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(D) Routes of Delivery: Case Studies

(1) Nasal delivery of peptide drugs

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Abbreviations: STDHF, sodium tauro-24,25-dihydrofusidate; SVP, small volume parenterals; i.v., intravenous; DEAE, diethylaminoethyl; LPC, lysophosphatidylcholine; hGH, human growth hormone; CMC, critical micellar concentration; AUC, area under the curve; LHRH, luteinizing hormone-releasing hormone; IgA, immunoglobulin A.

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Summary

This chapter summarises the problems associated with and the potential of nasal drug administration. The physiology and the anatomy of the nasal cavity are briefly discussed. Limitations of currently available nasal formulations are presented and solutions to the major problem, low bioavailability, are proposed. The biopharmaceutical properties and toxicity of both old and new enhancer systems are discussed. A dry particulate system, starch microspheres which are water insoluble but adsorb water, and sodium tauro-24,25-dihydrofusidate (STDHF), which is surface active, are two promising enhancer systems promoting the nasal absorption of drugs by different mechanisms. These systems are discussed in this review.

I. Introduction

Systemically acting peptides and proteins are normally administered by parenteral injection. These have consisted of traditional sterile preparations, e.g., small volume parenterals (SVP) or lyophilized products. Because of the problems related to injections such as phobia for needles/syringes, pain, etc., the search for a non-parenteral alternative has been intensive. One of the most promising options is the nasal route.

Nasal administration of drugs is not new and has been used since ancient times to give drugs locally or systemically. The subject has recently been reviewed by Chien et al. [1]. The nasal cavity has a rather porous endothelial membrane and the mucosa is richly vascularized. The total area is rather large owing to the anatomy of the cavity and the microvilli structure of the epithelial cells. The most important advantage with the nasal route is how the blood circulation in the nose is linked to the systemic circulation, thus avoiding first-pass hepatic metabolism. The absorption rate profiles of many non-protein drugs given nasally are almost similar to that for i.v. administration. Some of the drawbacks with the nasal route are low bio-availability for large proteins, and that the drug itself or some component in the formulation is toxic/irritative to the mucosa. The nasal mucosa is enzymatically active, which has to be considered when dealing with peptides and proteins. Further, the physiological status of the nasal cavity also influences drug absorption through the nose. This review will highlight the problems with nasal administration of peptides and attempts to overcome those problems. The anatomy and physiology of the nasal cavity will also be briefly described.

II. Nasal physiology

The primary function of the nose in humans is to modify the inspired air [2] in such a way that it is heated, humidified and filtered of particles of different kinds, i.e., dust and bacteria. Another major function is the olfaction. The anatomy and physiology of the nose are well adapted to meet these needs.

Unlike the lower airways that have a very low resistance to the airflow, the anatomy of the nasal cavity results in a high air resistance (Fig. 1). This structure ensures close contact between the air stream and the mucosal surface.

The nasal epithelium consists mostly of ciliated columnar cells, goblet cells, non-ciliated columnar cells and basal cells. The epithelium is ciliated behind the nostril. These ciliated cells transport mucus and trapped particles backwards to the pharynx with a flow-rate of approximately 5–6 mm/min. The nasal cavity has a depth of 12–15 cm and thus the total contact time for any particle administered is 20–30 min. Mucociliary clearance is one of the major physical barriers for the nasal absorption of drugs. The cilia transport a layer of mucus produced by the goblet cells, nasal glands and lacrimal glands [3]. The mucus consists of water electrolytes, ≈95–97%, 1–2% and 2–3% proteins, respectively. The protein content consists of glycoproteins, proteolytic enzymes, secretory proteins and plasma proteins. The proteolytic activity in the nasal mucus is a further hindrance to nasal absorption of drugs [4,5].

The pH in the mucus layer of the nasal cavity is about 5.5–6.5 [6], which is optimal for the proteolytic enzymes and the maintenance of the enzymatic barrier. Any deviation from the optimal pH, giving inactivation of the enzymes, can increase the probability of microbial infection.

The nasal glands are mostly cholinergically innervated, whereas the vascular system is adrenergically innervated [7]. Drugs that have an effect on these systems, locally or systemically, will also affect the status of the mucosal membrane. Changes in the nasal cavity by disease may also influence nasal

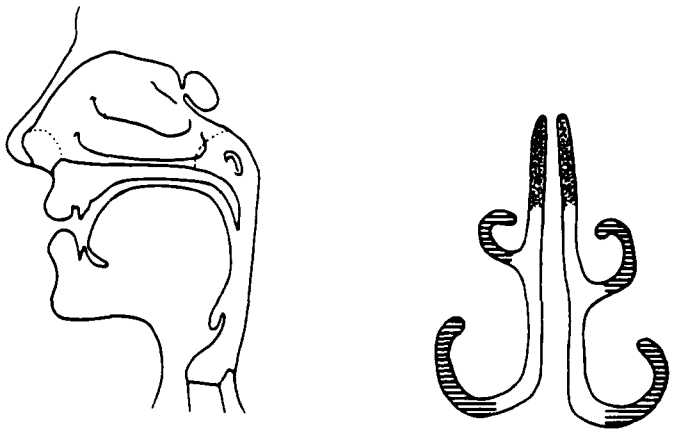

Fig. 1. Anatomy and physiology of the nose. Left: diagram of entire upper airway seen from the midline. The dashed line just beyond the nostril marks the beginning of the nasal valve, whereas the dotted line shows approximately the beginning of the ciliated epithelium region. The dashed line near the nasopharynx indicates the posterior termination of the nasal septum. Right: the stippled areas above indicate the olfactory airway. The clear areas represent the main nasal airway which is the site primarily reached by the medication with drops or aerosols. The hatched areas mark the meatal spaces. (From Ref. 2, reproduced with permission of Elsevier).

penetration. For instance, nasal obstruction caused by nasal polyposis reduces the absorption [8]. Chronic and allergic rhinitis decrease mucociliary clearance time due to extensive mucus production [9]. These and other pathological conditions will potentially modify the bioavailability of drug administered by the nasal route.

III. Some basic characteristics of existing nasal drug delivery systems

A few peptide formulations for nasal administration are available on the Swedish market [10]. These products disperse sprays or drops into the nasal cavity by means of rhinyle catheters, pipettes or metered dose spray pumps. The factors that govern the systemic bioavailability of a peptide given by the nasal route can be divided roughly into three categories:

- *physicochemical characteristics* of the peptide, such as molecular size, structure and hydrophilicity;
- *biochemical and physiological factors,* such as enzymatic degradation in the mucosa and nasal mucociliary clearance;
- *pharmaceutical formulation,* such as clearance and deposition of the delivery system in the nasal cavity, preservatives in the preparation and package.

The effect of drug hydrophilicity on the absorption rate has been clearly shown by Corbo et al. [11] using progesterone as a model drug. The monohydroxy, dihydroxy and trihydroxy derivatives were prepared and it was clear that the systemic bioavailability decreased with increasing hydrophilicity of the drug. A linear relation was obtained when the rate constant of absorption was plotted against the log partition coefficient (octanol/water).

According to McMartin et al. [12], there are two mechanisms of transport: a fast transport that is dependent on hydrophilicity and a slower rate dependent on molecular weight. The 'slower' transport rate is, nevertheless, fast enough to allow high absorption of low-molecular-weight hydrophilic drugs. The effect of molecular weight on absorption rate is related to the effective size of the molecule. Cyclic peptides are absorbed much better than linear ones [12].

Peptidase inhibitors may be used to circumvent presystemic metabolism of intranasal administered peptides. The nasal mucosa is by itself an enzymatic barrier consisting of several different proteolytic/hydrolytic enzymes. The aminopeptidase activities in nasal and ileal mucosal homogenates from the albino rabbit when measured at a protein concentration of approx. 10 mg/ml are similar [13]. The activities were given as the half-life of degradation of methionine enkephalin and were 16.3 $\pm$ 1.4 and 15.1 $\pm$ 2 min for nasal and ileal mucosa, respectively.

Hussain et al. [14] have recently evaluated a new aminopeptidase inhibitor, boroleucine, and its effect on the degradation rate of leucine enkephalin in the nasal cavity of rat using an in vitro perfusing method. Boroleucine at a concentration of 0.1 μM prevented degradation of the enkephalin and the effect

TABLE I

DIFFERENT ABSORPTION-PROMOTING SUBSTANCES/ADJUVANTS USED IN NASAL DRUG DELIVERY OF PAPTIDES/PROTEINS

Adjuvant	Refs.
Surfactants, non-ionic such as polyoxyethylene 9-laurylether	5,19–23
Surfactants, anionic such as sodium lauryl-sulfate and saponins	5,19,20
Bile salts and derivatives	5,19,20,22–28
Fatty acids/phospholipids	29,30
Starch microspheres/powder	31–34
Sodium tauro-24,25-dihydrofusidate	35–37
Bacitracin	38
Glycyrrhetinic acid derivatives	39
Gels	40
Bile salt-fatty acid mixed micelles	41,42

was reversed when the inhibitor was omitted. The inhibitory concentrations of bestatin and puromycin were 0.1 mM and 1 mM, respectively, but even at these levels equivalent effects to boroleucine were not achieved. Peptidase inhibitors like boroleucine are potential pharmaceutical adjuvants.

Inhaled/instilled particles are cleared from the nasal cavity by nasal mucociliary clearance. Thus every pharmaceutical system intended for intranasal use will interact with the nasal ciliary clearance mechanism. Preservatives such as methyl-*p*-hydroxybenzoate and propyl-*p*-hydroxybenzoate showed in a frog palate model to give reversible effect of the ciliary beat frequency while the effect of chlorobutanol was irreversible. In this model thiomersal gave no inhibiting effect of the ciliary beating [15]. Furthermore, the rheological properties of the mucus layer can change after contact with pharmaceutical formulations. This will certainly affect the clearance and exposure of drugs to the mucosa.

Instillation of drugs into the nasal cavity of humans also presents technical difficulties. In general, spray solutions are better than drops [16]. Several novel devices have been developed to secure a reproducible dosing of drug into the nose and to improve handling. Intranasal administration of drugs, especially peptides, is attractive, and for some peptides also effective. But, in general, the route is associated with low bioavailability, local toxicity/irritation and is adversely affected by local disorders such as rhinitis and pathophysiological changes. Nevertheless, it has been shown that the common cold and rhinitis do not decrease the bioavailability of buserelin and desmopressin [17,18]. Even though the nasal route is attractive with acceptable compliance, the overwhelming problem is bioavailability.

IV. Enhancer systems

To improve nasal peptide bioavailability, absorption-promoting systems/enhancers have to be used. Much biopharmaceutical research in this area during the past decade has been devoted to finding and testing different

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