Expert Opinion

From nose to brain: understanding transport capacity and transport rate of drugs

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The unique relationship between nasal cavity and cranial cavity tissues in anatomy and physiology makes intranasal delivery to the brain feasible. An intranasal delivery provides some drugs with short channels to bypass the blood–brain barrier (BBB), especially for those with fairly low brain concentrations after a routine delivery, thus greatly enhancing the therapeutic effect on brain diseases. In the past two decades, a good number of encouraging outcomes have been reported in the treatment of diseases of the brain or central nervous system (CNS) through nasal administration. In spite of the significant merit of bypassing the BBB, direct nose-to-brain delivery still bears the problems of low efficiency and volume for capacity due to the limited volume of the nasal cavity, the small area ratio of olfactory mucosa to nasal mucosa and the limitations of low dose and short retention time of drug absorption. It is crucial that selective distribution and retention time of drugs or preparations on olfactory mucosa should be enhanced so as to increase the direct delivery efficiency. In this article, we first briefly review the nose-to-brain transport pathways, before detailing the impacts on them, followed by a comprehensive summary of effective methods, including formulation modification, agglutinant-mediated transport and a brain-homing, peptide-mediated delivery based on phage display screening technique, with a view to providing a theoretic reference for elevating the therapeutic effects on brain diseases.

Keywords: capacity, nose-to-brain transfer, olfactory pathway, rate

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1. Introduction

Recent research results showed that not only metal ions [1-3] and viruses [4,5], but also micromolecule chemicals, peptide [6] and protein drugs, as well as gene [7,8] medicines, can be delivered from the nose cavity to the brain. Such an approach provides an effective means for relieving migraines [9,10], improving memory [11,12] and the treatment of other cerebrosis [13-15]. It is well known that the rate and capacity of drugs or exogenous materials entering the central nervous system (CNS), apart from the physicochemical properties, are also affected by the blood–brain barrier (BBB), blood–cerebrospinal fluid barrier (B-CSF-B)and nose–brain barrier (NBB), which are composed of brain capillary vessels and choroid plexus. The BBB is known to prevent most drugs from entering the brain, while intranasal administration may bring about rapid absorption and onset of effect on the CNS. Intranasal administration has long been used in Chinese Traditional Medicine. As early as the Han Dynasty (150 AD), Zhongjing Zhang used the method of dripping the ground juice of *Allium chinense G. Don* into the nasal cavity to revive a patient from unconsciousness in an emergency. In *Chinese Pharmacopeia*, there are the records of administering Tong Guan San,

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consisting of three herbs including Manchurian Wildginger, for relieving palsy and faint via nasal administration [16]. In addition, there is plenty in the literature on intranasal brain deliveries of peptide medicines such as calcitonin, vasoactive intestinal peptide, melatonin [17] and insulin [18], as well as reports on modern theories and practices of intranasal administration as a means for bypassing the BBB to deliver drugs directly to the brain for cerebrovascular or CNS diseases [19-22].

In the past two decades, intranasal drug administration as a non-invasive brain delivery method has developed quickly in terms of safety, efficiency and convenience. These advantages have made intranasal delivery a hot spot in the exploration of the brain drug targeting system. However, not all drug substances can gain access to the brain via the nose, and the transport capacity is affected by various factors, such as nasal physiology, the physicochemical properties of the compound and its formulation. Some analytical discussions are performed here on exploring effective ways to promote the transport rate and capacity of drug from nose to brain, such as formulation modification, agglutinant-mediated transport and nose-to-brain homing peptide-mediated transport based on phage display screening techniques.

2. Anatomy, physiology and brain delivery characteristics of the nasal cavity

The nasal cavity is a complex organ divided by the nasal septum into two cavities, whose inner sides are covered with mucosa. For their different functions and tissue structures each of the two nasal cavities is basically subdivided into three regions: the nasal vestibule, respiratory region and olfactory region. The nasal vestibule has almost no absorption function. The respiratory epithelium covers most of the dorsal and ventral nasal conchae [23,24]. Respiratory region mucosa, the largest part of the nasal cavity, is full of blood capillaries with abundant bloodstream. Except a small number of drugs that can enter the systemic circulatory system from the respiratory region and subsequently cross the BBB to CNS, some compounds can gain access to the caudal brain via the trigeminal nerve pathway or lymphatic and perivascular spaces upon lamina propria absorption [22]. The olfactory region, however, plays the most important part in the transportation of drugs to the CNS [25-27]. Human olfactory mucosa, located on the roof of the nasal cavity, contains olfactory cells, which are bipolar neurons with one pole in contact with the external environment and another pole in the lamina propria, forming olfactory nerves which enter the olfactory bulbs through the cribriform plate of ethmoid bone. Upon lamina propria absorption, drugs can transport intracellularly along this peripheral olfactory neurons pathway into olfactory bulbs and further distribute into the rostral brain [28], or transport extracellularly into the olfactory bulbs and CSF through the olfactory nerves and lymphatic or perivascular spaces [29]. Drugs can also enter the brainstem through the trigeminal nerve pathway after crossing the lamina propria. Thorne *et al.* [30] found ^{125}I-IGF-1 concentration to be 10 times higher in trigeminal nerves than in olfactory bulbs upon intranasal administration, which might prove the trigeminal nerves as the major pathway from nose to brain. Schaefer *et al.* [31] found that there were trigeminal nerve peptidergic fibers in the olfactory system (including olfactory epithelium, olfactory nerve and olfactory bulb). The olfactory system and trigeminal nerve system have different major pathways but with similar functions; they have interactions in both the CNS and peripheries. Therefore, the unique brain delivery characteristics possessed by intranasal administration can be added the direct transport pathway between the olfactory mucosa (and sometimes the trigeminal nerve) and the brain. However, the normal defensive mechanisms, including mucociliary clearance of the nasal cavity, which clears mucus adhering to the nasal mucosa, greatly affects drug precipitation and limits the time available for drug or drug preparation absorption. The permeability of the drug through the nasal mucosa is affected by viscosity of nasal secretion, solubility of drug in nasal secretions and diffusion rate through the slime layer mucus [32].

Although the brain direct transport pathways are extremely complicated, ample proofs have shown that drugs can be directly delivered to the CNS via the nasal route [26,33,34]. According to different transport rates, three major recognized drug pathways into the brain upon absorption via nasal mucosa [35] were briefly summarized: 1) olfactory nerve pathway: absorption is slow, with a duration from 1 – 2 to 24 h, due to the process of pinocytosis, internalization or simple diffusion, and then the axoplasm flow of olfactory neurons to the olfactory bulbs and further to the rhinencephalon; 2) olfactory mucosa epithelium pathway (olfactory pathway): this acts quickly, always within minutes. In this way, the substances absorbed into the lamina propria enter the CNS through the gaps surrounding the olfactory nerve tract; 3) blood circulation pathway: substances are absorbed through blood capillaries or respiratory mucosa, or enter the blood circulation via lamina propria of the olfactory region, then pass the BBB to CSF or brain tissues with different durations. Therefore, drugs may enter the CNS via one or several transport mechanisms over different periods of time.

3. Factors relating to the rate and capacity of drug transport from nose to brain

3.1 Physicochemical properties of the drug

The rate and capacity of drug transport from the nasal mucosa to the brain depends primarily on the drug's physicochemical properties, especially its molecular weight, lipophilicity and degree of dissociation.

3.1.1 Relative molecular weight

Most small molecular weight (< 400 Dalton) drugs can be freely transported into the brain through the nasal mucosa

epithelium specifically for odorant molecules [36]. Generally, drugs with a molecular weight above 1000 Dalton show poor capability in penetrating the physiological barrier, and the rate of mucosa permeation is highly sensitive to molecular size [37]. Sakane *et al.* [38] examined the influence of molecular weight (4400 Dalton fluorescent-labeled dextrans [FD4], 9400 [FD10], 18900 [FD20] and 40500 [FD40]) on the nose-to-brain transport of FD by determining their concentrations in cerebrospinal fluid (CSF) following i.v. and intranasal administration. As a result, no FD could be detected in CSF after i.v. administration. FD4, FD10 and FD20 were detected in CSF upon intranasal administration and their concentration decreased with increasing molecular weight. Meanwhile, their concentrations in plasma were much lower than those after i.v. administration.

Nevertheless, it is imperative to understand the uptake of higher molecular weight materials like some peptides and viruses to the brain through their special pathways. As for peptides, Born *et al.* [6] and Fehm *et al.* [39] administered three types of peptide intranasally: melanocortin (4 – 10) (MSH/ACTH (4 – 10)), vasopressin and insulin, and found that intranasal administration compared with i.v. administration could significantly increase drug concentration in the brain, indicating that the nasal mucosa pathway was more advantageous for hydrophilic high molecular weight drugs. Many large water soluble drugs also reach the brain following intranasal administration by traveling along the olfactory and trigeminal neural pathways [30,40,41]. Most viruses, when absorbed by nasal mucosa, could be taken up by neuron axon endings and transported to olfactory bulbs through axoplasma flow in olfactory nerve cells, and further reached the olfactory brain [4,42]. However, the rate and capacity of large molecular drug transport into the brain also had a relationship with drug transport pathway and whether there were specific receptors. For example, with an addition of wheat germ agglutinin (WGA) to horseradish peroxidase (HRP), which could not cross the NBB, WGA-HRP could be transported into the brain by conjugating with the WGA receptors on the mucosa [43,44].

3.1.2 *Lipophilicity*

Sakane *et al.* [45] investigated the influence of lipophilicity on drug transport from nose to brain using sulfonamides as model drugs and found that there existed a direct transport pathway for sulfonamides from nose to brain and within a certain range drug concentrations in CSF increased with their elevating lipophilicity. Our group studied the absorption of diltiazem and acetaminophen under a series of pH by the method of classical rat *in situ* nasal recirculation, and found that like most other biological membranes the nasal mucosa presented a 'lipid sieve' feature, making itself easy to penetrate by highly lipophilic drugs, with a well-defined linear correlation between the drug's oil–water distribution coefficient and its absorption rate constant [46].

3.1.3 *Degree of dissociation*

Sakane *et al.* [47] studied the relationship between degree of dissociation of the model drug sulphisomidine ($pK_a = 7.5$) and its direct transport from the nasal cavity to CSF by measuring its concentrations in plasma and CSF after rat nasal perfusion with a series of buffers (pH 5.5, 6.5, 7.4, 8.7 and 9.4). The nasal clearance increased with the elevation in the un-ionized fraction of the drug, and the ratio of the drug concentration in CSF to that in the nasal perfusion fluid changed in accordance with the un-ionized fraction of the drug, showing that both the nasal absorption and the drug transport conformed to the pH partition theory. Namely, the degree of ionization of an intranasally administered drug could affect both the absorption across the nasal epithelium and its transport into the CSF. The drug concentration in the CNS inversely correlated with its dissociation.

3.2 Drug concentration, dosage and dosing volume

Drug concentration, dosage and dosing volume are three major factors impacting drug nasal absorption in correlation to one another. The nasal absorption of most drugs increases with the increase of concentration, especially those with an absorptive mechanism of passive diffusion. In animal experiments, drugs were ordinarily administered by immersing the olfactory region. Within a certain dose range, the drug absorption and therapeutic effects would rise with an increasing dosage [48]. However, the volume of the nasal cavity is limited and the dosage for nasal administration is relatively low at 25 – 200 µl, thus constricting to a certain degree the amount of drug transport from nose to brain.

3.3 Nasal mucous membrane cilia clearance and dosage form

Following intranasal administration, the precipitation, clearance and absorption of a drug or its preparation are all completed in the nasal passage. The epithelium of the nasal passage is covered by a mucus blanket, which entraps particles and bacterium, to be cleared from the nasal cavity and renewed by cilia. The nasal mucous cilia play a defensive role in maintaining the normal physiological environment of the nasal cavity, and in the meantime are capable of clearing the drug or preparation particles together. Except for the nasal vestibule, olfactory membrane and a small anterior part of the conchae, the remainder is ciliated epithelium with numerous surface microvilli in the nasal cavity, including the epithelium of the respiratory system. Mucociliary clearance limits the time available for drug or drug preparation absorption, although in contrast the numerous microvilli on the ciliated nasal epithelium providing a huge membrane area greatly enhance drug absorption compared with non-ciliated epithelium. In order to promote drug transport to the brain, it makes sense to weaken the clearance effect of nasal mucous membrane cilia by prolonging retention or contact time of the drug at the absorption site, especially to

increase the deposition of drug on the olfactory mucosa [49]. In addition, adjusting the pH of the nasal formulation to 4.5 – 6.5 results in efficient drug permeation, as well as avoiding irritation [32]. Thus the preparation formula and medication can be adjusted to increase drug deposition and permeation on the mucosa of the olfactory epithelium or respiratory epithelium.

Different dosage forms have been developed for nasal administration, which include commonly used drops and, aerosols as well as powder, gelatin, emulsions, ointments, liposomes, microspheres, nanoparticles and ion exchange resin preparations [50]. Conventional drug powder and solution without mucous membrane adhesion are easily cleaned by the nasal cilia and only stay for 15 – 30 min in the nasal cavity, which leads to incomplete drug absorption. Bioadhesive polymer, starch microsphere and chitosan preparations [49,51,52] have been extensively used to increase the bioadhesive ability and thus the residence time on the epithelial surface. In addition, small, uncharged particles easily pass through the mucus layer, while large or charged particles may not easily cross the nasal slime layer [37,53], so intranasal administration of nanoparticles has potential advantages in brain drug delivery. Following intranasal administration, nanoparticles can easily get to the olfactorius and encephalic region along axons of the olfactory nerve, and then be distributed to the CNS, such as the cerebrum and cerebellum [54]. Morphine has been encapsulated in polysaccharidic nanoparticles by Betbeder *et al.* [55] and the mice brain availability and antalgic effect upon nasal mucous administration was shown to be significantly greater than that of a common morphine preparation. Moreover, the effect lasted longer, suggesting that the nanoparticles encapsulating morphine were transported directly through the nasal–brain passage to the CSF. Vyas *et al.* [56] prepared mucoadhesive micro-emulsions of sumatriptan and its succinate for rat intranasal administration, and both observed a higher brain drug-direct-transport percentage for mucoadhesive micro-emulsions and better brain-targeting efficiency, compared with non-mucoadhesive micro-emulsions. This may be in relation to mucoadhesives and (assistant) surfactants added in the micro-emulsion prescription. The study conducted by Kumar *et al.* [57] also showed that nano-emulsions and bioadhesive nano-emulsions could be quickly and efficiently transported to the brain upon an intranasal administration.

3.4 The enzyme barrier on olfactory mucosa

Drugs administrated intranasally are not only cleared by cilia movements but are also influenced by the enzymatic system in the nasal cavity. Candace *et al.* [58] proved that P-glycoprotein (P-gp) on nasal mucosa attenuated the brain accumulation of nasal instilled P-gp substrates. However, co-administration of drug (for instance, verapamil) and enzyme (CYP3A4 and P-gp) substrate rifampin resulted in the complete elimination of P-gp-mediated transport of verapamil and significantly enhanced its brain uptake. Adult CF-1 mice (mdr1a[+/+] and mdr1a[-/-]) were intranasally administered ritonavir, quinidine and DPDPE, respectively, and the results all demonstrated significant differences in brain uptake.

The proteolytic enzyme and other mucosa secretases in the mucosal secretions together can form the 'enzyme barrier' in the nasal cavity, which produces a 'pseudo-first pass effect' and decreases the delivery amounts and therapeutic effects of proteins and polypeptides. In the human nasal cavity are found enzyme isoforms of cytochrome P450 such as CYP1A, CYP2A and CYP2E, as well as carboxylesterases, glutathione *S*-transferases, etc [59]. For most enzymes in the nasal cavity of mammals, the amounts on the olfactory mucosa are higher than those on the respiratory mucosa. For instance, P450 is found sixfold more on the olfactory mucosa than on the respiratory mucosa in the nasal cavities of dogs, macaques and rats (except for acetaldehyde dehydrogenase).

3.5 Influence of animal species

The size of the surface area of the olfactory mucosa and its proportion of the total area of nasal mucosa varies with different animal species. Rodents are the most frequently used experimental animals. However, the olfactory area of rats spreads over large parts of nasal mucosa (about 50% of the total area of nasal mucosa), while the human area only covers a small part of the roof of the nasal cavity (about 3 – 5%). Thus, olfactory area drug delivery would be much easier for murines than for humans [23]. Besides, CSF volume and its spreading rate significantly affect the brain uptake of drugs following an intranasal administration, which varies largely in different species. Mice, rats, rabbits and humans produce 0.018, 0.18, 0.6 and 21 ml CSF per hour, respectively, and it takes them 2, 1, 4 and 5 h respectively to renew once [35]. Therefore, the physiological environment of the nasal cavities of rabbits is closer to that of humans. However, since most experimental studies are comparative studies, the experimental data and brain-targeted intranasal delivery tendency derived from murines could still be applied as a reference for investigations on humans.

3.6 Administration position of animals

Using a rat model, Van den Berg *et al.* [60] studied the influence of different positions of the rat's head fixed in a stereotaxic frame on the hydrocortisone uptake by CSF via intranasal delivery. The results showed that putting the rat in the supine 90° angle position significantly increased the absorption of drugs into CSF, by about twofold compared with the upright 90° angle position. Although successful delivery to the CSF does not ensure absolutely efficient delivery to the brain itself, it will possibly conduce to drug transport to the brainstem and caudal brain or enter the CNS parenchyma through the channels associated with the olfactory or peripheral trigeminal system, and also facilitate the treatment of the brain diseases on the ependymal lining

of the ventricles. The deeper (near 15 mm in the rat) the application cannula was inserted into the olfactory region, the more absorption was ensured in the CNS [61]. It is thus clear that the administration position of animals has a certain influence on the brain uptake of drugs. The supine position and the praying-to-Mecca position [62] may better, as drugs can be accumulated in the olfactory region, which is likely to further increase the brain uptake of drugs. However, patients may need the help of others to administer the drug intranasally in these preferred positions.

3.7 The influence of anesthetics

Animal experiments usually use anesthetics, so both the category of anesthetic (ether, urethane, pentobarbital, chloral hydrate, etc) and its administration route (inhalation, intraperitoneal injection, etc) could affect the rate and capacity of nasal absorption. Compared with the conscious condition, the anesthetized condition can bring about a higher absorption in the olfactory epithelium, as well as more effective contact time with the mucosa epithelium, which may further increase the intranasal brain delivery of drugs. Hanson *et al.* [63] confirmed that hypocretin-1 intranasally administered to conscious mice (6.9 nmol) resulted in lower brain concentrations than administration to anesthetized mice, because the latter were on their backs for longer (25 min) than the former (about 3 – 4 min). However, there only exist records of influence of anesthetics on systemic absorption following intranasal administration and on brain uptake after i.v. administration, while few published records on the influence of types of anesthetics and anesthesia administration on brain delivery exist regarding intranasal administration. For example, Susan *et al.* [64] compared the intranasal insulin uptake by rats and found that an intraperitoneal injection of pentobarbital and fentanyl might decrease a rat's nasal mucosa cilia clearance rate, thus increasing drug uptake, and the effect of lowering blood sugar was significantly superior to that of inhaling Halothane and no anesthesia groups. Halothane inhalation could reduce myocardial contractile force and heart output, and increase breathing frequency, which might cause the increase of nasal mucosa cilia clearance and in turn reduce drug uptake. Toyama *et al.* [65] evaluated the effects of anesthesia (including inhaling isoflurane and intraperitoneal injection of ketamine/xylazine mixture) on brain uptake of fluorodeoxyglucose (^{18}F-FDG) in mice, and the results showed that FDG brain uptake (%ID/g) of the anesthesia group was significantly lower than that of the control group (28 and 39%, respectively). Administration in the anesthetized state also influences the nose-to-systemic circulation absorption, which may also affect the brain uptake.

4. Approaches to enhance nose-to-brain drug delivery

Although there are existing brain direct transport pathways in both the respiratory region and the olfactory region mucosa, the key point in enhancing direct drug delivery to the CNS via the nasal cavity is to increase the deposition and enrichment of drugs or their preparations on the olfactory mucosa, thereby diffusing more directly from the olfactory mucosa to the brain. At present, various scientific approaches have been developed to improve the efficiency of drug transport from the nose to CNS for the treatment of central nervous disorders. It is suggested that novel approaches are the combination of a bioadhesive formulation or an absorption enhancer [32,66] and an active targeting mediated by an agglutinant [67-69] or a brain-homing peptide from screening of phage display libraries [70]. In addition, iontophoresis, phonophoresis, electrotransport [71] and several other innovative devices (Optinose™, OptiNose UK Ltd, UK; DirectHaler™, DirectHaler A/S Co., Denmark; and ViaNase™, Kurve Technology, Inc., USA [62,72]) have also been successfully applied.

4.1 Preparation of prodrugs

Molecular weight and lipophilicity are critical physicochemical factors influencing the transport rate and capacity of direct drug uptake from the nose to the brain and CSF. Rapid absorption is attributed to lipophilicity of drugs, while slow absorption is mainly affected by the molecular weight. Prodrug strategies aim to modify the structure of the parent drug with favorable physicochemical and biological properties for absorption. Developments have been made in intranasal prodrugs for the treatment of CNS diseases [73]. Kao *et al.* [74] synthesized several alkyl ester water soluble prodrugs of L-dopa, which were administered intranasally to rats, the results showing that following an intranasal delivery the L-dopa level of the butyl ester prodrug was significantly higher than that of the parent drug in CSF, and the drug concentration in CSF was also notably higher than an equivalent i.v. dose. Prodrug modification is an effective approach to enhancing drug delivery to the CNS via the intranasal route. However, the modification may alter the activity of the drug, so that, for example, proteins could not readily be modified to be more lipophilic without seriously disrupting their spatial structures, thus greatly reducing, if not eliminating, their biological activity.

4.2 Modification with formulations

It is evident that effective brain uptake is closely related to the nasal formulations and devices which are designed to provide drug deposition in the olfactory mucosa, extend residence time and maintain a high local drug concentration for diffusion. With the help of some preparation methods, intranasally administrated drugs with low BBB permeability upon i.v. administration could be taken to the brain. Dalpiaz *et al.* [75] prepared *N*-cyclopentyladenosine (CPA) mannitol-lecithin and chitosan hydrochloride microparticles for administration to rats with intranasal administration of a CPA aqueous suspension and i.v. infusion of a CPA solution as the control, and the results showed that CPA microparticles preparations significantly increased drug delivery

to CSF via intranasal administration, while free CPA was not able to reach the CSF from the bloodstream or nasal cavity. Furthermore, the CPA amounts that transited into the CSF following a nasal administration of chistosan microparticles were about 10-fold higher than those of mannitol-lecithin microparticles, and the CPA level in CSF 60 min after the administration of the former was three orders of magnitude higher than that of the latter. The rapid transit of CPA directly into the brain by mucoadhesive chitosan microparticles may be attributed to the mucoadhesive properties of chitosan microparticles and its characteristics to unlock the tight junction.

4.3 Addition of absorption enhancers and/or enzyme inhibitors

Penetration enhancers such as surfactants, beta cyclodextins, bile salts, phospholipids and lysophospholipids can significantly increase drug permeability across the nasal mucosa [32,76], while enzyme inhibitors can improve the stability of drugs and protect them from efflux or enzymes metabolism, in particular protein and peptide drugs, thus enhancing drug delivery from the nose to brain. Gwak *et al.* [66] investigated the analgesic effects of intranasally delivered leucine enkephalin with or without enzyme inhibitors and/or absorption enhancers in mice using the acetic acid-induced writhing test. The writhing inhibition rates of the enzyme inhibitors and absorption enhancers were about four and two times higher than those of the controls, respectively, and their analgesic activities were extremely good with prolonged analgesia duration. Xie *et al.* [77] studied the biodistribution of intranasally administrated nerve growth factor (NGF) in rats and investigated the effect of addition of enzyme inhibitor (bacitracin) on the brain uptake of NGF, with the results showing that combined with bacitracin, 80% of intact NGF molecules were uptaken by the brain, while the brain NGF concentration of free NGF group was fairly low. The protective effect of enzyme inhibitors provided prerequisites for the brain uptake of NGF. However, attention must be drawn to the toxicity problem of absorption enhancers on the nasal cilia.

4.4 Agglutinant-mediated transport

Histochemical studies found that various saccharide groups exist on the nasal mucous membrane, among which *N*-acetylglucosamine and L-fucose were significantly more expressed on the olfactory mucosa than on the respiratory mucosa [78,79]. These saccharides can specifically bind to WGA and ulex europaeus agglutinin I (UEA I), respectively, on the nasal mucous membrane, conveying signals to the cells, and then inducing endocytosis and transit [80] to the brain. Based on the physiological nature mentioned above, Gao *et al.* [67-69] prepared lectin-bearing PEG–polylactic acid (PLA) nanoparticles, which used the specific glycosyl combination between WGA or UEA I and saccharide groups on the olfactory mucosa to enhance the enrichment of nanoparticles in the rat olfactory membrane and further delivery to the brain. After an intranasal administration of vasoactive intestinal peptide (VIP)-loaded WGA-NP, the active VIP amounts were found to be 5.66, 6.61 and 7.74 times higher in the olfactory bulb, cerebrum and cerebellum, respectively, than that following an intranasal VIP solution administration [68]. Compared with unconjugated PLA nanoparticles, the brain VIP amount delivered by WGA-NP was also significantly higher. Furthermore, pharmacodynamics results showed that VIP-loaded WGA-NP could significantly improve spatial memory in ethylcholine aziridinium-treated rats, suggesting that lectin-conjugated drug delivery systems could provide a new strategy to enhance the nose to brain delivery. Besides, although the immunogenicity of WGA [81] and the nasal ciliotoxicity of WGA-NP are negligible, the long-term toxicity awaits further investigation.

4.5 Folic acid-mediated transport

Folic acid and its derivatives alone or in combination with other drugs, such as cholinesterase inhibitors and acetylcholinesterase inhibitors, can directly enter the CNS and provide a rapid effect on the prevention or treatment of Alzheimer's disease and stroke [82]. However, the transport mechanism of folic acid-mediated nose-to-brain delivery is still under investigation.

4.6 Brain homing peptide-mediated

In the last two decades, phage display libraries have been extremely powerful tools in searching for tissue-homing peptides [83-85] and for selecting peptides that bind to specific receptors or antibodies [86,87]. Screening phage-displayed peptide libraries after different administration routes, such as i.v. delivery [83,88], transdermal delivery [89], intramuscular delivery and intranasal delivery [90], against specific targeting tissues presents a direct and fast method of identifying novel peptides for targeting of drug delivery vectors. Pasqualini *et al.* [83] injected phage libraries i.v. into mice and subsequently rescued the phage from individual organs. We focused on peptide sequences that direct phage to the brain, because relatively few phages from the unselected libraries were bound to a specific organ. To select peptides homing to the brain, the phage libraries were administrated intranasally, recovered from the brain, amplified repeatedly *in vitro*, and redelivered intranasally to obtain sufficiently enriched peptides targeting to parenchymatous, CSF or cerebropathia. Then the valid homing motifs were identified and may be grafted to surface molecules of drugs or preparations like liposomes with specific targeting properties. Solomon and co-workers [90] delivered phage-displayed anti-β-amyloid antibodies via intranasal administration into the brains of mice. Janda [70] also delivered the therapeutic protein agent directly into the CNS from the nasal cavity by a phage-based approach, and realized effective treatment of cocaine addiction in animal models.

In summary, whether adopting a modifying formula/preparation or through agglutinant and homing brain

peptides-mediated transports, the high performance of nasal delivery to the brain is closely related to the direct transport pathways. Both the respiratory region and the olfactory region may have direct transport pathways. However, it is hard to realize the selective transportation (along the nerve pathway to the brain, or entering into systemic circulation) of the drug or its preparation upon respiratory mucosal absorption. Although increasing drug distribution on the respiratory mucosa may increase brain concentration of some special drugs transported through the trigeminal nerve pathway, such as insulin-like growth factor, this method also elevates the risk of systemic side effects. Therefore, the most effective and safest way to increase brain delivery is to enhance the distribution of drugs on the olfactory mucosa.

5. Prospect

At present, the main methods used for brain drug targeting is receptor, absorptive and carrier-mediated transcytosis at the BBB following systemic administration. These methods are effective to some extent but need complicated preparation processes and i.v. injection. In contrast, intranasal brain delivery system is easy to prepare and administer, bearing good research value and application prospects. The key factor is to further enhance the transport capacity from the nose to the brain, and at the same time reduce local irritations, potential toxicity, as well as long-term toxicity derived from the preparation.

6. Expert opinion

Early records of drug delivery from the nasal cavity to the brain have been found from ancient China. In *Treatise on Febrile and Miscellaneous Diseases* edited by Zhongjing Zhang in the Han Dynasty, there were methods of dripping the ground juice of *Allium chinense G. Don* into the nasal cavity to revive the patient from unconsciousness in an emergency. In *Compendium of Materia Medica* by Shizhen Li in the Ming Dynasty, fuming the nose with the smoke of a flaming paper point of croton oil was used to treat a stroke. Although some compounds in the smoke might not be directly transported to the brain via the nose cavity to bring about the effect, the mechanism (cerebral ischemia or encephalorrhagia) [91,92] of stroke and cerebral apoplexy is associated with pars encephalica. There was also a theory of the existence of pathways from the nose to the 12 regular meridians in Traditional Chinese Medicine. Thus modern physiology and anatomy demonstrate the existence of nose-to-brain pathways endowing a nasal drug delivery with unique brain delivery characteristics. Nasal cavity mucosa is primarily composed of two parts, respiratory and olfactory mucosa, through which drugs can be absorbed and directly enter the CNS, bypassing the BBB. Thus, the nose-to-brain pathway may enhance brain drug delivery and therapeutic effect on CNS diseases. Wang *et al.* [93] reported that following an intranasal and i.v. delivery of antineoplastic methotrexate, the area under drug concentration of the intranasal group in cerebrospinal fluid was 2.42 times of that of the i.v. group. In addition, intranasal methotrexate can maintain an effective concentration in both the olfactory bulb and cerebrospinal fluid for more than 4 h. Furthermore, there are intranasal therapies for Alzheimer's disease [94-96] and the AIDS virus with brain metastases, etc [97]. The advantages of intranasal delivery are presented in those drugs with an extremely low brain concentration upon routine delivery.

Intranasal drug delivery bears not only merits but also challenges. Usually less than 1% of an administered drug can be nasally transported to the brain. To improve direct transport of adequacy, the dose still requires the joint efforts of neuroscientists, cell biologists and pharmaceutical scientists. In recent years, many approaches have been reported on how to enhance nose-to-brain delivery, such as introducing absorption enhancers [59], prodrug formation [74] as β-estradiol [98] and water soluble L-DOPA prodrug [75], chitosan connective or modified nanoparticle formulation, amongst others. [49,62]. However, rapid nasal mucosa clearance and cilia toxicity limit the dosage absorption to the brain. The most efficacious strategy is to increase the selectivity of the olfactory mucosa absorption. To date, there has been little literature on such kind of transport system that can mediate effectively a nose-to-brain delivery. However, the existence of highly expressed glycoprotein on the epithelial cell of olfactory mucosa, lectin and lectin-conjugated drug delivery system has been shown to be a promising new strategy to enhance a nose-to-brain delivery. Our group developed WGA-conjugated PLA nanoparticles (WGA-NP) for intranasal delivery in rats, the WGA-NP showing higher affinity to olfactory mucosa than to respiratory region mucosa, achieving the accumulation of WGA-NP on olfactory mucosa and increase of brain transport. Compared with unconjugated PLA nanoparticles, the brain drug amount delivered by WGA-NP was 1.58-fold higher. Following the intranasal administration of VIP-loaded WGA-NP, pharmacodynamics results showed that VIP-loaded WGA-NP can significantly improve spatial memory in ethylcholine aziridinium-treated rats [69].

Further investigations into intranasal drug delivery systems will bring new potential for the treatment of brain diseases.

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