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

Received 28 April 2004; revised 14 July 2004; accepted 18 November 2004

Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/jps.20318

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.
 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

Correspondence to: Gary M. Pollack (Telephone: (919) 962-0055; Fax: (919) 966-0197; E-mail: gary_pollack@unc.edu)

Journal of Pharmaceutical Sciences, Vol. 94, 1187–1195 (2005)

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 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.

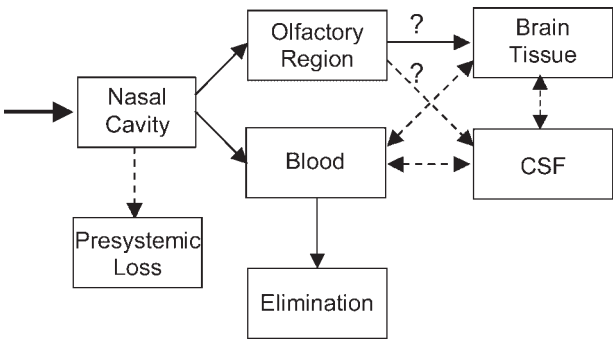

Figure 1. Scheme depicting the possible fate of a solute delivered nasally. Dashed lines (---) indicate limited substrate delivery via this route. Question marks indicate routes for which the exact pathway is unclear. Figure adapted from Illum.[12]

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,