Bioorganic & Medicinal Chemistry 26 (2018) 2888–2905

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

Nose-to-brain peptide delivery – The potential of nanotechnology

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ARTICLE INFO

Article history:
Received 30 August 2017
Revised 26 October 2017
Accepted 2 November 2017
Available online 4 November 2017

Keywords:
Nose-to-brain delivery
Intranasal drug administration
Therapeutic peptides
Protein drugs
Olfactory
Nanomedicine
Nanoparticles
Polymer-based nanocarriers
Lipid-based nanocarriers

ABSTRACT

Nose-to-brain (N-to-B) delivery offers to protein and peptide drugs the possibility to reach the brain in a non-invasive way. This article is a comprehensive review of the state-of-the-art of this emerging peptide delivery route, as well as of the challenges associated to it. Emphasis is given on the potential of nano-sized drug delivery carriers to enhance the direct N-to-B transport of protein or peptide drugs. In particular, polymer- and lipid- based nanocarriers are comparatively analyzed in terms of the influence of their physicochemical characteristics and composition on their *in vivo* fate and efficacy. The use of biorecognitive ligands and permeation enhancers in order to enhance their brain targeting efficiency is also discussed. The article concludes highlighting the early stage of this research field and its still unveiled potential. The final message is that more explicatory PK/PD studies are required in order to achieve the translation from preclinical to the clinical development phase.

1. Introduction

Neurological disorders, such as Alzheimer's disease, Parkinson's disease, Multiple sclerosis etc., but also diseases like obesity, behavior disorders and sexual dysfunction have been directly associated to different modalities of brain dysfunction. These debilitating diseases are nowadays continuously growing, affecting more and more people worldwide. In addition to the social burden and the individual suffering that they cause, the treatment of these diseases is also associated with very high costs.[1] Up to date, most of the drugs intended to treat CNS disorders and other brain related diseases are administered systemically and, for this, a prerequisite is that they are able to cross the blood–brain barrier (BBB).[2,3] Unfortunately, there is a significant number of drugs, notable peptide and protein drugs which could potentially have a powerful effect in the CNS provided that they could overcome the BBB or acquire other routes of access to the brain.

Nose-to-brain (N-to-B) delivery may represent a non-invasive method that enables the delivery of complex drugs to the CNS, while avoiding the BBB. This route is based on the principle that drugs can access the CNS following a "shortcut" from the nose directly to the brain along the trigeminal or olfactory nerves, located at the upper part of the nasal cavity. The increasing numbers of peptide and protein drugs which may be of interest to treat chronic CNS diseases and the recent identification of important brain functions have stimulated research in the nose-to-brain delivery field. Within this field, the level of evidence of the value of nanotechnology for the direct CNS targeted peptide delivery is still limited, however the knowledge generated over the last decade about this specific topic has raised some expectancies.[4,5]

Based on this background information, the main objective of this article is to focus on the potential of nanotechnology-mediated peptide delivery to the brain via the nose. More precisely, this review will provide the reader with a view of the challenges associated to this modality of administration, followed by the current status of the nose-to-brain peptide transport, and it will end with a critical analysis of the value of nanotechnology as compared to that of penetration enhancers for helping peptide drugs to reach brain targets.

2. Challenges and barriers to N-to-B peptide delivery

In early 1937, Faber reported for the first time the possibility of a direct passage from the nose to the brain, after administering a

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https://doi.org/10.1016/j.bmc.2017.11.001
0968-0896/

dye in the nostrils of rabbits.[6] Still, it was only in the late 90s, that the growing interest in the field of brain delivery motivated the scientific community to start exploring this alternative route.[7–13] Mechanistic studies in animal models have proven that N-to-B drug transport takes place either by extracellular or transcellular transport mechanisms along the olfactory epithelium or via the trigeminal nerve, after administration of the drug into the nasal cavity (Fig. 1).[14–19] Despite this increasing interest, the mechanisms underlying this direct N-to-B pathway are not fully elucidated yet.

2.1. Pathways related to the transport of peptides from the nose directly to the brain

The olfactory region is located at the top part of the nasal cavity under the cribiform plate in close proximity to the olfactory bulb, interlocking the nose with the brain (Fig. 1). More specifically, the olfactory epithelium consists of three types of cells, namely the basal epithelial cells, sustentacular cells, and the olfactory neurons with their cilia extending towards the nasal cavity (Fig. 2).[16,20] More detailed information about nasal physiology can be found in previous reviews.[16,18,19,21]

After administration of the drug into the nasal cavity, N-to-B drug transport may occur through the olfactory epithelium, either (i) by axonal transport after internalization into the neurons, (ii) by paracellular transport across the spaces between cells and, notably across the channels next to the olfactory nerves, or (iii) by transcellular transport across the basal epithelial cells (Fig. 2).[14–17,22,23] The paracellular pathway is considered to be the dominant transport mechanism based on animal studies, and it allows a more rapid drug transport (usually <30 min) than the others, which can last from a few hours up to days.[16,24] This could be explained by the slow regeneration of the olfactory neurons (every ~1 month) and the coexistence of mature and newly formed neurons, resulting in the absence of tight junctions in some parts of the olfactory epithelium.[24] This leakiness, in combination with the bulk flow of the cerebrospinal fluid (CSF) into the brain, enables the transport of the intranasally administered drugs to the CNS.[16] However, the predominance of one specific transport mechanism vs. the others depends on the properties of the drug or the delivery system used.[25] Depending on the pathway, the drug may reach the olfactory bulb by intraneuronal uptake and, from there, it may go into the brain regions connected to the olfactory tract (i.e., the piriform cortex, hypothalamus, amygdala) and finally disseminate through the CNS, and/or it may diffuse directly from the CSF into the whole CNS (Fig. 2).[26]

Based on studies in different animal models, some authors have proven that direct N-to-B drug delivery can also take place along the less explored trigeminal nerve, parts of which extend from the brainstem through the nasal respiratory epithelium, and provide thus a direct passage to the caudal and the rostral parts of the brain (Fig. 3).[24,25,27–30] Still, the contribution of the trigeminal pathway is not fully understood and is considered to be less relevant than the olfactory track.[31]

2.2. Challenges encountered in the transport of peptides from the nose directly to the brain

Despite the potential of this patient-friendly drug delivery route to the CNS, there are significant challenges associated to this modality of administration. Nose-to-brain transport is significantly affected by the surface and structural properties of the administered biomolecules (e.g., size and lipophilicity, degree of ionization). Proteins, because of their larger size (>1000 Da) and hydrophilicity, are transported in a far less extent than smaller lipophilic molecules. Another important factor is the presence of metabolic enzymes (cytochrome P450, esterases and transferases) in the mammalian olfactory mucosa.[15,32–35] On the other hand, from an anatomical point of view, the localization of the olfactory epithelium in the roof of the nasal cavity makes it difficult for drugs to gain access to the targeted region.[36,37] To address these pitfalls and enhance the bioavailability of the protein molecules, different approaches have been suggested, such as the use of permeation enhancers, cell penetrating molecules, mucoadhesives or nano-based drug delivery systems.[4,5,38–48] The last ones have the additional advantage of protecting the therapeutic load, while improving its interaction with the olfactory region. However, a limitation of this route, is related to the low volumes that can be administered (maximal dosing volume in humans is 0.4 mL), which implies the need of designing nanocarriers with a high drug loading capacity.[49] Lastly, it is worth mentioning that so far, the mechanistic studies have been mainly performed in animals, whereas the studies in humans have focused on the evaluation of the drugs therapeutic effects, or, in some exceptional situations

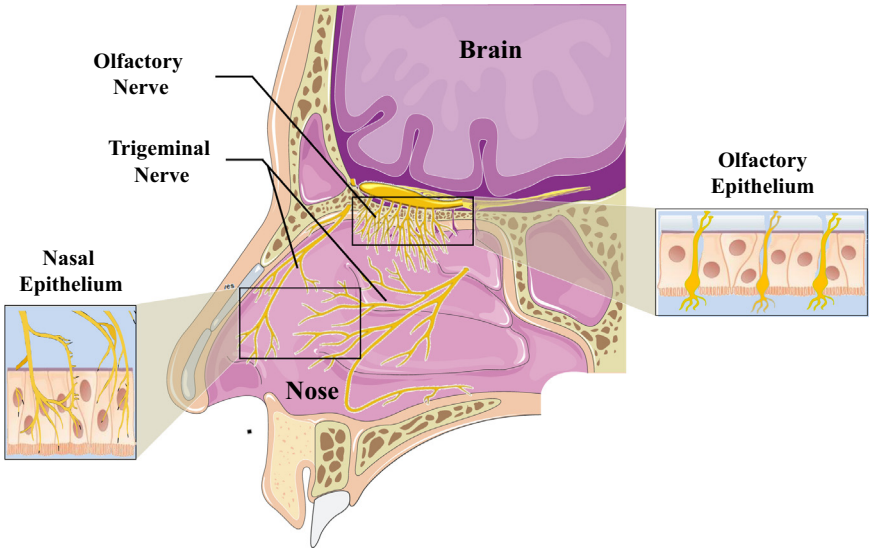

Fig. 1. Olfactory and Trigeminal nerve position in the nasal cavity.