal cavity contains lining with mucus layer and hairs perform various functions namely, entrapment of inhaled particles and pathogens. Additionally , resonance of produced sounds, mucociliary clearance MMC, immunological activities and metabolism of endogenous substances are also essential functions of nasal structures[42].The Anatomical and histological characteristics of the different areas of nasal cavity are allow these functions to be performed optimally. Anatomically, human nasal cavity fills the space between the base of the skull and the roof of the mouth; it is supported by the ethmoid bones above and by the ethmoid, maxillary and inferior conchae bones laterally. The total volume of the human nasal cavity is 15-20mL and the total surface area is approximately 150 cm2. It is divided by a nasal septum into two halves equal in symmetry, with openings at the face through nostrils and extending posterior to the nasopharynx[28,29,30].



Nasal Vestibule

OLFACTORY REGION:

The olfactory region is located in the roof of the nasal cavity and extends down the septum and lateral wall. The part of the CNS that is directly exposed to the external environment is neuroepithelium. The olfactory zone is pseudo stratified but contains specialized olfactory receptor cells important for smell perception[31]. This area contains some small serous glands (glands of Bowman) which produce secretions acting as a solvent for odorous substances.

ADVANTAGES OF NASAL ROUTE [32]

1. It provides Easy accessibility and needle free drug application.
2. The drug can be administered without the necessity of trained personnel.
3. Improving patient compliance compared to parenteral routes.
4. It provides good penetration of, mainly lipophilic, low molecular weight drugs through the nasal mucosa.
5. It provides rapid absorption and fast onset of action due to a relatively large absorptive surface and high vascularization.
6. Nasal administration of suitable drugs would therefore be effective in emergency therapy as Substitute to parenteral administration routes.
7. It avoids the hepatic first-pass metabolism and thus potential for dose reduction compared to oral delivery.
8. Potential for direct delivery of drugs to the central nervous system via the olfactory region .
9. Direct delivery of vaccine to lymphatic tissue and secretory immune response at distant mucosal sites.

DISADVANTAGES OF NASAL ROUTE

1. The residence time of drug reduces due to the mucociliary clearance.
2. It is not applicable to all drugs.
3. Due to the lack of adequate aqueous solubility it shows insufficient absorption.
4. Depending on aqueous solubility of drug it requires high volume of dose (25-200ml).
5. Some drugs can cause nasal irritation.
6. Some drugs may undergo metabolic degradation in the nasal cavity.
7. It is less suitable for chronically administered drugs.
8. Those drugs which require sustained blood levels should not be considered for nasal delivery because there is no traditional way of formulating sustained release type nasal dosage forms[32].

MECHANISM OF NASAL ABSORPTION[33]

The absorbed drug from the nasal cavity passes through the mucus layer. The small, unchanged drugs easily pass through this

layer but large, drugs which are charged find difficulty to cross it. The principle protein of the mucus is mucin which has the tendency to bind to the solutes and hinders diffusion of drug molecules. Structural changes in the mucus layer are possible as a result of environmental changes like change in pH, temperature. Many absorption mechanisms were proposed earlier but only two mechanisms have been widely used, such as-

(a) First mechanism- It is also known as the paracellular transport. An aqueous route of transport is involved which is slow and passive. There exists an inverse correlation between intranasal absorption and the molecular weight of water-soluble compounds. Those drugs which have molecular weight greater than 1000 Daltons show poor bioavailability.

(b) Second mechanism- It is also known as the transcellular process. It involves transport through a lipoidal route. It is mainly responsible for the transport of lipophilic drugs that show a rate dependency on their lipophilicity. The drug also crosses the cell membranes by an active transport route via carrier-mediated means.

CONCLUSION:

Intranasal delivery is having concur benefits. It is both quick and non-invasive. Nasal delivery bypasses the BBB and targets the CNS. It minimizes systemic exposure and thus reduces systemic side effects. The major advantage is that it is a needle-free application mode and application site in the nasal cavity allow a rapid onset of local and systemic drug actions. It does not require any modification of the therapeutic agent being delivered and offers a wide range of drugs that can be incorporated. Intranasal delivery may provide the treatment and prevention of many different neurologic and psychiatric disorders. An enhanced bioavailability of drugs is found without destruction of drug by hepatic metabolism and provides a less dose administration than oral route. Recently the safety issue has been given great importance by the researchers during the research stage, and this issue will become critical when the drug is to be delivered is for a long term therapy. With the proper formulation and dosage form design, the permeability and the surrounding environment of the mucosa can be controlled and altered to accommodate drug permeation. The nasal drug delivery is a convenient alternate route for systemic delivery of orally inefficient drugs. It also provides non-invasive delivery of potent peptide and perhaps protein drugs. The intranasal route is a possible alternative to parenteral routes. The need for a safer and sufficient nasal permeation and absorption enhancers

is a major component for a promising future in the area of nasal drug delivery. It diminishes systemic exposure and thus reduces the side effect.

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