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Review

Quantitative analysis of drug delivery to the brain *via* nasal route

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ABSTRACT

The blood–brain barrier (BBB) prevents drugs' permeability into the brain and limits the management of brain diseases. Intranasal delivery is a convenient route of drug administration that can bypass the BBB and lead to a direct delivery of the drug to the brain. Indeed, drug accumulation in the brain following intranasal application of a drug solution, or of a drug encapsulated in specialized delivery systems (DDSs), has been reported in numerous scientific publications. We aimed to analyze the available quantitative data on drug delivery to the brain *via* the nasal route and to reveal the efficiency of brain drug delivery and targeting by different types of nasally-administered DDSs.

We searched for scientific publications published in 1970–2014 that reported delivery of drugs or model compounds to the brain *via* intranasal and parenteral routes, and contained quantitative data that were sufficient for calculation of brain targeting efficiency. We identified 73 publications (that reported data on 82 compounds) that matched the search criteria and analyzed their experimental settings, formulation types, analytical methods, and the claimed efficiencies of drug brain targeting: drug targeting efficiency (%DTE) and nose-to-brain direct transport (%DTP).

Outcomes of this analysis indicate that efficiency of brain delivery by the nasal route differs widely between the studies, and does not correlate with the drug's physicochemical properties. Particle- and gel-based DDSs offer limited advantage for brain drug delivery in comparison to the intranasal administration of drug solution. Nevertheless, incorporation of specialized reagents (*e.g.*, absorption enhancers, mucoadhesive compounds, targeting residues) can increase the efficiency of drug delivery to the brain *via* the nasal route. More elaborate and detailed methodological and analytical characterizations and standardized reporting of the experimental outcomes are required for reliable quantification of drug targeting to the brain by the nasal route. Quantitative analysis of these data will facilitate the development of DDSs with high brain targeting efficiency.

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1. Introduction

Conventionally, the nasal route has been exploited to deliver drugs that treat local disorders such as, rhinorrhea, nasal congestion, sinusitis and nasal infections. Subsequently, nasal delivery was exploited for systemic delivery of certain drugs, such as small molecular weight drugs, peptides and small proteins, as an alternative to their administration by parenteral injections [1]. Several nasal formulations of systemically-acting drugs have been approved for clinical use [2], but some of these drugs (*e.g.*, nasal desmopressin for primary nocturnal enuresis and nasal salmon calcitonin for postmenopausal osteoporosis) were withdrawn from clinical use due to safety concerns.

During the last few decades, the nasal route has been increasingly applied in attempts to deliver drugs to the brain for the purpose of treatment of specific brain diseases (*e.g.*, the neurodegenerative and psychiatric diseases, epilepsy, *etc.*). There are several reasons why 'nose-to-brain' delivery is of great interest to the pharmaceutical academia and industry, including: 1) This route can deliver the drug directly to the brain, bypassing the blood–brain barrier (BBB), which is considered to be impermeable for almost 100% of the macromolecular drugs and over 98% of the small molecule drugs [3]; 2) this route avoids gastrointestinal and hepatic first-pass metabolism that can inactivate a substantial fraction of the administered drug; and 3) intranasal delivery may decrease the onset of action of CNS drugs, especially for the anti-pain and anti-migraine medications [4]. These and other potential benefits of intranasal drug delivery are especially appealing, taking into account the relative inefficiency of drug delivery to the brain *via* systemic routes [5].

Intranasal drug delivery appears to be a rapidly developing field. However, the exact mechanisms that can lead to efficient drug delivery to the brain following intranasal administration are not completely elucidated. An accumulating amount of evidence demonstrates that drug can reach the brain following intranasal administration *via* several direct and indirect pathways (see Fig. 1A). The drug that is deposited in the nasal cavity can escape enzymatic degradation and the normal rapid clearance by the mucociliary system, undergo uptake to the cells of the olfactory or the trigeminal nerve pathways, or be absorbed into the systemic circulation (see the recent reviews that describe in detail these pathways: [6–9]).

The olfactory pathway consists of the olfactory epithelium, olfactory tract, anterior olfactory nucleus, piriform cortex, amygdala, and hypothalamus. It has been suggested that drugs can reach the CNS *via* extracellular or intracellular transport along olfactory nerves [6], and that this pathway can be the major route for brain delivery of certain drugs following intranasal administration.

Branches of the trigeminal nerve innervate the respiratory and olfactory epithelia of the nasal cavity. Thus, the trigeminal pathway, which is often overlooked by the researchers, can be an important direct pathway of drug delivery to the brain [6]. Three branches of the trigeminal nerve (ophthalmic division, maxillary division, and mandibular division) merge at the trigeminal ganglion, enter the CNS in the pons, and terminate in the spinal trigeminal nuclei in the brainstem. Therefore, cross-talk between the trigeminal and olfactory routes of brain drug delivery is possible.

In addition to these direct pathways, drug can enter the brain indirectly, *via* blood vasculature and/or lymphatic system (see Fig. 1A). The nasal mucosa is highly vascularized, and the blood vessels (lined with continuous and fenestrated endothelium) allow passage of drugs (in free or maybe even in particle-encapsulated form), following nasal drug administration in nano-drug delivery systems. The drug that has been absorbed into the systemic circulation has to cross the BBB in order to reach the CNS. It is possible that the BBB is breached (temporarily or for prolonged periods of time, in small or big regions of the brain) in certain pathological conditions [10,11]. Therefore, efficiency

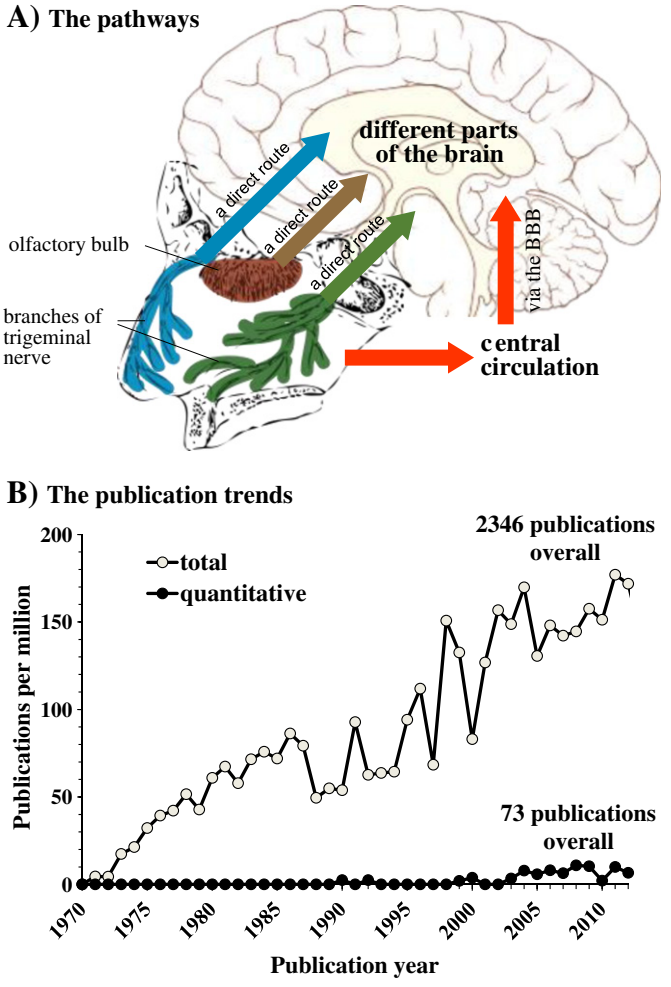

Fig. 1. The pathways of drug delivery to the brain following intranasal administration, and the publication trends in this research field. A. The scheme of the pathways of drug delivery to the brain from the nasal cavity. Following intranasal administration, the drug can reach the brain *via* one of the direct routes (*via* the olfactory and/or trigeminal nerves), or indirectly, by absorption to the central circulation and passage through the blood–brain barrier. The brain drug targeting efficiency index (%DTE) reflects relative accumulation of the drug in the brain following intranasal administration as compared to the systemic (intravenous) administration. The nose-to-brain direct transport percentage (%DTP) reflects the percentage of the dose that reaches the brain *via* direct routes. B. The publication trends in the field of drug/DDS brain delivery and targeting *via* the nasal route. The open circles — the publications that matched the search criteria (see Section 2.1 and the Supplementary materials); the closed circles — identified publications that contained quantitative data (see Section 2.1) and have been used for data analysis. To prevent bias due to the expansion of the PubMed database, the number of identified publications has been normalized by the individual years' count of publications in the database.