Intranasal route: An innovative technique for brain targeting

Accepted 13th January, 2018

ABSTRACT

The complex arrangement of Blood-Brain Barrier (BBB) restricts the entry of drugs into the brain. The intranasal route is a widely accepted route for the delivery of many therapeutic agents due to the fact that it bypasses BBB. Direct nose to brain drug delivery has been proved to be an excellent platform for brain targeting through surface engineering of neurotherapeutic-loaded carrier systems resulting in enhanced product performance. There is a unique pathway through nasal mucosa to brain by which many upcoming therapeutic agents, which have brain as target site, will also be delivered through this route to brain. At present, macromolecules, stem cells, DNA plasmids, chemotherapeutic agents etc are delivered by intranasal route.

Key words: Noninvasiveness, intranasal drug delivery, brain targeting, blood brain barrier, central nervous system.

INTRODUCTION

Intranasal therapy has been an accepted form of treatment in the Ayurveda system of Indian medicine long ago. Nasal therapy is also called "NASYA KARMA". It is one of the PANCHAKARMA mentioned in Ayurveda, and it is the process by which drug is administered through the nostrils. If 'Nasyakarma' is done properly and regularly, it alleviate disease, such as cervical spondylitis, headache, facial paralysis, hemiplegia, diseases of nose frozen shoulder, mental disorder and skin complaints. It enhances the activity of sense organs and prevent the disease of the head (URDHWANGA) (Chien and Chang, 1987). The early 1980s saw the introduction of nasal route as a promising systemic delivery alternative to other conventional drug delivery system. Nasal mucosa has been considered as potential co-administration route to achieve faster and higher level of drug absorption because it is permeable to more compounds than the gastrointestinal tract due to lack of pancreatic and gastric enzymatic activity, neutral pH of the nasal mucus and less dilution by gastrointestinal contents (Paun et al., 2010). It is a useful delivery method for drugs that are active in low doses and show no minimal oral bioavailability, such as proteins and peptides (Jadhav et al., 2007).

Advantages (Pardridge, 1999; Illum, 2000; Hussain, 1998; Sandor, 2009)

1. Rapid absorption, higher bioavailability, therefore, lower dose.
2. Fast onset of therapeutic action.
3. Avoidance of liver first pass metabolism and metabolism by GIT.
4. Minimum irritation to the gastrointestinal membrane.
5. Reduced risk of overdose.
6. Non-invasive, ease of convenience along with self medication.
7. Improved patient compliance.
8. It can be a beneficial adjunct product to an existing product.

Disadvantages (Basu and Bandopadhyay, 2010; Upadhyay et al., 2011)

1. Concentration is achievable in different regions of the brain and spinal cord varies with each agent.
2. Delivery is expected to decrease with increasing
molecular weight of drug.
3. Some therapeutic agents may be susceptible to partial degradation in the nasal mucosa or may cause irritation to the mucosa.
4. The absorption enhancers used to improve nasal drug delivery system may have histological toxicity which is yet to be clearly established.
5. Absorption surface area is less when compared to GIT.
6. Once the drug is administered, it cannot be removed.
7. Nasal irritation.

NASAL ANATOMY AND PHYSIOLOGY

Externally, nose consist of paired nasal bones and upper and lower lateral cartilages (Figure 1). The nasal cavity is divided by nasal septum. The lateral nasal wall consists of inferior and middle turbinates and occasionally a superior or supreme turbinate bone. The nasal membrane composed of ciliated pseudostratified glandular columnar epithelium. Mucociliary transport relies on mucus production and ciliary function (Díaz et al., 2013). The level of congestion and nasal membrane are controlled by Blood and autonomic nerve supply. The contributions of nerve supply are from the facial nerve originating from the inferior salivatory nucleus and follow along the distribution of the facial nerve through the sphenopalatine ganglion. The internal and external carotid artery systems supply the posterior aspect of the nasal cavity (Figure 1). Olfactory nerve endings originate in the olfactory bulb under the frontal lobe and pass directly through the cribriform plate as second-order neurons entering the nasal cavity. Olfactory nerves are found on the superior portion of the septum, superior turbinates, and cribriform region (Costanzo et al., 1992; Levy et al., 2013).

NASAL VESTIBULE

The nasal vestibule is a small dilated space just internal to the naris, that is lined by skin and contains hair follicles.

RESPIRATORY SECTION

The respiratory section of the nasal cavity refers to the passages through which air travels into the respiratory system. The respiratory section of each nostril contains four conchae (protrusions or bumps) which are also referred to as turbinate bones or lobes and are covered by the nasal mucosa. Conchae (also named turbinates) are the curved bony projections pointed downwards and medially. Below and lateral to every concha is a corresponding meatus. Superior and middle nasal conchae are the projections from the medial surface of the ethmoidal labyrinth. Inferior concha is a separate bone. The superior concha is smallest and inferior concha is largest in size. Meatuses are the passages (recesses) below the
overhanging conchae (Dondeti et al., 1996). They are visualized as soon as conchae are removed. Inferior meatus is the largest and is located underneath the inferior nasal concha. Middle meatus is located underneath the middle concha. The meatuses of the nasal cavity connect to the paranasal sinuses (Lethem, 1993).

**OLFACTORY REGION**

The olfactory receptors (receptors for smell sensations) are found in this section of the nasal cavity. Bowman's glands are also found in this section of the nasal cavity.

Three types of cells constitute olfactory epithelium, that is, basal, supporting, and olfactory receptor cells. Stem cells are the basal cells that give rise to olfactory receptor cells. The continuous turnover and new supply of these neurons are unique to the olfactory system. Supporting cells are scattered over the receptor cells and have numerous microvilli and secretory granules, which empty their contents onto the mucosal surface (Illum, 1999; Illum, 2003). The receptor cells are actually bipolar neurons containing specialized cilia, which provide the transduction surface for odorous stimuli.

The conchae (turbinate bones) of the nasal mucosa expand the total surface area of the mucosa and create turbulence in air entering the respiratory passage. This causes air to swirl as it moves through the nasal cavity and increases contact between infiltrating air and the nasal mucosa, allowing particles in the air to be trapped before entering other parts of the respiratory system (e.g. the lungs) (Mygind, 1979).

The olfactory system functions to process sensory information related to smell.

**Bowman's gland**

Bowman's glands secrete the majority of the mucus which overlies the nerves of the olfactory system. They also secrete the pigment which gives this mucus its yellow colour. Mucus secreted by these glands dissolves odours as they enter the nose, enabling them to interact with the olfactory receptors.

**PATHWAYS OF NASAL DRUG DELIVERY**

**Olfactory pathway**

The possible mechanism by which drugs are transported from nose to brain is not yet clear, but olfactory pathway plays a vital role. Basal cells and neural cells replace each other during their constant motion and due to this constant motion and replacement, nasal mucosa becomes permeable resulting in enhanced delivery of drug to the brain. The three different pathways across the olfactory epithelium includes:

**Paracellular pathway:** This is through the tight junctions between sustentacular cells and olfactory neurons. Hydrophilic drugs are most probably absorbed by diffusion through aqueous channels (pores). This pathway is slow and passive. This route is responsible for transport of hydrophilic drugs and it shows rate dependency on the molecular weight of a drug (Oberdorster et al., 2004). Drugs with a molecular weight up to 1000 Da without absorption enhancer shows good bioavailability, which can be extended to drugs with molecular weight up to 6000 Da with absorption enhancer (Garcia-Garcia et al., 2005).

**Transcellular pathway:** This occur across the sustentacular cells most likely by receptor-mediated endocytosis, fluid phase endocytosis or by passive diffusion. Passive diffusion is a common transport pathway for lipophilic drugs.

**Olfactory nerve pathway:** In this pathway, drug is taken up into the neuronal cell by endocytosis or pinocytosis mechanisms and transported by intracellular axonal transport to the olfactory bulb (Figure 2) (Talegaonkar and Mishra, 2004).
Figure 3: Nose to brain transport.

**Trigeminal pathway**

Trigeminal nerve, which connects the nasal passages to the brain plays an important role in IN delivery of drug. Respiratory region occupies major portion of nasal cavity and innervated by trigeminal nerves (Bhise et al., 2008; Dhuria et al., 2010). Trigeminal nerve is fifth (V) cranial nerve having three branches; ophthalmic nerve, maxillary nerve and mandibular nerve and is responsible for sensation in nasal cavity. Olfactory pathway delivers drug to rostral area of brain, whereas trigeminal pathway does not only targets rostral, but also caudal area of the brain, making it difficult to differentiate whether intranasally administered drug is translocated to rostral area by olfactory or trigeminal pathway. A unique feature of the trigeminal nerve is that it enters the brain from the respiratory epithelium of the nasal passages at two sites: i) through anterior lacerated foramen near the pons and ii) through the cribriform plate near olfactory bulb, creating entry points into both caudal and rostral brain areas following intranasal administration (Figure 3) (Thorne et al., 2004; Upadhyay et al., 2011).

**BRAIN TARGETTING STRATEGIES**

Various techniques (Figure 4), which used to disrupt the BBB and help in the transport of drug molecules across this barrier to the CNS, have been studied. These are thus explained.

**Invasive strategies**

**Disruption of BBB by chemicals**

Various invasive techniques are used for the disruption of the BBB and enhance the delivery of drug to the brain (Figure 4). Osmotic disruption of BBB is one of the invasive techniques in which shrinkage of endothelial cells takes place for a short period of time and leakage of drug to the CNS through opening of tight junctions (Rapoport and Robinson, 1986). On injecting intracarotid hypotonic solution of mannitol, tight junctions were opened and subsequently promote the delivery of chemotherapeutic agents to the brain. This technique is less specific and
inefficient and the major drawbacks are transport of plasma protein to CNS, disturbed glucose uptake, neurotoxicity of cerebral tissues, altered brain functions and technicality related issues. Bradykinin and histamine act as vasoactive agents which disturb the BBB and improve the transportation of drugs to CNS. The roles of bradykinin are the activation of B2 receptors, leakage of endothelial cells based on modulation of caveolin-1 and caveolin-2 and permeability enhancement of brain tumor microvessels via (KATP) channels (Zhang et al., 2007).

**Focus ultrasound enhanced delivery**

Another versatile approach for enhancing drug transportation to the CNS is by the use of ultrasound waves which reversibly and transiently open the BBB. In this type of drug delivery, microbubbles (MBs) is used as a contrast agent. These bubbles were administered systemically and worked on acoustic energy principle to exert pressure on endothelial cells and open the tight junctions, resulting in increased permeability of BBB and
improved delivery of drug to the brain. These MBs operate in collaboration with low intensity Focus Ultrasound (FUS) and this combined system is called MB facilitated FUS. MB-FUS system decreases the acoustic energy requirement, focusing the acoustic energy within blood vessels. Different antitumor agents, such as trastuzumab (Azad et al., 2015), temozolomide (Wei et al., 2013), methotrexate (Mei et al., 2009), nucleotides, that is, siRNA (Burgess et al., 2012) and stem cells (Alkins et al., 2013) have been successfully delivered with the help of FUS. FUS-MB system is effectively used with other DDSs for brain targeted delivery.

**Craniotomy-based drug delivery**

Craniotomy-based drug delivery is the direct way of targeting the specific part of the brain without exposure to peripheral organs via intracerebral or intraventricular injection. In intraventricular delivery, drug reservoir implanted in the scalp provided the controlled release of a drug and is connected to the ventricles in the brain through catheter (Begley et al., 1998; Jaehde et al., 1992). Higher concentration of drugs is achieved without distribution to the interstitial fluid of brain. Intraventricular system directly delivers the drug to the ventricles and subarachnoidal part of the brain and is suitable for therapy of meningioma and metastatic cells of CSF (Groothuis et al., 2000). Intracerebral system directly injects or infuses the drug into brain parenchyma through catheter (MacKay et al., 2005) and controlled devices maintain the delivery (Mahoney and Saltman, 1996). This system depends on the diffusion mechanism and provides slow distribution of drugs within the brain, as diffusion decreases with increase in distance. Hence, intracerebral delivery requires large doses of a drug to achieve desired therapeutic response (Nicholson and Sykova, 1998).

**Convection-enhanced delivery**

This system involves continuous infusion method and pressure gradient to distribute large volume of drugs at target tissues via intracranial catheter. This delivery overcomes the disadvantages of intracerebral delivery system. It has certain limitations of drug entry to surrounding tissue: difficult to design, instability of drug and low therapeutic level of drug in the target area. Coupling of CED with liposomes improved the efficiency of CED for brain tumor targeting. Liposomal delivery significantly inhibited tumor volume and increased the survival rate.

**Polymeric wafers based delivery systems**

Development of polymeric devices for targeted and controlled delivery of therapeutic moieties lead to advancement in polymer technology. This involves the controlled release of drug at targeted site. Wafers based on polyanhydride were implanted in tumor resection area, crossed the BBB, gradually released and distributed the drug into the brain and targeted site (Brem et al., 1991; Gallia et al., 2005). Polyanhydride based polymer shows effective results in animals with minimum toxicity. Wafers have certain limitations of less penetration into deep brain tissue, cyst formation, meningitis, impaired wound healing and abscess formation.

**Non-invasive strategies**

These strategies utilizes the endogenous mechanism for transport of drug across the BBB.

**Prodrug approach**

With increase in lipophilic characters in drug molecule, it facilitates better permeation. This approach, based on chemical modifications in the drug molecule to modulate its lipophilic behavior, increases permeability and water solubility. Targeted prodrugs contain chemical entity along with parent drugs designed to approach enzymes or transport system at the targeted site to be converted to active moiety. Peptidase enzymes in the brain removed the spacer and released the active drug (Pavan and Dalpiaz, 2011). Prodrug approach has been successfully utilized for delivery of neurotherapeutics to treat neurological disorders. This approach retains the drug at the brain for longer period of time.

**Efflux pump inhibition**

The presence of efflux pump in the BBB is another barrier to effective drug transportation to the brain. Efflux by the active P-glycoprotein (P-gp) presents on the apical membrane of the endothelial cells of BBB results in poor drug availability at the targeted brain tissues. P-gp has more affinity for lipophilic and cationic drugs (De Boer and Gaillard, 2007). Most of the low molecular weight drugs, such as nitrosoureas, are substrate for P-gp and are restricted from entering the brain. Inhibition of P-gp efflux is a useful approach to save the therapeutic efficacy of potent drugs. Dopamine, pharmacologically effective for the treatment of Parkinson's disease, is unable to cross BBB disease. L-dopa is transported through L-amino acid transporter across the BBB and converted to dopamine in the brain.

**Cell based therapy**

This therapy utilizes macrophages and many types of stem
cells as carriers for delivery to brain. It is an effective delivery for neurological disorders and brain tumors. The macrophages with phagocytosis property are migrated towards the brain by transcellular or paracellular transport. During brain tumor and inflammatory conditions, macrophages are attracted and infiltrated towards the brain. Macrophages are suitable candidates for targeted delivery of NPs and diagnostic and imaging agents to the brain tumor and neurodegenerative diseases. Stem cells could be used as vector for delivery of cytokines, oncolytic viruses, and suicide genes to the brain (Hong et al., 2009; Shah, 2012; Kranzler et al., 2009). Stem cells could be effective cargo for oncolytic virus to treat the glioma. In a study, Mesenchymal Stem Cells carrying oncolytic herpes simplex virus exhibited efficacious results in glioma-bearing mice (Duebgen et al., 2014).

**Intranasal drug delivery**

Drug administered through nasal route of administration is absorbed into the systemic circulation. Drug absorption through nasal respiratory epithelium follows transcellular and paracellular absorption, carrier-mediated transport, and absorption through trancytosis mechanism (Roy, 2012). Nasal drug delivery to the brain posed a big challenge of BBB-mediated restriction. Administration of drug deep into the nasal cavity approach the nasal mucosa and lead to direct transmission of drug into brain via olfactory pathway. Olfactory pathway consists of olfactory neurons that carry drugs from the olfactory mucosa to the brain and it is a slow process of drug transmission. Olfactory epithelium pathway is a faster way of drug transportation (Jackson et al., 1979). Drug is passed through olfactory epithelium via paracellular mechanism into perineural space and transferred directly to the brain.

**RECENT ADVANCEMENTS IN BRAIN TARGETED DRUG DELIVERY SYSTEM**

**Antibodies mediated drug delivery**

Restriction posed by the BBB and low brain permeability of the antibodies limit the potential of antibody mediated therapy for neurological diseases. mAbs are much large in size and unlike small molecules, unable to cross BBB and approach target sites in the brain (Smolnik et al., 1999; Liu et al., 2001). Although, no mAb has been approved for brain targeted therapy, but several mAbs are under clinical trials especially for the treatment of Alzheimer’s disease.

Bispecific antibody (bsAb) is newly designed Ab with two different binding specificities. bsAbs are introduced for chemotherapy with one binding specificity targeting the tumor cell and the other targets the antigen on immune cells (Danielyan et al., 2009). Recent application of bsAbs targeted delivery across BBB. bsAbs is constructed with one specificity to promote transportation across BBB via receptor mediated transport and second specificity to target the specific site in the brain for desired therapeutic effect. Several BBB crossing bsAbs were formulated and evaluated for brain targeted delivery, such as bsAb with transferrin receptor (TfR) binding domain to cross BBB and single-chain variable region fragments (scFv) specificity against amyloid beta peptide.

**Laser light based technology**

This technology is beneficial in the disruption of BBB and helpful in glioma targeted delivery. Due to this, laser light defects are created in the endothelial cells and it becomes leaky, allowing the transport of therapeutic agents to parenchymal tissues. Combination therapy of 5- aminolevulinic acid (5-ALA) with laser light opened the tight junctions between the endothelial cells for longer period of time. Laser could be combined with other strategies to potentiate BBB disruption. Ultrashort laser pulses are successful in the transport of nanoparticles, genetically engineered viruses and numerous therapeutic agents to the brain.

**APPLICATION**

**Delivery of macromolecules**

Large molecular size and susceptibility to enzymatic degradation is the prime reason behind low bioavailability of such compounds. Proteins and peptides are generally administered parenterally owing to their physicochemical instability and susceptibility to hepatogastrointestinal first-pass elimination. IN delivers large number of protein based molecules to the brain, such as corticotropin-releasing hormone (CRH), neurotrophic factors, insulin and MSH/ACTH (Reitz et al., 2012).

**Delivery of stem cell and DNA plasmids**

By nasal administration of DNA plasmids, the level of plasmid in brain is 3.9 - 4.8 times higher than the plasmid concentration in lungs and spleen and reaches the brain within 15 min following intranasal administration. IN delivery of Neural stem/progenitor cells (NSPC) rapidly migrate to malignant glioma via olfactory pathway. IN delivery of NSPC provides non-invasive and chronic therapy for treating gliomas and other CNS disorders.

**Delivery of chemotherapeutic agents**

Anticancer drugs, when administered by parenteral or oral route to target the brain tumors, do not only limit the
efficacy of these agents by BBB, but also caused serious side effects on other organs; therefore, the nasal route of drug delivery has been explored by researchers. Chemotherapeutic agents, such as Perillyl alcohol (POH) (Balyasnikova et al., 2014), NSPCs ( Fonseca et al., 2011), glioma-adapted vesicular stomatitis virus strain (VSVrp30) (Ozduman et al., 2008), methotrexate (Shingaki et al., 2010) and telomerase inhibitors (GRN163) (Hashizume et al., 2008), have been successfully delivered to target brain tumors by nasal route.

CONCLUSION

An innovative drug delivery system is one which delivers the desired concentration of drug to the required site. Intranasal delivery bypasses the BBB to target CNS, reducing systemic exposure of drug, thereby reducing the systemic side effects and target the particular area. Direct nose to brain drug delivery system is a potential strategy to overcome the obstacles presented by the BBB. It is an attractive option of drug delivery due to its non-invasiveness. A variety of neurotherapeutic agents, including small drug molecules, proteins, peptides, hormones and biological cells such as stem cells, can be delivered by this route, thereby yielding new insights into prevention and management of different neurological disorders. It is uncertain, however, whether the drug is being released from the carrier system in the nasal cavity and transported to CNS, or the carrier system is transported along the olfactory and/or trigeminal nerve pathways into the CNS where the drug is released. Thus, more basic research is required to determine the possible transport pathway of therapeutic carrier to the CNS and their further fate in the biological system.

REFERENCES

A nice review highlighting the major applications of direct nose to brain delivery.
Pathway. 1

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