MINIREVIEW

Nasal Drug Administration: Potential for Targeted Central Nervous System Delivery

CANDACE L. GRAFF, GARY M. POLLACK

Division of Drug Delivery and Disposition, School of Pharmacy, University of North Carolina, Chapel Hill, North Carolina 27599 7360

ABSTRACT: Nasal administration as a means of delivering therapeutic agents preferentially to the brain has gained significant recent interest. While some substrates appear to be delivered directly to the brain via this route, the mechanisms governing overall brain uptake and exposure remain unclear. Some substrates utilize the olfactory nerve tract and gain direct access to the brain, thus bypassing the blood brain barrier (BBB). However, most agents of pharmacologic interest likely gain access to the brain via the olfactory epithelium, which represents a more direct route of uptake. While the traditional BBB is not present at the interface between nasal epithelium and brain, P-glycoprotein (and potentially other barrier transporters) is expressed at this interface. In addition, work in this laboratory has demonstrated that P-glycoprotein throughout the brain can be modulated with nasal administration of appropriate inhibitors. The potential for targeted central nervous system delivery via this route is discussed. © 2005 Wiley Liss, Inc. and the American Pharmacists Association J Pharm Sci 94:1187 1195, 2005

Keywords: Nasal delivery; central nervous system; brain; blood brain barrier

Delivery of drugs to the central nervous system (CNS) remains a challenge in the development of efficacious agents for central targets, mainly due to the impenetrable nature of the blood–brain barrier (BBB). In general, the BBB limits substrate penetration based on several characteristics, including lipophilicity, molecular size, and specificity for a variety of ATP-dependent transport systems. Expression of efflux transporters [i.e., P-glycoprotein (P-gp)] in the endothelial cells that form the BBB limits the ability of many lipophilic compounds, including potential therapeutic agents, to reach target sites in the CNS (for review, see Graff and Pollack[1]). Due to the critical importance of effective drug delivery to the brain, a number of approaches (e.g., utilizing prodrugs,[2] inhibiting efflux transporters,[3] disrupting the endothelial tight junctions that, along with the cell membrane, form the physical barrier,[4] and use of nasal administration[5]) have been evaluated to minimize the effects of the BBB. The utility of the nasal route as a portal for preferential delivery of therapeutic agents to the brain is the focus of this mini-review.

The concept of nasal administration providing a means to deliver drugs directly to the CNS by bypassing the BBB is not entirely appropriate in its argument. Although some drugs may be delivered directly to the brain parenchymal tissue via the nasal route, BBB transport proteins, including but perhaps not limited to P-gp, are operative at this site and serve to limit the ability of substrates to access the brain via this route.[6] Furthermore, co-administration of a P-gp inhibitor by nasal instillation eliminates the barrier

function of this efflux transporter, resulting in enhanced delivery of P-gp substrates to the brain. Therefore, CNS drug delivery via the nasal route appears to be faced with obstacles that are similar to brain delivery after systemic administration. However, there may be unique opportunities associated with the use of nasal delivery to enhance overall brain uptake and maximize central pharmacologic effects.

Nasal Delivery

A drug administered by the nasal route may enter into the blood of the general circulation, may permeate the brain directly, or in some cases may follow both pathways (Fig. 1). However, many of the factors controlling the drug flux through each of these pathways remain unclear. In general, there are three routes along which a drug administered into the nasal cavity may travel. These routes include (1) entry into the systemic circulation directly from the nasal mucosa, (2) entry into the olfactory bulb via axonal transport along neurons, and (3) direct entry into the brain. The evidence supporting the role of each of these routes for a variety of model substrates is summarized in Table 1. This table is not intended to be comprehensive in nature, but rather to highlight some of the solutes from various classes that have been shown to follow one or more of these pathways.

A drug that enters into the systemic circulation must be absorbed through the nasal mucosa. The fraction of the administered dose absorbed by this route will depend on the contact time with, and the solubility and metabolic stability of the drug in, the mucus, as well as the rate of
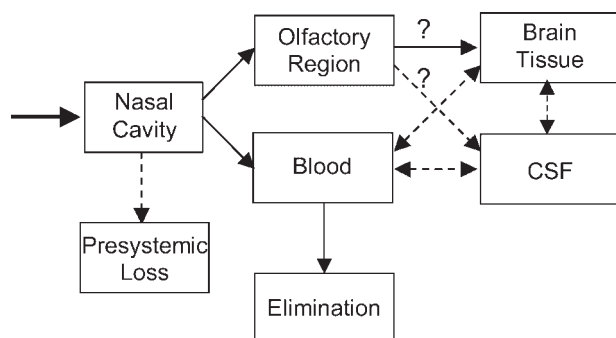

Figure 1. Scheme depicting the possible fate of a solute delivered nasally. Dashed lines (---) indicate limited substrate delivery via this route. Question marks indicate routes for which the exact pathway is unclear. Figure adapted from Illum.[12]

nasal mucus clearance.[7] Administration via this route avoids hepatic/gastrointestinal first-pass effects, and therefore may provide extensive relative absorption for substrates that have poor oral bioavailability.[8] This particular route does not present any advantage for the delivery of agents to the CNS per se, as the substrate must traverse the BBB from the systemic circulation after absorption from the nasal mucosa.

A drug may be carried along the olfactory neuron by intracellular axonal transport to the olfactory bulb. This olfactory nerve pathway would allow the drug to be taken up into the neuronal cell (located in the olfactory epithelium) by endocytosis, with subsequent transport into the CNS. This route appears to be utilized by some metals,[9] as well as macromolecules, viruses,[10] and particulates, including proteins,[11] and represents the only path from the nose to the brain by which the BBB may be bypassed. Despite the ability of this route to deliver agents to the olfactory bulb, transport to CNS sites beyond the olfactory system is unclear. Furthermore, this route is slow, and therefore does not account for the rapid appearance of some solutes in the brain and/or CSF following nasal administration.[12]

The mechanisms governing direct delivery of substrates to the brain (parenchymal tissue and/or CSF[13]) via the olfactory epithelium are not well understood. This pathway requires that the substrate enter the olfactory epithelium at a point other than the affector neuron.[14] Subsequently, a solute may be able to diffuse into the CSF that surrounds the brain from the perineural space. While this means of entry is feasible, it likely is not a pharmacologically viable route. The diffusion of the drug through the CSF into brain tissue would be against the flow of CSF,[15] and the diffusion path is long considering the rapid turnover of CSF.[16] This rapid CSF turnover will particularly affect larger molecules (>1000), whereas it likely will have less of an affect on smaller, highly diffusible molecules. Furthermore, while this pathway may constitute one route of entry into brain tissue,[17] it is not likely to be the primary direct route. Although measurable drug concentrations have been observed in CSF following nasal administration (e.g., cephalexin,[18] zidovudine[19]), the actual pathway has not been elucidated and the pharmacologic consequences are not clear. There are both a physical and a biochemical barrier present between the CSF and the brain parenchyma, and thus the drug concentration(s) between the brain and CSF typically will not be equivalent.[1] Clearly,

Table 1.   Transport Pathways Followed by Various Solutes Administered via the Nasal Route

Solute	Animal Model	Type of Administration	Pathway Followed[a]	References
Metals				
Aluminum	Rabbit	Nasal infusion	Direct (?)	43
Manganese	Rat	Inhalation	Olfactory nerve	44
Cadmium	Rat	Nasal infusion	Olfactory nerve	9
Nickel	Rat	Nasal application	Olfactory nerve	45
Antivirals/antibiotics				
Zidovudine	Rat	Nasal suspension	CSF; systemic	19
Cephalexin	Rat	Nasal solution	CSF; systemic	18
Sulfonamides	Rat	Nasal perfusion	CSF; systemic	46
Viruses				
Hepatitis virus	Mouse	Nasal inoculation	Olfactory nerve	10
Herpes simplex encephalitis virus	Mouse	Nasal drops	Direct; systemic; olfactory nerve	47,48
Rabies	Mouse	Nasal inoculation	Olfactory nerve	49
Pneumococci	Mouse	Nasal drops	Direct	50
Other drugs				
Dopamine	Mouse	Nasal drops	Direct; olfactory nerve	51
Cocaine	Rat	Nasal perfusion	Direct (?)	15

[a]Direct: nasal cavity → olfactory epithelium → CNS; Olfactory nerve: nasal cavity → olfactory epithelium → olfactory nerve → olfactory bulb; CSF: nasal cavity → CSF; Systemic: nasal cavity → systemic circulation.

a comprehensive understanding of the mechanisms governing this direct epithelial pathway is necessary in order to investigate the use of nasal administration as a practical means of delivering agents to the brain, and as such, this mini-review will focus on this route.

Olfactory Epithelium

The olfactory epithelium (also known as the olfactory mucosa) is located at the roof of the nasal cavity. The olfactory epithelium has a pseudostratified, columnar structure and is composed of three main cell types: receptor (or olfactory) cells, supporting cells, and basal cells. The olfactory receptor cells are elongated bipolar neurons that have cell bodies located at various depths within the epithelium, with one end in the nasal olfactory epithelium and the other end extending through the holes in the cribiform plate of the ethmoid bone, terminating in the olfactory bulb.[20,21] The supporting cells are covered with microvilli and extend from the mucosal surface of the neuro-epithelium to the basal membrane.[14] The basal cells are located at the basal surface of the neuro-epithelial layer and continue to differentiate to become new receptor cells.[22] It has been suggested that there is free communication between the nasal submucosal interstitial space and the olfactory perinueronal space, which appears to be continuous with a subarachnoid extension that surrounds the olfactory nerve as it penetrates the cribiform plate.[23,24] For a more complete description of the relevant anatomy of the olfactory region, please see the review by Illum.[12]

Evidence for Direct Nose-to-Brain Transport in Humans

Only a few studies, utilizing pharmacologic effect as a surrogate for drug entry into the CNS, provide evidence for the transport of drugs from the nasal cavity to the CNS in humans. Overall, these studies seem to confirm observations in animal models. Pietrowsky et al.[25] conducted a double-blind crossover study in 15 healthy adults who received either 20 IU of arginine-vasopressin (AVP) nasally or 1.5 IU AVP intravenously on three different occasions, with a saline solution as a control treatment. Event-related potentials (ERP, representing a measure of brain wave activity) were recorded while subjects performed an auditory attention task. Intranasal administration of AVP substantially increased a component of the ERP (P3), while there was no apparent increase after intravenous administration of AVP or nasal administration of saline. Moreover, plasma concentrations were higher

after i.v. administration of AVP as compared to nasal administration. This study provides functional evidence for increased delivery of AVP to the CNS via nasal as opposed to intravenous administration. Furthermore, the effect produced by nasal AVP was rapid, and therefore was attributed to a direct delivery of AVP to the CNS, although the exact pathway was not elucidated.

It also has been reported that intranasal administration of angiotensin II (ANG II) resulted in direct CNS activity.[26] In a balanced cross-over design, 12 healthy adults were treated with ANG II intravenously or intranasally (placebo was included as a control). For intravenous and intranasal administration, similar plasma concentrations of ANG II were obtained. While both routes of administration resulted in comparable acute increases in blood pressure, the pharmacodynamic profiles differed. After intravenous administration, blood pressure remained elevated, whereas it returned to baseline after nasal administration. In addition, intranasal ANG II counteracted the decrease in norepinephrine circulating observed after intravenous administration of ANG II, and enhanced plasma concentrations of vasopressin. These responses were similar to the effects observed after an intracerebroventricular administration of ANG II in animals.

A double-blind, within-subject crossover study was conducted in 18 healthy adults to investigate the effects of insulin (20 IU) delivered nasally.[27] In this study, auditory evoked potentials (AEP, representing a measure of cortical sensory processing) were recorded while the subjects performed a vigilance task (oddball paradigm). Blood glucose and serum insulin were not affected by nasal insulin, suggesting that systemic exposure was minimal. However, nasal insulin reduced the amplitudes of the two components of the AEP, and increased latency, when compared to placebo.

These results suggest that nasally administered insulin is able to enter the brain directly from the nasal cavity. While there are receptors located within the olfactory bulb (mostly related to chemoreception), to exploit this route for a pharmacologic endpoint, the substrates must be able to reach the target receptors, which likely are located within the brain parenchyma. While these studies indicate that some compounds appear to elicit pharmacodynamic responses following nasal delivery, the actual distribution of compounds following nasal administration is not well understood. Clearly, a more comprehensive understanding of this distribution is necessary, and could be achieved via comprehensive kinetic analysis using tissue slices or microdissection, or by using noninvasive techniques such as PET imaging

Common Features with the Blood–Brain Barrier

The nasal cavity has many features in common with the BBB, including the presence of tight junctions and the expression of transport proteins and metabolic enzymes. Specifically, tight junctions are observed in both the nasal mucosa and the olfactory epithelium. There is significant expression and activity of a series of cytochrome P450 (CYP) isoforms, including CYP1A2, 2A, 2B, 2C, 2E, and 3A.[28,29] In addition, a variety of other metabolic enzyme systems, including NADPH-cytochrome P450 reductase, epoxide hydrolase (EH), glucuronosyltransferase (UGT), and glutathione transferase (GST) have shown significant activity in the nasal cavity.[30,31] Finally, both P-gp and multidrug resistance protein (MRP1) have been demonstrated in the nasal mucosa.[32] The potential expression of, and the role of multidrug resistance-related transporters in, the olfactory epithelium was unclear until very recently. However, P-gp has been shown to be expressed in to the olfactory epithelium and in the endothelial cells that line the murine olfactory bulb, as well as in excised bovine olfactory epithelium.[33] The functional significance of the transporter at this site is the focus of continuing investigation.

Problems with Studying Nasal Delivery

As with any biomedical research area, many of the studies performed to date have examined nasal delivery by utilizing rodent models. Species differences between these animals and humans in nasal and brain anatomy and physiology may confound the extrapolation of results to humans. In general, olfactory transport is expected to be more pronounced in rodents due to the anatomical differences in the olfactory region between rodents and humans, as well as due to the experimental conditions utilized. Interspecies differences in nasal and brain anatomy and physiology must be considered before any assessment can be made regarding the utility of this method for drug delivery in humans. For instance, the olfactory bulb represents a relatively large portion of the CNS in rodents, and the nasal olfactory mucosa covers approximately 50% of the total nasal epithelium in rats and 45% in mice.[34,35] These structures are proportionately smaller in

humans; the olfactory mucosa covers approximately 5% of the total nasal epithelium in humans.[34] These anatomical differences may predispose the rat, more so than humans, to olfactory deposition and potential olfactory transport of some compounds, and suggest that this route of brain delivery may be less substantial in humans as compared to the rat. The CSF volume ($\sim$160 mL in humans vs. 35 μL in mice) is replaced every 1.5 h in mice compared to every 5 h in humans, which may impact the interpretation of nose-to-brain drug delivery studies (particularly for larger molecules), especially those in experimental protocols that utilize CSF concentrations as an indication of brain uptake.[16,36] In addition, many experimental paradigms require that the animal be placed on its back to allow sufficient bathing of the olfactory area with a solution of the substrate of interest, which would likely enhance uptake. Additional research will be required to clarify the potential significance of the olfactory route of delivery of substrates to the brain in humans, and these limitations will need to be considered when interpreting the data collected from animals to date.

Targeted CNS Delivery

Several studies have been designed to examine the potential of the nasal route for enhancing the delivery of substrates to the brain. It has been proposed that nasal administration may allow a substrate to reach a target in the brain at a higher concentration than would be feasible with other routes of administration. For example, it was shown that [³H]-dopamine achieved a 27-fold increase in olfactory bulb concentrations when administered nasally compared to systemic (intravenous) delivery.[5,37] However, for most drugs studied to date, the overall amount detected in brain tissue is usually only 2%–3% of the administered dose after nasal instillation. Again, this highlights the need for a more comprehensive understanding of the brain distribution of compounds following nasal administration.

For P-gp substrates, the amount of substrate delivered to brain tissue after nasal administration was dependent on the presence of P-gp at the nose–brain barrier. In fact, the impact of P-gp on the brain uptake of nasally-administered substrates was similar to that for substrates administered systemically. Furthermore, it has been demonstrated that the effect of P-gp on the brain uptake of nasally-administered substrates can be modulated by utilizing appropriate transport inhibitors.[6] This observation led us to question whether nasal delivery could modulate the effect of P-gp on brain uptake only when the substrate was administered nasally, or whether the effect may be more generalized. In other words, could nasal delivery offer a means to target the BBB broadly but specifically, in apparent opposition to the prevailing hypothesis that nasal delivery serves to circumvent the BBB?
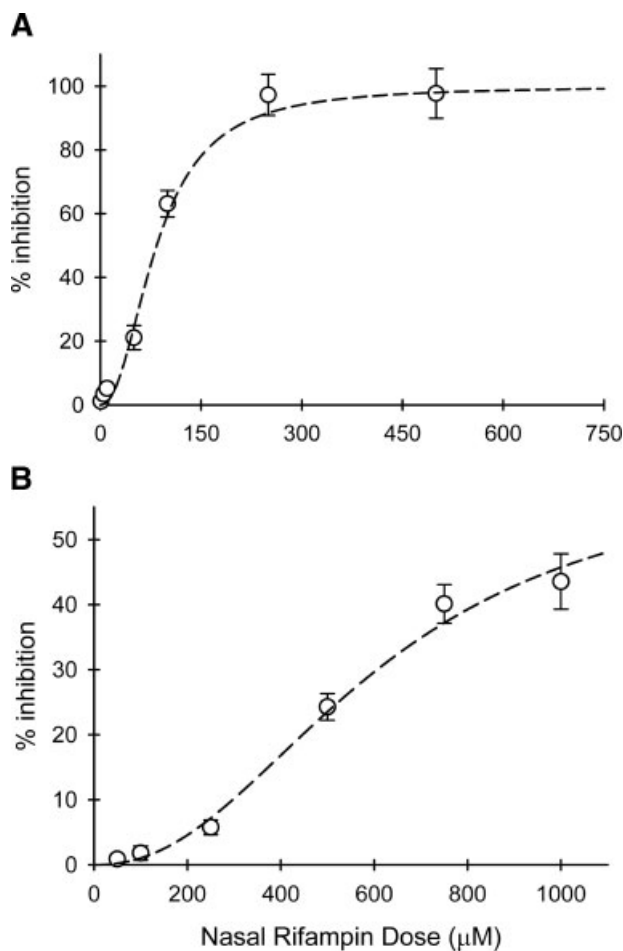

Figure 2. Dose-response relationship for inhibition of P-gp-mediated efflux transport of ³H-verapamil by nasally administered rifampin. Symbols represent mean $\pm$ SD for $n = 4$ per rifampin dose; the fitted line represents a sigmoidal Hill equation. Panel (A) represents nasal ³H-verapamil administration and is characterized by $E_{max} = 99 \pm 3\%$, $ED_{50} = 81 \pm 5$ μM, $\gamma = 2.7 \pm 0.4$ (parameter estimate $\pm$ standard error). Panel (B) represents systemic ³H-verapamil administration (i.v.) and is characterized by $E_{max} = 61 \pm 19\%$, $ED_{50} = 620 \pm 200$ μM, $\gamma = 2.2 \pm 0.5$ (parameter estimate $\pm$ standard error). Figures adapted from Graff and Pollack.[6]

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.

fastcase®
Smarter legal research.