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Intranasal delivery of biologics to the central nervous system ☆

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ABSTRACT

Treatment of central nervous system (CNS) diseases is very difficult due to the blood–brain barrier's (BBB) ability to severely restrict entry of all but small, non-polar compounds. Intranasal administration is a non-invasive method of drug delivery which may bypass the BBB to allow therapeutic substances direct access to the CNS. Intranasal delivery of large molecular weight biologics such as proteins, gene vectors, and stem cells is a potentially useful strategy to treat a variety of diseases/disorders of the CNS including stroke, Parkinson's disease, multiple sclerosis, Alzheimer's disease, epilepsy, and psychiatric disorders. Here we give an overview of relevant nasal anatomy and physiology and discuss the pathways and mechanisms likely involved in drug transport from the nasal epithelium to the CNS. Finally we review both pre-clinical and clinical studies involving intranasal delivery of biologics to the CNS.

Contents

Abbreviations: Aβ, beta amyloid; ANG II, angiotensin II; AVP, arginine vasopressin; BBB, blood–brain barrier; ChAT, choline acetyltransferase; CNS, central nervous system; CSF, cerebrospinal fluid; EPO, erythropoietin; Ex, exendin; GALP, galanin-like peptide; GBC, globose basal cell; HBC, horizontal basal cell; HRP, horseradish peroxidase; IGF-1, insulin-like growth factor-1; INF-β1b, interferon β1b; IN, intranasal; IV, intravenous; MCAO, middle cerebral artery occlusion; MOG, myelin oligodendrocyte protein; MSC, mesenchymal stem cells; MW, molecular weight; NGF, nerve growth factor; OEC, olfactory ensheathing cell; OSN, olfactory sensory neuron; PACAP, pituitary adenylate cyclase-activating polypeptide; siRNA, small interfering RNA; TGF-β1, transforming growth factor β1; TJ, tight junctions; VEGF, vascular endothelial growth factor; V_1, ophthalmic division of trigeminal nerve; V_2, maxillary division of trigeminal nerve; V_3, mandibular division of trigeminal nerve; WGA-HRP, wheat germ agglutinin-horseradish peroxidase; ZO, zonula occludens.

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1. Introduction

The blood–brain barrier (BBB) is located at the level of the cerebral microvasculature and is critical for maintaining central nervous system (CNS) homeostasis. Although the BBB restricts the entry of potentially neurotoxic substances into the brain, it also presents a major obstacle to the delivery of therapeutics into the CNS for disease treatment. The BBB exhibits a low rate of pinocytosis and possesses tight junctions (TJ) which form a seal between opposing endothelial membranes [1]. The presence of TJ at the BBB creates a high transendothelial electrical resistance of 1500–2000 Ω·cm^2 compared to 3–30 Ω·cm^2 across most peripheral microvessels [2,3]. This high resistance is associated with very low permeability, i.e. the BBB greatly restricts paracellular diffusion of solutes from the blood into the brain. Typically, only small, lipophilic molecules appreciably cross the normal, healthy BBB via transcellular passive diffusion, although some limited transport of certain peptides and peptide analogs has been reported [4]. Essential nutrients such as glucose or iron gain entry into the CNS through specific transporters such as the glucose transporter 1 or receptors such as the transferrin receptor [5,6]. Receptors and transporters for gastrointestinal hormones involved in regulating metabolism are expressed at the BBB in order to convey information between the CNS and periphery [7]. In addition to its low paracellular permeability and low rate of pinocytosis, the BBB also expresses a high number of drug transporters (e.g. P-glycoprotein) which further restrict brain entry of many endogenous and exogenous substances that would otherwise be predicted to cross the BBB based on molecular weight (MW) and lipophilicity considerations [8,9].

Although there are many examples of small MW drugs which cross the BBB, nearly all large MW substances are severely restricted from crossing the BBB under normal conditions; indeed, the only examples of large MW drugs approved for clinical use in treating a neurological illness are those that act via peripheral mechanisms (e.g. type I interferons for treating multiple sclerosis). Many large MW substances have shown substantial promise in treating aspects of CNS diseases based on studies utilizing in vitro systems and animal models. However, it will likely be necessary to implement drug delivery strategies that overcome the formidable obstacles presented by the various barriers of the CNS (the BBB and blood–cerebrospinal fluid (CSF) barriers) for these studies to ultimately be translated to the clinic [10]. Intraparenchymal, intracerebroventricular, and intrathecal injections/infusions are capable of delivering therapeutics directly to the CNS, but these routes of administration are invasive and likely not practical for drugs which need to be given chronically. The intranasal (IN) route of administration provides a non-invasive method of bypassing the BBB to potentially deliver biologics such as peptides, proteins, oligonucleotides, viral vectors, and even stem cells to the CNS. The IN route has long been associated with a number of advantages (Table 1), e.g. rapid onset of effects using non-injectable administration methods and a growing record of experience with approved formulations (e.g. nasal spray of the 3.5 kDa polypeptide hormone calcitonin has been used for many years to treat postmenopausal osteoporosis); the major disadvantage of the route (Table 1), aside from the challenge of reproducibility, is that limited absorption across the nasal epithelium has restricted its application to particularly potent substances, although this can be overcome by use of permeation enhancers in some cases [11]. While nasal delivery has probably been the most successful of the alternative transmucosal routes as a portal of entry into the systemic circulation for substances that cannot be given orally [12], with a large number of intranasally applied drugs in clinical use [11], research into whether the IN route might deliver potentially therapeutic amounts of larger biologics such as proteins to the CNS was first described only a little over a decade ago [13,14]. Delivery of biologics and a variety of other substances from the nasal passages to the brain has now been documented in numerous animal and clinical studies [15–17]. Here we will provide an overview of relevant nasal anatomy and physiology and discuss the pathways and transport mechanisms that may be involved in the distribution of biologics from the nasal cavity to the CNS. We will also summarize the findings of key studies that convincingly show entry and/or efficacy of biologic drugs introduced to the CNS using the intranasal route of administration.

2. Nasal anatomy

2.1. General considerations

The nasal cavity extends from the nostrils (nares) to the nasopharynx and is divided longitudinally by the nasal septum [18]. The human nasal cavity only extends approximately 12–14 cm in length yet has a large absorptive surface area of ~160 cm^2 due to three bony structures called turbinates or conchae (inferior, middle and superior) which also aid in filtering, humidifying and warming inspired air [18]. Tables 2 and 3 summarize important comparative aspects of nasal anatomy with respect to humans, monkeys and rats, three of the most commonly used species in studies evaluating systemic absorption and brain targeting following intranasal administration. Several differences in the nasal anatomy and physiology of rats and primates are notable [19]. Primates are oronasal breathers while rats are obligate nasal breathers and rely more heavily on their keen sense of smell. The architecture of the rat nasal passage is generally more complex than that of the primates, with a significantly higher surface area-to-volume ratio. Importantly, mucociliary clearance (propulsion of mucus on the surface of the nasal epithelium by

Table 1
Advantages and disadvantages of intranasal drug delivery.

Advantages	Disadvantages
Non-invasive/reduced infection risk from application/low risk of disease transmission	Limited to potent drugs/small volumes (25–200 μl)
Ease of self-administration/dose adjustment	Active mucociliary clearance
Large surface area for absorption (human ~160 cm^2)	Enzymatic degradation by nasal cytochrome P450/peptidases/proteases (pseudo first-pass effect)
Rapid absorption/fast onset of action	Low permeability for hydrophilic drugs without absorption enhancers necessitates large doses
Rich, vascular submucosa and lymphatic system	Low pH of nasal epithelium
Avoid hepatic first-pass elimination	Interindividual variability
Possible direct pathways to the CNS bypassing the blood–brain barrier	Low CNS delivery efficiencies for proteins measured thus far (<0.05%)