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Review Article

Intranasal delivery of systemic-acting drugs: Small-molecules and biomacromolecules

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ABSTRACT

As a non-invasive route, intranasal administration offers patient comfort and compliance which are hurdled in parenteral drug therapy. In addition, the current recognition that the high permeability and vascularization of nasal mucosa coupled to the avoidance of the first-pass elimination and/or gastrointestinal decomposition ensure higher systemic drug absorption than oral route has contributed to the growing interest for intranasal delivery of drugs that require considerable systemic exposure to exert their therapeutic actions (systemic-acting drugs). Nevertheless, several features may hamper drug absorption through the nasal mucosa, particularly the drug molecular weight and intrinsic permeability, and, therefore, several strategies have been employed to improve it, propelling a constant challenge during nasal drug (formulation) development.

This review will firstly provide an anatomical, histological and mechanistic overview of drug systemic absorption after nasal administration and the relevant aspects of the therapeutic interest and limitations of the intranasal systemic delivery. The current studies regarding the nasal application of systemic-acting small drugs (analgesic drugs, cardiovascular drugs and antiviral drugs) and biomacromolecular drugs (peptide/protein drugs and vaccines) will also be outlined, addressing drug pharmacokinetics and pharmacodynamic improvements.

1. Introduction

The intranasal administration is widely used as the logical choice for the topic treatment of local diseases in the nose and paranasal sinuses including the allergic or infectious rhinitis, nasal polyposis and sinusitis. Nevertheless, given the nasal mucosa's high vascularization, fairly wide absorption area, porous and thin endothelial basement membrane of the nasal epithelium, intranasal administration has also become a portal for systemic drug delivery [1,2]. Indeed, it is today regarded as a potential alternative route for systemic delivery of small drugs that are conventionally administered by parenteral routes or that undergo extensive first-pass metabolism after oral administration [3,4]. More recently, the interest on intranasal delivery of larger molecules not absorbed via oral route, such as peptide–protein drugs and vaccines, has also becoming a remarkable reality even though the nasal absorption of these compounds decreases with their molecular weight [5]. The nasal route is less suitable for chronic drugs that must be frequently administered daily as well as for drugs that require sustained blood levels unless they are included in pharmaceutical formulations like sustained-release dosage forms.

Underlying the wide focus on exploiting nasal cavity for systemic drugs delivery is the rapid and direct systemic absorption of compounds that circumvent gastrointestinal and hepatic first-pass metabolism, enabling a reduction of the administrated dose, a rapid achievement of relevant therapeutic blood levels, a quicker onset of pharmacological action and fewer side effects than other administration routes. However, the success of systemic drug

Abbreviations: ACTH, adrenocorticotropic hormone; ALCRV, alginate microspheres containing carvedilol; AUC, area under the plasma concentration *vs.* time curve; C_{max}, maximum plasma concentration; CMC, carboxymethylcellulose; GLA, glutaraldehyde; GnRH, gonadotropin-releasing hormone; HPßCD, Hydroxypropyl-β-cyclodextrin; MW, molecular weight; Log *P*, Octanol–water partition coefficient; NALT, nasal-associated lymphoid tissue; PEG, polyethylene glycol; PTH, parathyroid hormone; rhG-CSF, recombinant human granulocyte-colony stimulating factor; RMßCD, randomly methylated-b5-cyclodextrin; t_{max}, time to reach maximum plasma concentration.

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delivery at nasal cavity is limited mainly by the mucociliary clearance which quickly clears the drug from the absorption site, reducing considerably the time available for its direct transport into the systemic bloodstream. The poor contact of formulations of small or large drugs with the nasal mucosa and particularly their low absorption when administered as simple aqueous solutions have implied the development of alternative strategies to improve the nasal bioavailability [2]. Among the most frequently alternative formulations commercially available are solution-based formulations coupled with mucoadhesive systems which may incorporate enzyme inhibitors and nasal permeation enhancers. The first diminishes the enzymatic activity at mucosa, while the latter increases the permeability of the drug, enhances the drug nasal residence time and improves the therapeutic efficacy of the systemic drugs [1,6–10]. The preparation of nano- or micro-particulate systems with various polymers has also been widely tested particularly for incorporating macromolecular drugs.

Although actual general reviews summarize the anatomy and the physiology of the nasal administration and the major factors that affect the nasal drug delivery, the present updated review aims to take a step further by discussing intranasal formulation strategies and delivery systems used to optimize nasal bioavailability of systemic-acting drugs. Thus, in this paper, the critical aspects concerning the intranasal delivery of the systemic drugs will be firstly reviewed. The wide variety of small and large therapeutic agents currently marketed or under development as nasal formulations for systemic actions will be also described, presenting together the pharmacokinetic features studied in animals or/and humans as well as the most innovative methods that have been used to modulate the systemic drug exposure.

2. Anatomical, physiological and mechanistic features behind intranasal delivery of systemic-acting drugs

Researchers became interested in the nasal route for the systemic delivery of medication due to the high degree of vascularization and permeability of nasal mucosa. The nasal mucosa, unlike the skin, does not present a highly keratinized stratum corneum; instead, it forms numerous microvilli underlined with a very rich vascularity. Indeed, the main site for systemic entry of drugs is the respiratory region around the inferior turbinate and it is the largest area of the nasal cavity. The nasal respiratory mucosa is a highly vascularized membrane lined by a pseudostratified columnar epithelium. It rests on the collagen basement membrane and the lamina propria which is richly supplied with blood vessels, nerves, glands and immune cells [3,9]. The epithelium is mainly composed of basal cells, ciliated column cells (which are covered by a layer of long cilia), non-ciliated column cells and globlet cells (Fig. 1). The former lie on the basement membrane and, besides being the progenitors of the other cell types, the basal cells are believed to help in the adhesion to the basement membrane; the columnar cells correspond to the majority of the epithelium cells and their apical surface containing microvilli considerably increase the surface area of the respiratory epithelium available for systemic drug absorption; the globlet cells secrete mucin, contributing in part for the production of the mucus layer. This nasal mucus layer is only 5 μm thick and it consists of 95% of water, 2.5–3% of mucin and 2% of electrolytes, proteins, lipids, enzymes, antibodies, sloughed epithelial cells and bacterial products [9]. Particularly due to the adhesive characteristics of the nasal mucus, inhaled particles, pathogens and xenobiotics may be trapped and transported by the propulsive coordinated force of cilia towards the pharynx, exhibiting a clearance half-time of only 15–20 min [11]. In order to resist stress and communicate with each other, neighbouring epithelial cells are closely held together by tight junctions, desmosomes and gap junctions. However, these attachments form a dynamic, adjustable, semi-permeable diffusion barrier that may prevent the passage of several compounds [12].

It is important to highlight that the blood supply of the nasal mucosa is absolutely essential for the systemic drug delivery [11,13]. The arterial blood supply of nasal mucosa comes mainly from ophthalmic, sphenopalatine and facial arteries. The arterial blood flow irrigates a dense bed of capillaries and large venous sinusoids that exist near the turbinate respiratory zone. On the other hand, the venous return involves the sphenopalatine, facial and ophthalmic veins. These veins drain into the internal jugular vein that subsequently drains into the right heart chambers (via the subclavian vein and the superior vena cava) [1,13]. These anatomical features explain the absence of hepatic first-pass effect of drugs administered by intranasal route. Moreover, blood flow rate significantly influences the systemic nasal absorption of drugs since it is essential to maintain the gradient of concentration from the site of absorption to blood and guarantee drug absorption by diffusion. Consequently, changes in local vascular homoeostasis (mediated by pathological conditions and/or drugs) may have significant repercussions on the rate and extent of systemic absorption of intranasally administered drugs and must therefore be carefully assessed [9]. The richly supplied vascular nature of the nasal mucosa, coupled with its vast surface area, permeable chorion and porous basal membrane inevitably makes the nasal

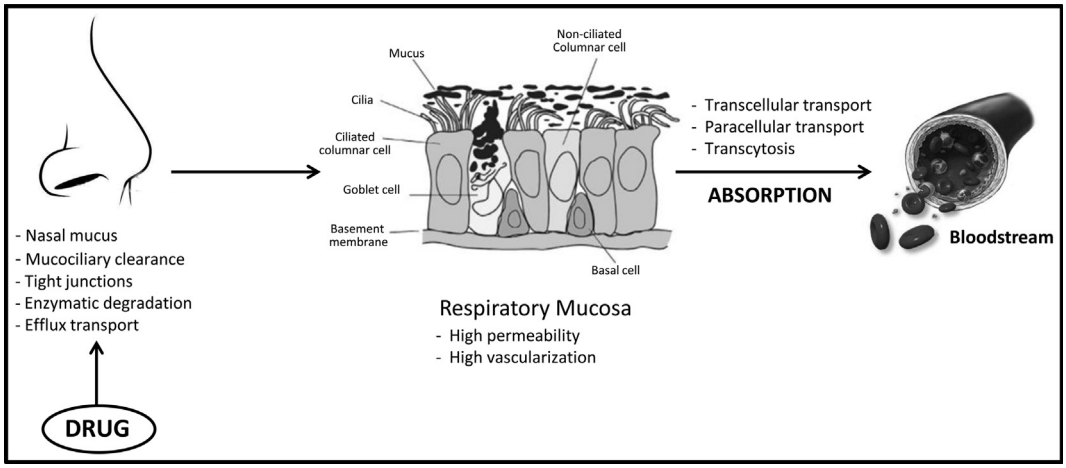

Fig. 1. Schematic representation of the respiratory mucosa and the possible pathways involved in the transport of drugs from nose to systemic bloodstream. Factors that influence systemic absorption of nasal drugs are also represented.