Intranasal delivery: An approach to bypass the blood brain barrier

S. Talegaonkar, P. R. Mishra

ABSTRACT

The blood brain barrier (BBB) represents one of the strictest barriers of *in vivo* therapeutic drug delivery. The barrier is defined by restricted exchange of hydrophilic compounds, small proteins and charged molecules between the plasma and central nervous system (CNS). For decades, the BBB has prevented the use of many therapeutic agents for treating Alzheimer's disease, stroke, brain tumor, head injury, spinal cord injury, depression, anxiety and other CNS disorders. Different attempts were made to deliver the drug across the BBB such as modification of therapeutic agents, altering the barrier integrity, carrier-mediated transport, invasive techniques, etc. However, opening the barrier by such means allows entry of toxins and undesirable molecules to the CNS, resulting in potentially significant damage. An attempt to overcome the barrier *in vivo* has focused on bypassing the BBB by using a novel, practical, simple and non-invasive approach *i.e.* intranasal delivery. This method works because of the unique connection which the olfactory and trigeminal nerves (involved in sensing odors and chemicals) provide between the brain and external environments. The olfactory epithelium acting as a gateway for substances entering the CNS and peripheral circulation is well known. Also, it is common knowledge that viral infections such as common cold, smallpox, measles, and chicken pox take place through the nasopharynx. The neural connections between the nasal mucosa and the brain provide a unique pathway for the non-invasive delivery of therapeutic agents to the CNS. This pathway also allows drugs which do not cross the BBB to enter the CNS and it eliminates the need for systemic delivery and thereby reducing unwanted systemic side effects. Intranasal delivery does not require any modification of therapeutic agents and does not require that drugs be coupled with any carrier. A wide variety of therapeutic agents, including both small molecules and macromolecules can be rapidly delivered to the CNS using this method. The present review discusses the various applications, advantages and limitations of this novel approach.

KEY WORDS: CSF, nasal drug delivery, protein, polypeptide drugs

Introduction

Recent advances in the fields of pharmacology and molecular neurobiology have led to a greater understanding of disease processes, allowing development of new classes of therapeutic agents that can interact with specific intracellular and extracellular targets.[1,2] Several drugs, peptides, biological response modifiers, and monoclonal antibodies are available and have proven value (a) in inhibiting a variety of malignant and infectious diseases; (b) in ameliorating neurotransmitter, enzyme, or growth imbalances in culture systems; (c) in animal models using direct intracranial administration. However, therapeutic efficacy *in vivo*, particularly with regard to the CNS is frequently diminished or nullified by the inability of the agent to reach and maintain effective concentrations in the brain for an appropriate length of time. Frequently, the molecule is too large or has polar functional groups and the blood brain barrier (BBB) limits its access to the CNS.

The BBB is a system of layers of cells at the cerebral capillary endothelium, the choroid plexus epithelium, and the arachnoid membranes, which are connected by tight junctions (zonulae occludens) and which together separate the brain and the cerebrospinal fluid (CSF) from the blood.[3] These tight endothelium junctions can be 100 times tighter than junctions of other capillary endothelium.[4] Thus, the barrier has many properties similar to a continuous cell membrane, allowing lipid-

soluble molecules transport across the membrane where hydrophilic solutes demonstrate minimal permeation.[5] The BBB impedes the use, for example, of many of the newer genetically engineered drugs, such as humane recombinant neurotrophic factors and other therapeutic agents that can protect brain cells from damage and promote nerve repair. This impediment created by BBB can be overcome by three broad categories of techniques, namely

(i) **Delivery across the BBB** by manipulation of the drug to make BBB permeable to it (prodrug approach), utilization of carriers or transporters. However, these methods are complex and require drugs to possess certain specific characteristics and hence do not work effectively for all therapeutic agents. Drugs are administered by classical intravenous or intraperitoneal injections, or through the digestive tract, lung, or skin. However, part of these lipophilic chemicals are subject to being metabolized in the liver, resulting in a modification in the amount of circulating drug available to the brain. Moreover, the liver, kidney, intestine, skin, lung and also tissues separating the brain from the bloodflow, express enzymes able to metabolize xenobiotics. Another part of the dosage may be excreted by the kidney before entry into the CNS, rendering the precise amount of the drug that finally enters the brain difficult to be estimated. Similarly, drug delivery by intracerebroventricular (*icv*) devices (catheter, or osmotic pumps for intraventricular drug infusion) or by surgical implantation of devices that release an active molecule near its pharmacological target for variable time durations, has its own limitations.

(ii) **Direct delivery to the brain** by *icv* administration or surgical implantation, allows the administration of a precise amount of drug to the brain but requires invasive neurosurgery, hence is restricted to a limited number of applications (e.g., the administration of water soluble anticancer drugs, or treatment of intractable pain by direct central administration of morphine, to prevent fatal side-effects due to over-dosage).[6] (Figure 1)

(iii) **Bypassing the BBB:** The third and the emerging approach is to bypass the BBB by intranasal delivery, which provides a practical, non-invasive, rapid and simple 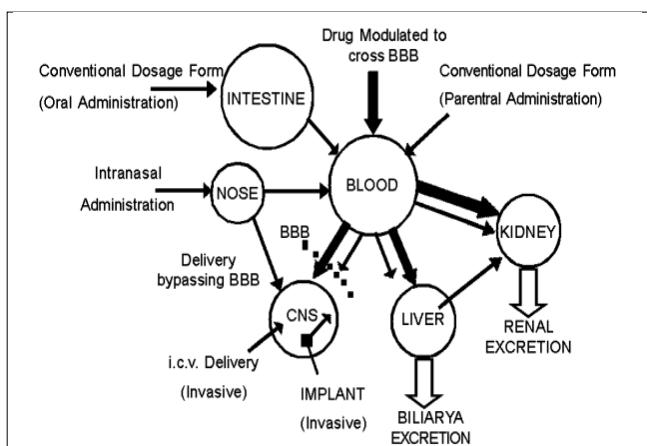method to deliver the therapeutic agents to the CNS. This method works because of the unique connection between the nose and the brain that has evolved to sense odors and other chemical stimuli. This method is the thrust of this article.

Recently, Illum[7] has thoroughly reviewed the possibilities, problems, and solutions of nasal drug delivery. She has reported that it is feasible to deliver challenging drugs efficiently such as small polar molecules, peptides and proteins and even the large proteins and polysaccharides like vaccines or DNA plasmids exploited for DNA vaccines. On the basis of clinical trials (Phase I and II) it is reported that the intranasal route is feasible for the transport of the drug to the CNS.

Intranasal delivery does not require any modification of the therapeutic agents and does not require that drugs be coupled with any carrier like in case of drug delivery across the BBB. A wide variety of therapeutic agents, including both small molecules and macromolecules can be successfully delivered, including to the CNS, using this intranasal method (Table 1).

Advantages

The advantages of intranasal delivery are considerable. This method is:

(1) Non-invasive, rapid and comfortable
(2) Bypasses the BBB and targets the CNS, reducing systemic exposure and thus systemic side effects
(3) Does not require any modification of the therapeutic agent being delivered
(4) Works for a wide range of drugs. It facilitates the treatment of many neurologic and psychiatric disorders
(5) Rich vasculature and highly permeable structure of the nasal mucosa greatly enhance drug absorption
(6) Problem of degradation of peptide drugs is minimized up to a certain extent
(7) Easy accessibility to blood capillaries
(8) Avoids destruction in the gastrointestinal tract, hepatic "first pass" elimination and gut wall metabolism, allowing increased, reliable bioavailability.

Limitations

(1) Concentration 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) Nasal congestion due to cold or allergies may interfere with this method of delivery
(5) Frequent use of this route results in mucosal damage (e.g. infection, anosmia).

How does it work?

To understand the mechanism, pathways, distribution and absorption of therapeutic agents administered to the CNS by the intranasal route, a brief description of the nasal physiology is considered necessary.

Nasal physiology

The nose is divided into two nasal cavities via the septum.

Figure 1: Different methods of drug administration to the CNS

Table 1

Small molecules and macromolecules being studied for nasal delivery

	Small molecules	*Macro molecules*
Adreno corticosteroids		
Antibiotics	Gentamicin, Cephalosporin, Penicillins, Tyrothricin	Amino acids
Antimigraine drugs	Dihydroergotamine, Ergotamine tartrate	**Peptides**
Antiviral drug	Enviroxime	Calcitonin, Secretin,Thyrotropin-releasing
Cardiovascular drugs	Isosorbide dinitrate, Propranolol, Verapamil, Hydralazine, Nitroglycerin, Clofilium tosylate	hormone (TRH), Cerulein, Enkephalin analogs- Leucine enkephalin, Mekephamid
Central nervous system drugs		Pentagastrin, SS-6, Substance P, Kyotorphin,
a. Stimulants	Cocaine, Lidocaine	Cholecystokinin
b. Depressants	Diazepam, Lorazepam	
Autonomic nervous system drugs		
a. Sympathomimetics	Dopamine, Dobutamine, Ephedrine, Epinephrine, Phenyle phrine, Tramazoline, Xylometazoline	**Polypeptides and proteins**
b. Parasympathomimetics	Methacholine, Nicotine	a. Albumins
c. Parasympatholytics	Atropine, Prostaglandins, Ipratropium, Scopolamine	b. Anterior pituitary hormones - Adreno-corticotropic hormone, Gonadotropin-releasing hormone, Growth hormone
Diagnostic drugs	Dye T-1824, Phenolsulfonphthalein, Potassium ferrocyanide, Vital dyes	c. Biological products - Interferon, Vaccines
Histamine and antihistamines		d. Horseradish peroxidase
a. Histamine		e. Pancreatic hormones - Insulin, Glucagon
b. Antihistamines-	Meclizine	f. Posterior pituitary hormones - Oxytocin, Vasopressin
c. Mast cell stabilizers -	Disodium cromoglycate	
Narcotics and antagonists	Buprenorphine, Naloxone	
Sex Hormones	Estradiol, Progesterone, Norethindrone, Testosterone	
Inorganic compounds	Colloidal carbon, Colloidal gold, Inorganic salts, Lead carbonate P and Thorium B	
Vitamins	Folic acid, Cyanocobalamin	

The volume of each cavity is approximately 7.5 mL and has a surface area around 75 cm.[2,8,9] There are three different functional regions in the nose-vestibular, respiratory, and olfactory. Of these, the respiratory region is the most important for systemic drug delivery.[9] The respiratory epithelium consists of basal, mucus-containing goblet, ciliated columnar and non-columnar cell types.[9,10] The Celia move in a wavelike fashion to transport particles from the pharynx area for ingestion.[9,11] Additionally, the cells in this region are covered by 300 microvilli, providing a large surface area for absorption.[9] Below the epithelium is lamina propria. This is the region where blood vessels, nerves, serous glands, and mucus secretory glands may be found.[10] The lamina propria also houses a dense network of capillaries, many of which are very permeable for drug absorption.[8,12]

The nasal epithelium is covered by a mucus layer that is renewed every 10 to 15 min.[12] The pH of mucosal secretion ranges from 5.5 to 6.5 in adults and from 5.0 to 6.5 in children.[13] The mucus layer entraps particles, which are then cleared from the nasal cavity by the cilia. The rate of mucus flow through the nose is approximately 5 to 6 mm/min resulting in particle clearance within the nose every 20 min.[8,14]

The nasal cavity also houses numerous enzymes.[14-16] In humans, cytochrome P450 enzyme isoforms that have been identified are CYP1A, CYP2A and CYP2E.[17] Other enzymes detected in the human nose include carboxylesterases and glutathione S-transferases.[18-20]

In addition to its function as a passageway for respiration, the nasal cavity also has a key role in the sense of smell. The olfactory nerves, which originate as specialized olfactory nerve endings (chemoreceptors) in the mucous membrane of the roof of the nasal cavity above the superior nasal conchae, are the sensory nerves of smell. On each side of the septum nerve fibers pass through the cribriform plate of the ethmoid bone of the olfactory bulb where interconnections and synapses occur. From the bulb, a bunch of nerve fibers pass through the olfactory tract and reach the olfactory area in the temporal lobe of the cerebral cortex in each hemisphere, where the impulses are interpreted and odor is perceived. Another set of nerves emanating from the nasal cavity is the maxillary branch of the trigeminal nerves, which are general sensory nerves[21] (Figure 2).

Mechanisms

Two mechanisms are involved in the nasal delivery, a fast rate that depends on lipophilicity, and a slower rate that depends on molecular weight. McMartin *et al* studied[22] the transport of SS-6 (an octapeptide) and horseradish peroxidase through a rat's nasal cavity. Their absorption studies are consistent with the non-specific diffusion of the penetrant molecules through aqueous channels located between the nasal mucosal cells, which impose a size restriction on nasal permeability. The data indicate that good bioavailabilities can be achieved for molecules up to 1000 Da (without enhancers) and good availability can be extended to at least 6000 Da with enhancers.
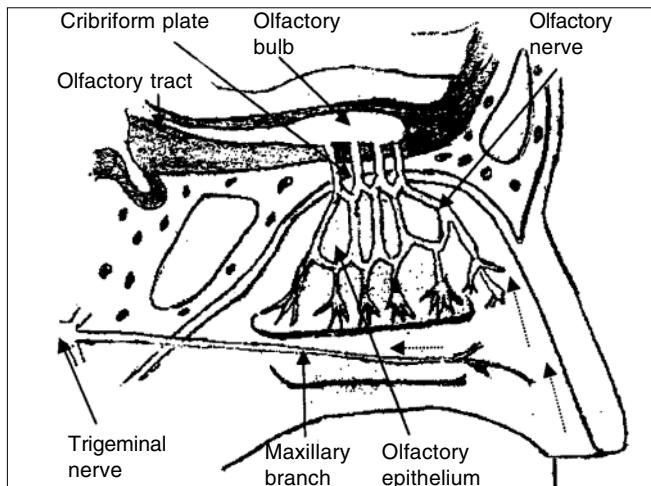
Figure 2: Pathways showing drug administration to the CNS by the intranasal route

The transport mechanisms of different substances like insulin, mannitol or propranolol across the nasal mucosal tissue were studied by Wheatly *et al.*[23] The transport of these substances occurs by a passive transport mechanism. The addition of deoxycholate (0.1%) reversibly increased the transepithelia conductance across the nasal membrane and enhanced the transport of mannitol and insulin. The transport of tyrosine and phenylalanine across rat mucosa was also studied by using an in-situ perfusion technique.[24] It was found that both amino acids were absorbed by an active saturable transport process, which appeared to be Na$^+$ dependent, and transport may have required metabolic energy as a driving force.

Water-soluble substances such as sodium cromoglycate are absorbed well and nasal absorption probably depends on aqueous channel diffusion (pores).[25] The molecular size of the compound will be a determinant in the rate of absorption in such a channel.

Pathways

The olfactory epithelium is a gateway for substances entering the CNS and the peripheral circulation. The neural connections between the nasal mucosa and the brain provide a unique pathway for the non-invasive delivery of therapeutic agents to the CNS.[9,11,26] The olfactory neural pathway provides both an intraneuronal and extraneuronal pathway into the brain.[27-29] The intraneuronal pathway involves axonal transport and requires hours to days for drugs to reach different brain regions. While the extraneuronal pathway probably relies on bulk flow transport through perineural channels, which deliver drugs directly to the brain parenchymal tissue and/or CSF. The extraneuronal pathway allows therapeutic agents to reach the CNS within minutes.[30-33] Intranasal delivery of agents to the CSF is not surprising as CSF normally drains along the olfactory axon bundles as they traverse the cribriform plate of the skull and approach the olfactory submucosa in the roof of the nasal cavity, where the CSF is then diverted into the nasal lymphatics.[34-36] Thorne *et al*[26] have reported that the trigeminal neural pathway may also be involved in rapidly delivering protein therapeutic agents, such as insulin-like growth factor-1 to the brain and spinal cord following intranasal administra-

tion. The transport of drugs across the nasal membrane and into the bloodstream may involve either passive diffusion of drug molecules through the pores in the nasal mucosa or some form of non-passive transport.[37] The potential pathways involved in the nasal absorption of drugs are shown in Figure 2.

Drug distribution

Drug distribution in the nasal cavity is an important factor that affects the efficiency of nasal absorption. The mode of drug administration may affect this distribution, which in turn can help determine the extent of absorption of a drug. Nasal deposition of particles is related to the individual's nasal resistance to airflow.[38] With nasal breathing, nearly all the particles having an aerodynamic size of 10-20 mm are deposited on the nasal mucosa.[39] The deposition of particles in the respiratory tract is a function of particle size and respiratory patterns. The density, shape, and hygroscopicity of particles, and the pathological conditions in the nasal passage will influence the deposition of the particle, whereas the particle-size distribution will determine the site of deposition and affect the subsequent biological response in animals and humans.[40] Furthermore, improvement of the delivery system and drug formulation is necessary to achieve a better clinical effect and easier handling by patients.

Three mechanisms are usually considered in assessing particle deposition in the respiratory tract, *i.e.,* inertia, sedimentation and diffusion, the first being the dominant mechanism in nasal deposition.[41] Any particle with an aerodynamic diameter of 50 mm or greater does not enter the nasal passage. It was demonstrated that 60% of aerosolized particles of 2-20 mm are deposited in the anterior regions of the nostrils, 2-3 mm from the external nares.[42] The site of drug deposition within the nasal cavity depends on the type of delivery system and the technique used in application.[43]

Drug absorption

The first step in the absorption of drugs from the nasal cavity is passage through the mucus.[44] Small, uncharged particles easily pass through this layer. However, larger or charged particles may find it more difficult to cross. Mucin, the principal protein in the mucus, has the potential to bind solutes, hindering diffusion. Additionally, structural changes in the mucus layer are possible as a result of environmental changes (*i.e.,* pH and temperature).[44] After a drug's passage through the mucus, there are several mechanisms for absorption through the mucosa.[45] These include transcellular or simple diffusion across the membrane, paracellular transport via movement between cells, and transcytosis by vesicle carriers.[22] Obstacles to drug absorption are, potential metabolism before reaching the systemic circulation and limited residence time in the cavity.

Nasal absorption is affected by molecular weight, size, formulation pH, pKa of molecule, and delivery volume among other formulation characteristics. Molecular weight still presents the best correlation to absorption.[46,47] The apparent cut-off point for molecular weight is approximately 1,000

daltons, with molecules less than 1,000 having better absorption.[23]

Shape is also important. Linear molecules have lesser absorption than cyclic-shaped molecules.[22] Additionally, particles should be larger than 10 mm, otherwise the drug may be deposited in the lungs.[48]

Hydrophilicity has been found to decrease a drug's bioavailability.[49] pH is also an important formulation factor for drug absorption. Both the pH of the nasal cavity and pKa of a particular drug need to be considered to optimize systemic absorption. Nasal irritation is minimized when products are delivered with a pH range of 4.5 to 6.5.[50]

Volume and concentration are also important considerations. The delivery volume is limited by the size of the nasal cavity. An upper limit of 25 mg/dose and a volume of 25 to 150 mL/nostril have been suggested.[50]

Applications

Delivery of protein therapeutic agents /Macromolecules to CNS

In the age of advanced peptide, protein, and vaccine research, nasal administration of such compounds provides an attractive delivery route. In case of oral administration, the bioavailability of protein molecules tends to be relatively low due to their large molecular size and rapid enzymatic degradation.[51] Because of their physicochemical instability and susceptibility to hepato-gastrointestinal "first pass" elimination, peptide/protein drugs are generally administered parenterally. It is on this background that intranasal administration seems a promising option. Most nasal formulations of peptide/protein drugs have been made up in simple aqueous or saline solutions with preservatives. Recently, more R&D work has been directed towards the development of nasal drug delivery systems for peptide/proteins. Currently, in the United States only four intranasal pharmaceutical products for systemic delivery have been marketed i.e. desmopressin (DDAVP), lypressin (Diapid), oxytocin (Syntocinon), and nafarelin acetate (Synarel).

Delivery of protein therapeutic agents to the CNS clearly involves extraneuronal transport as it occurs within minutes rather than hours. A number of protein therapeutic agents have been successfully delivered to the CNS using intranasal delivery in a variety of species. Neurotrophic factors such as NGF,[30-32] IGF-I,[33] FGF[52] and ADNF12 have been intranasally delivered to the CNS in rodents.[53] Studies in humans, with proteins such as AVP,[54] CCK analog,[55] α-MSH/ACTH[56,57] and insulin[58,59] have revealed that they are delivered directly to the brain from the nasal cavity. Hussain[60] recently reviewed animal models to study nasal absorption and the effect of physicochemical and biopharmaceutical properties of drugs on the rate and extent of absorption. The review also discusses factors affecting peptide absorption and methods to improve the nasal bioavailability of peptides.

The bioavailability of protein molecules tends to be relatively low due primarily to their large molecular size and rapid enzyme degradation. As the number of amino acids increases beyond about 20, bioavailability becomes very low.[51] To overcome these issues, much research has been conducted in the areas of absorption enhancers and bioadhesive agents. Absorption enhancers are used to increase the bioavailability. They are basically surfactants, glycosides, cyclodextrin and glycols. They improve absorption through many different mechanisms, such as increasing membrane fluidity, increasing nasal bloodflow, decreasing mucus viscosity, and enzyme inhibition.[46] The classic example of a polypeptide compound with low nasal bioavailability is calcitonin. Its molecular weight is approximately 3,500 daltons and contains 32 amino acids in length. When calcitonin was given intranasally to rats and rabbits using a number of different cyclodextrins, its absorption as measured by a decrease in serum calcium concentration, was significant in comparison to the formulation without additive.[61]

Another technique aimed to increase nasal absorption is the utilization of bioadhesive agents. These compounds promote binding of drugs to biological material in the nasal cavity, thereby extending their residence time and allowing increased absorption. Common bioadhesive materials are carbopol, cellulose agents, starch, dextran, and chitosan.[62-67]

Liu *et al*[68,69] have demonstrated the therapeutic benefit of intranasal delivery of proteins in stroke studies. They have shown that intranasal IGF-I reduces infarct volume and improves neurologic function in rats with middle cerebral artery occlusion (MCAO). A preliminary report indicates that intranasal treatment is effective even when delayed for 4 h after the onset of MCAO.[70] Gozes *et al*[71] have shown that intranasal administration of a Vasoactive Intestinal Peptide Analog (VIP analog, containing 28 amino acids) prevented learning and memory impairments resulting from cholinergic blockade in rats treated with aziridium. They also demonstrated that a nine amino-acid fragment of ADNF (ADNF-9) and an ANDF-like peptide (NAP) also protected against short-term memory loss in the same animal model.

Research in humans has also provided evidence of direct delivery of macromolecules to the CNS from the nasal cavity. Kern *et al*[72] have demonstrated CNS effects of intranasal corticotropin-releasing hormone (CRH) without altering plasma cortisol or CRH levels. Perras *et al*[73] have reported that intranasal delivery of growth hormone-releasing hormone (GHRH) not only increased rapid eye movement sleep and slow wave sleep in humans, but also decreased growth hormone.

Al-Ghananeem *et al*[74] carried out a study on the utility of the nasal route for delivery of 17β-estradiol, using its water-soluble prodrug. The study revealed that CSF concentration of 17β-estradiol following intranasal delivery of prodrug was higher compared to an equivalent intravenous dose. This result has a significant value in the treatment of Alzheimer's disease.

The efficacy of peptide/protein delivered intranasally is highly dependent on the molecular structure of the drugs and their size. Respiratory epithelial cells are capable of absorbing peptide/protein by a vesicular transport mechanism, followed by transfer to the extracellular spaces, and subsequent uptake by the submucosal vascular network.[75]

Delivery of DNA plasmids to the CNS

Of the several routes available for immunization, the nasal route is particularly attractive because of the ease of ad-

ministration and the induction of potent immune responses, particularly in the respiratory tract. However, adjuvants and delivery systems are required to enhance immune responses following nasal immunization. The use of microparticles [poly(lactide co-glycolide)] as adjuvants and delivery systems for protein and DNA vaccines for nasal immunization were reviewed by Vajdy et al.[76] It has also been reported that after nasal administration of DNA plasmids, the level of plasmid in the brain was, 3.9 to 4.8 times higher than the plasmid concentration in the lungs and spleen. It was also found that the plasmid DNA reached the brain within 15 min following intranasal administration.[77] The higher distribution of plasmid to the brain after intranasal administration indicates that nasal administration might be a potential route for the delivery of therapeutic genes to the brain with reduced side-effects in the other organs. The plasmid administered in this study was very large as was the plasmid detected in the brain.

Delivery of small molecules to the CNS

Many small molecules have been shown to be transported directly to the brain and/or CSF from the nasal cavity. This has been reviewed by Illum[9] and Mathison et al.[11] Anand kumar et al[78] and David et al[79] have demonstrated intranasal delivery of estrogen and progesterone respectively, to the CSF. Studies have also shown that drugs such as L-NAME[80] and cocaine (at the lower end of the lipophilicity scale)[81] have a higher CSF and olfactory bulb concentration after nasal administration than that obtained after parenteral administration. The properties of small molecules, including size and lipophilicity affect delivery to the CNS following intranasal delivery.[82-84]

Sakane et al[85] reported that following intranasal administration of the antibiotic cephalexin to rats, higher CSF concentration was reached at 15 min but it declined to approximately half that concentration at 30 min. Because cephalexin does not cross the BBB well and because CSF concentration was 166-fold higher after intranasal administration than after systemic administration in spite of similar blood levels, it was concluded that cephalexin entered the CSF directly from the nasal cavity. Using a series of fluorescein isothiocyanate-labeled dextrans (FITC-dextran) with increasing molecular weights, it was found that dextrans with molecular weights of up to 20,000 daltons could be transported directly from the nasal cavity of rats into the CSF.[80] The concentration of the FITC-dextrans in the CSF increased with decreasing molecular weight. These FITC-dextrans are not found in the CSF after intravenous administration. Similarly, a comparison of the brain olfactory bulb concentrations achieved 30 min after intranasal administration of 7.4 n mol dopamine (153 daltons)[86] with those obtained after intranasal administration of 7.4 n mol nerve growth factor (NGF) (26,500 daltons)[16,17] to rats, revealed a five-fold higher delivery of the lower molecular weight dopamine. Comparing the percentages of the original dose remaining in the brain 30 to 45 min after intranasal administration of dopamine (0.12%)[87] and NGF (0.023%)[32] in rodents revealed a similar difference. In addition, with most small molecules, a significantly higher molar dose can be delivered intranasally than with larger protein or DNA therapeutic agents. Thus, considerably higher concentrations of small molecules are achievable in the CNS with intranasal delivery. Ishikawa et

al[88] reported that powder formulation of elcatonin utilizing $CaCO_3$ improves the nasal bioavailability by increasing residence time in the nasal cavity and thus enhances the systemic bioavailability. Recently Bergstrom et al[89] studied the uptake of picolinic acid (PA) in the brain. [3H]PA was administered via unilateral nasal instillation or *i.v.* injection to mice. Autoradiography demonstrated rapid uptake of radioactivity in the olfactory nerve layer and in the ipsilateral olfactory bulb following nasal instillation, which was maintained at a high level even after 4 h. On the other hand *i.v.* injection of [3H]PA demonstrated selective uptake and retention of radioactivity in the olfactory bulb. Hussain et al[90] have found that intranasal administration of folic acid effectively results in complete and very rapid absorption into the CNS. This provides a method of rapidly and reliably delivering folic acid, alone or in combination with other compounds, to the systemic circulation to produce a beneficial effect in the treatment or prevention of Alzheimer's disease and stroke. Li et al[91]-reported rapid onset intranasal delivery of diazepam using ethyl-laurate-based microemulsion. At a 2 mg/kg dose, the maximum drug plasma concentration was arrived within 2-3 min, and the bio-availability (0-2 h) after nasal spray compared with *i.v* injection was about 50%. The results suggest that this approach may be helpful during emergency treatment of status epilepticus.

Illum et al[92] have studied the effect of chitosan-morphin nasal formulation *vis-a-vis* slow *i.v.* infusion of morphine in healthy volunteers who reported sedation at the earliest time point after nasal administration compared with *i.v.* administration. This suggests that after nasal administration morphine may be able to reach CNS more rapidly than after *i.v.* administration.

Conclusion

In summary, the advantages of intranasal delivery are considerable. It is both rapid and non-invasive. It bypasses the BBB and targets the CNS, reducing systemic exposure and thus systemic side effects. Even for drugs that can cross the BBB, it can reduce systemic side effects by reducing the need for the drug to enter the systemic circulation. It does not require any modification of the therapeutic agent being delivered and should work for a wide range of drugs. Intranasal delivery may facilitate the treatment and prevention of many different neurologic and psychiatric disorders.

References

1. Greig NH, Genka S, Rapoport SI. Delivery of vital drugs to the brain for the treatment of brain tumors. J Control Release 1990;11:61-78.
2. Pomponi M, Giacobini E, Brufani M. Present state and future development of the therapy of Alzheimer's disease. Aging 1990;2:125-53.
3. Rapoport SI. Blood brain barrier in physiology and medicine. New York: Raven Press; 1976.
4. Butte AM, Jones HC, Abbot NJ. Electrical resistance across the blood-brain barrier in anaesthetized rats; a development study. J Physiol 1990;429:47-62.
5. Smith QR. Advances in Neurology. In: Wurtman R, editors. Alzheimer's Diseases. New York: Raven Press; 1990. Vol. 51. p. 217-22.
6. Begley DJ, Bradbury MW, Kreuter J. editors. The blood brain barrier and drug delivery to the CNS. New York: Marcel Dekker; 1998. p. 122.
7. Illum L. Nasal drug delivery – possibilities, problems and solutions. J Control Release 2003;87:187-98.

8. Mygind N, Anggard A. Anatomy and physiology of the nose-pathophysiology alterations in allergic rhinnitis. Clin Rev Allergy 1984;2:173-88.

9. Illum L. Transport of drugs from the nasal cavity to the central nervous system. Eur J Pharm Sci 2000;11:1-18.

10. Schipper NG, Verhoef JC, Merkus FW. The nasal mucocilliary clearance: relevance to nasal drug delivery. Pharm Res 1991;8:807-14.

11. Mathison S, Nagilla R, Kompella UB. Nasal route for direct delivery of solutes to the central nervous system: fact or fiction? J Drug Target 1998;5:415-41.

12. Chien YW, Chang SF. Intranasal drug delivery for systemic medication. Crit Rev Ther Drug Carrier Syst 1987;4:67-194.

13. Hehar SS, Mason JDT, Stephen AB, Washington N, Jones NS, Jackson, SJ, *et al.* Twenty four hour ambulatory nasal pH monitoring. Clin Otolaryngol 1999;24:24-5.

14. Chien YW, Su KSE, Chang S. Nasal systemic drug delivery. USA: Marcel Dekker; 1989. p. 1-38.

15. Reed CJ. Drug metabolism in the nasal cavity: relevance to toxicology. Drug Metab Rev 1993;25:173-205.

16. Dahl AR, Lewis JL. Respiratory tract uptake of inhalants and metabolism of xenobiotics. Annu Rev Pharmacol Toxicol 1993;32:383-407.

17. Thornton-Manning JR, Dahl AR. Metabolic capicity of nasal tissue interspecies comparisons of xenobiotic- metabolizing enzymes. Mutat Res 1997;380:43-59.

18. Lewis JL, Nikula KJ, Novak R, Dahl AR. Comparative localization of carboxylesterase in F344 rat, beagle dog and human nasal tissue. Anat Rec 1994;239:55-64.

19. Aceto A, Llio, CD, Angelucci S, Longo V, Gervasi PG, Federici G. Glutathione transferases in human nasal mucosa. Arch Toxicol 1989;63:427-31.

20. Krishna NS, Getchell TV, Awasthi YC, Gatechell ML, Dhooper N. Age and gender-related trends in the expression of glutathione S-transferases in human nasal mucosa. Ann Otol Rhinol Laryngol 1995;104:812-22.

21. Ross, JS, Wilson KJW, Waugh, A, Grant, A, Ross and Wilson Anatomy and Physiology in health and illness. Churchill Livingstone; 2001. p. 206-7.

22. McMartin C, Hutchinson LE, Hyde R, Peters GE. Analysis of structural requirements for the absorption of drugs and macromolecules from the nasal cavity. J Pharm Sci 1987;76:535-40.

23. Wheatly MA, Dent J, Wheeldon EB, Smith PL. Nasal drug delivery: An *in vitro* characterization of transepithelial electrical properties and fluxes in the presence or absence of enhancer. J Control Release 1988;8:167-77.

24. Tengamnuay P, Mitra AK. Transport of tyrosine and phenylalanine across the rat nasal mucosa. Life Sci 1988;43:585-93.

25. Fisher AN, Brown K, Davis SS, Parr GD, Smith DA. The effect of molecular size on the nasal absorption of water soluble compounds in the albino rat. J Pharm Pharmacol 1987;39:357-62.

26. Thorne RG, Frey WH 2nd. Delivery of neurotrophic factors to the central nervous system: Pharmacokinetic considerations. Clin Pharmacokinet 2001;40:907-46.

27. Thorne RG, Emory CR, Ala TA, Frey WH 2nd. Quantitative analysis of the olfactory pathway for drug delivery to brain. Brain Res 1995;692:278-82.

28. Balin BJ, Broadwell RD, Salcman M, el-Kalliny M. Avenues for entry of peripherally administered protein to the central nervous system in mouse, rat, squirrel and monkey. J Comp Neurol 1986;251:260-80.

29. Broadwell RD, Balin BJ. Endocytic and exocytic pathways of the neuronal secretory process and trans-synaptic transfer of wheat germ agglutinin-horseradish peroxidase *in vivo*. J Comp Neurol 1985;242:632-50.

30. Frey WH, Liu J, Thorne RG, Rahman YE. Intranasal delivery of ^{125}I-labeled nerve growth factor to the brain via the olfactory route. In: Iqbal K, Mortimer JA, Winblad B, Wisniewski HM, editors. Research advances in Alzheimer's disease and related disorders. New York: John Wiley and Sons Ltd; 1995. p. 329-35.

31. Frey WH, Liu J, Chen X, Thorne RG, Fawcett JR, Ala TA. Delivery of ^{125}I-NGF to the brain *via* the olfactory route. Drug Delivery 1997;4:87-92.

32. Chen XQ, Fawcett JR, Rahman YE, Ala TA, Frey WH. Delivery of nerve growth factor to the brain *via* the olfactory pathway. J Alzheimers Dis 1998;1:35-44.

33. Frey WH, Thorne RG, Pronk G. Delivery of Insulin like growth factor-1 to the brain and spinal cord along olfactory and trigeminal pathways following intranasal administration: a noninvasive method for bypassing the blood brain barrier. Soc Neurosci Abstract 2000;26:1365-70.

34. Kida S, Pantazis A, Weller RO. CSF drains directly from the subarachnoid space into nasal lymphatics in the rat: anatomy, histology and immunological significance. Neuropathol Appl Neurobiol 1993;19:480-8.

35. Lowhagen P, Johansson BB, Nordborg C. The nasal route of cerebrospinal fluid drainage in man: A light microscope study. Neuropathol Appl Neurobiol 1994;20:543-50.

36. Foldi M. The brain and lymphatic system (I). Lymphology 1996;29:1-9.

37. Hirai S, Yashiki T, Matsuzawa T. Absorption of drugs from the nasal mucosa of rat. Int J Pharm 1981;7:317-25.

38. Hounam RF, Black A, Walsh M. The deposition of aerosol particles in the nasopharyngal region of the human respiratory tract. Aerosol Sci 1971;2: 47-61.

39. Bates DV, Fish BR, Hatch TF, Mercer TT, Marrow PE. Deposition and retention models for internal dosimetry of human respiratory tract. Task group on lung dyanamics. Health Phys 1966;12:173-207.

40. Proctor DF, Andersen I, Lundqvist G. Clearance of inhaled particles from humane nose. Arch Intern Med 1973;131:132-9.

41. Kublik H, Vidgren MT. Nasal delivery systems and their effect on deposition and absorption. Adv Drug Deliv Rev 1998;29:157-77.

42. Mygind N, Vesterhauge S. Aerosol distribution in the nose. Rhinology 1978;16:79-88.

43. Mygind N. Nasal allergy. 2nd ed. Oxford: Blackwell; 1973.

44. Khanvilkar K, Donovan MD, Flanagan DR. Drug transfer through mucus. Adv Drug Deliv Rev 2001;48:173-93.

45. Martin E, Verhoef JC, Cullander C, Romeijn SG, Nagelkerke JF, Merkus FW. Confocal laser scanning microscopic visualization of the transport of dextrans after nasal administration to rats: effects of absorption enhancers. Pharm Res 1997;14:631-7.

46. Agarwal V, Mishra B. Recent trends in drug delivery systems: intranasal drug delivery. Indian J Exp Biol 1999;37:6-16.

47. Fisher AN, Brown K, Davis SS, Parr GD, Smith DA. The effect of molecular size on the nasal absorption of water-soluble compounds in the albino rat. J Pharm Pharmacol 1987;39:357-62.

48. Jones NS, Quraishi S, Mason JD. The nasal delivery of systemic drugs. Int J Clin Pract 1997;51:308-11.

49. Corbo D, Liu J, Chien YW. Drug absorption through mucosal membranes: effect of mucosal route and penetrant hydrophilicity. Pharm Res 1989;6:848-52.

50. Romeo VD, De Meireles J, Sileno AP, Pimplaskar HK, Behl CR. Effects of physiochemical properties and other factors on systemic nasal drug delivery. Adv Drug Del Rev 1998;29:89-116.

51. Wearly LL. Recent progress in protein and peptide delivery by noninvasive routes. Crit Rev Ther Drug Carrier Syst 1991;8:331-94.

52. Kucheryanu VG, Kryzhanovsky GN, Kudrin VS, Yurasov VV, Zhigaltsev IV. Intranasal fibroblast growth factors: delivery into the brain exerts antiparkinsonian effect in mice. In: Torchilin V, Veronese FM, editors. Proceedings of the 26th Internl. Symposium on controlled release of bioactive materials. Boston MA: Controlled release society Inc; 1999. p. 643.

53. Gozes I, Bardea A, Reshef A, Zamoostiano R, Zhukovsky S, Rubinraut S, *et al.* Neuroprotective strategy for Alzheimer disease: intranasal administration of a fatty neuropeptide. Proc Natl Acad Sci 1996;93:427-32.

54. Pietrowsky R, Struben C, Molle M, Fehm HL, Born J. Brain potential changes after intranasal administration *Vs.* intravenous administration of vasopressin: evidence for a direct nose-brain pathway for peptide effects in humans. Biol Psychiatry 1996;39:332-40.

55. Pietrowsky R, Thieman A, Kern W, Fehm HL, Born JA. A nose-brain pathway for psychotropic peptides: evidence from a brain evoked potential study with cholecystokinin. Psychoneuroendocrinology 1996;21:559-72.

56. Smolnik R, Molle M, Fehm HL, Born J. Brain potentials and attention after acute subchronic Intranasal administration of $ACTH_{4-10}$ desacetyl-a-MSH in humans. Neuroendocrinol 1999;70:63-72.

57. Fehm HL, Smolnik R, Kern W, McGregor GP, Bickel U, Born J. The melanocortin melanocyte-stimulating hormone/adrenocotropin (4-10) decreases body fat in humans. J Clin Endocrinol Metab 2001;86:1144-8.

58. Kern W, Born J, Schreiber H, Fehm HL. Central nervous system effects of intranasally administered insulin during euglycemia in men. Diabetes 1999;48:557-63.

59. Hinchcliffe M, Illum L. Intranasal insulin delivery and therapy. Adv Drug Deliv Rev 1999;35:199-234.

60. Hussain AA. Intranasal drug delivery. Adv Drug Deliv Rev 1998;29:39-49.

61. Schipper NGM, Verhoef JC, Merkus FWHM. Methylated beta-cyclodextrin is able to improve the nasal and intramuscular administration of salmon calcitonin. Calcif Tissue Int 1995;56:280-2.

62. Illum L, Dodane, V, Iqbal, K. Chitosan technology to enhance the effectiveness of nasal drug. Drug Del Technol 2002;2:1-7.

63. Illum L. Animal models for nasal delivery. J Drug Target 1996;3:717-24.

64. Illum L. Bioadhesive formulations for nasal peptide delivery. In: Mathiowitz E, Chickering DE, Lehr C, editors. Bioadhesive drug delivery systems. USA: Marcel Dekker; 1999. p. 507-41.

65. Illum L. Chitosan and its use as pharmaceutical excipient. Pharm Res 1998;15:161-70.

66. Illum L, Watts P, Fisher AN, Gabble-gill, Davis SS. Novel chitosan based delivery systems for nasal administration of a LHRH-analogue. STP Pharma 2000;10:89-94.

67. Illum L, Fisher AN, Gabble-gill I, Davis SS. The effect of bioadhesive starch microsphere on the absorption enhancing effect of enhancing agents administered nasally. Int J Pharm 2001;222:109-19.

68. Liu XF, Fawcett JR, Thorne RG, DeFor TA, Frey WH. Intranasal administration of insulin-like growth factor-I bypass the blood brain barrier and protects against focal cerebral ischemic damage. J Neuro Sci 2001;187:91-7.

69. Liu XF, Fawcett JR, Thorne RG, Frey WH 2nd. Non-invassive intranasal insulin-like growth factor-I reduces infarct volume and improves neurologic function in rats following middle cerebral artery occlusion. Neurosci Lett 2001;308:91-4.

70. Liu XF, Fawcett JR, DeFor TA, Frey W. The window of opportunity for treatment of focal cerebral ischemic damage with noninvasive Intranasal administration of Insulin-like growth factor-I. J Stroke Cerebrovascular Dis 2001;10:194-8.

71. Gozes I, Giladi E, Pinhasov A, Bardea A, Brenneman DE. Activity-dependent neurotrophic factor: Intranasal administration of femotmolar-acting peptides improve performance in a water maze. J Pharmacol Exp Ther 2000;293:1091-8.

72. Kern W, Schiefer B, Schwarzenburg J, Stange EF, Born J, Fehm HL. Evidence for central nervous effects of corticotropin-releasing hormone on gastric acid secretion in humans. Neuroendocrinology 1997;65:291-8.

73. Perras B, Marshall L, Kohler G, Born J, Fehm HL. Sleep and endocrine changes after intranasal administration of growth hormone-releasing hormone in young and aged humans. Psychoneuroendocrinology 1999;24:743-57.

74. Al-Ghananeem AM, Traboulsi AA, Dittert LW, Hussain AA. Targeted brain delivery of 17 β-estradiol *via* nasally administered water soluble prodrugs. AAPS Pharm Sci Tech 2002;3:1-8.

75. Stratford RE Jr, Lee VH. Aminopeptidase activity in homogenates of various absorptive mucosa in albino rabbit : Implication in peptide delivery. Int J Pharm 1986;30:73-82.

76. Vajdy M, O'Hagan DT. Microparticles for intranasal immunization. Adv Drug Deliv Rev 2001;51:127-41.

77. Oh YK, Kim JP, Hwang TS, Ko JJ, Kim JM, Yang JS, *et al.* Nasal absorption and biodistribution of plasmid DNA: an alternative route of DNA vaccine delivery. Vaccine 2001;19:4519-25.

78. Anand Kumar TC, David GFX, Umberkoman B, Saini KD. Uptake of radioradioactivity by body fluids and tissues in rhesus monkeys after intravenous injection or intranasal spray of tritium-labelled estradiol and progesterone. Curr Sci 1974;43:435-9.

79. David GF, Puri CP, Anand Kumar TC. Bioavailability of progesterone enhanced by intranasal spraying. Experentia 1981;37:533-4.

80. Sippel JM, Giraud GD, Holden WE. Nasal administration of the nitric oxide synthase inhibitor L-NAME-induces daytime somnolence. Sleep 1999;22:786-8.

81. Chow HS, Chen Z, Matsuura GT. Direct transport of cocaine from the nasal cavity to the brain following intranasal cocaine administration in rats. J Pharm Sci 1999;88:754-8.

82. Sakane T, Akizuki M, Yamashita S, Nadai T, Hashida M, Sezaki H. Direct drug transport from the rat nasal cavity to the cerebrospinal fluid: the relation to the dissociation of the drug. J Pharm Pharmacol 1994;46:378-9.

83. Sakane T, Akizuki M, Yamashita S, Nadai T, Hashida M, Sezaki H. The transport of a drug to the cerebrospinal fluid from the rat nasal cavity: the relation to the lipophilicity of the drug. Chem Pharm Bull 1991;39:2456-8.

84. Sakane T, Akizuki M, Yamashita S, Nadai T, Hashida M, Sezaki H. Direct drug transport from the rat nasal cavity to the cerebrospinal fluid: the relation to the molecular weight of drugs. J Pharm Pharmacol 1995;47:379-81.

85. Sakane T, Akizuki M, Yamashita S, Nadai T, Hashida M, Sezaki H. The transport of cephalexin to the cerebrospinal fluid directly from the nasal cavity. J Pharm Pharmacol 1991;43:449-51.

86. Dahlin M, Jansson B, Bjork E. Levels of dopamine in blood and brain following nasal administration to rats. Eur J Pharm Sci 2001;14:75-80.

87. Dahlin M, Bergman U, Jansson B, Bjork E, Brittebo E. Transfer of dopamine in the olfactory pathway following nasal administration in mice. Pharm Res 2000;17:737-42.

88. Ishikawa F, Katsura M, Tamai I, Tsuji A. Improved nasal bioavailability of elcatonin by insoluble powder formulation. Int J Pharm 2001;224:105-14.

89. Bergstrom U, Franzen A, Eriksson C, Lindh C, Brittebo EB. Drug targeting to brain: transfer of picolinic acid along the olfactory pathways. J Drug Target 2002;10:469-78.

90. Hussain A, Dittert LW, Traboulsi A. Brain delivery of folic acid for the prevention of Alzheimer's disease and stroke. US: Patent 6; 2002. p. 369,058.

91. Li L, Nandi I, Kim KH. Development of an ethyl laurate-based microemulsion for rapid-onset intranasal administration of diazepam. Int J Pharm 2002;237:77-85.

92. Illum L, Watts P, Fisher AN, Hinchcliffe M, Norbury H, Jabbal-Gill I, *et al.* Intranasal delivery of morphine. J Pharmacol Exp Ther 2002;301:391-400.