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Review article

Nanotechnology for enhanced nose-to-brain drug delivery in treating neurological diseases

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ABSTRACT

Despite the increasing global incidence of brain disorders, achieving sufficient delivery towards the central nervous system (CNS) remains a formidable challenge in terms of translating into improved clinical outcomes. The brain is highly safeguarded by physiological barriers, primarily the blood-brain barrier (BBB), which routinely excludes most therapeutics from entering the brain following systemic administration. Among various strategies investigated to circumvent this challenge, intranasal administration, a noninvasive method that bypasses the BBB to allow direct access of drugs to the CNS, has been showing promising results. Nanotechnology-based drug delivery systems, in particular, have demonstrated remarkable capacities in overcoming the challenges posed by nose-to-brain drug delivery and facilitating targeted drug accumulation within the brain while minimizing side effects of systemic distribution. This review comprehensively summarizes the barriers of nose-to-brain drug delivery, aiming to enhance our understanding of potential physiological obstacles and improve the efficacy of nasal delivery in future trials. We then highlight cutting-edge nanotechnology-based studies that enhance nose-to-brain drug delivery in three key aspects, demonstrating substantial potential for improved treatment of brain diseases. Furthermore, the attention towards clinical studies will ease the regulatory approval process for nasal administration of nanomedicines targeting brain disease.

1. Introduction

Brain diseases, particularly brain tumors, Alzheimer's disease (AD), Parkinson's disease, etc., with escalating morbidity rates, intricate pathogenesis, and limited efficacy of available therapeutics, have posed a major challenge to global health [1]. Despite the increasing prevalence and economic burden of brain illness, there is still a dearth of drugs that successfully achieve clinical translation [2]. The biggest obstacle in the delivery of drugs to the central nervous system (CNS) lies in overcoming the blood-brain barrier (BBB) [3–6]. This extensive, multicellular and dynamic interface tightly controls the passage of various molecules from the vasculature into the extracellular space of the CNS, thereby safeguarding CNS homeostasis against toxins and pathogens. However, the existence of BBB also poses a hindrance for certain drugs and large biopharmaceutical molecules attempting to enter the brain [5,7]. Intraparenchymal, intracerebroventricular, or intrathecal injections offer the possibility of delivering drugs to the CNS directly, but these invasive routes are undesirable for long-term administration. The intranasal drug administration is a promising way that provides a non-invasive method of bypassing the BBB to potentially deliver various biologics to the CNS [8,9]. As an appealing alternative to traditional oral or parenteral routes for the direct delivery of drugs to the brain, intranasal delivery has long been associated with several advantages, including ease of self-use, noninvasiveness, rapid onset of action, and high cerebral bioavailability. This is critical for diseases whose pathology primarily involves the CNS (e.g., common brain disorders, lysosomal storage disease (LSD), etc.), as the nose-to-brain route of administration offers new thinking about bypassing the BBB and directly targeting lesion sites. A record of experience with approved formulations based on intranasal delivery has been reported (Table 1), which paves the way for a new era in the treatment of neurological disorders.

The nasal cavity possesses a unique set of anatomical features that

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enable different designs to achieve satisfactory drug administration requirements. The mucosal region, housing the olfactory and trigeminal nerves, facilitates direct and rapid drug entry into the brain. Moreover, the nasal-related lymphoid tissues harbor immune cells that can be harnessed for mucosal immune activation in the development of nasal spray vaccines [10,11]. Additionally, the abundant subcutaneous capillary network in the respiratory region enables swift systemic delivery of intranasal drugs, meeting both requirements for systemic therapy and facilitating indirect routes for brain disease treatment [12]. Despite all the above merits in nose-to-brain drug delivery, there still remain diverse challenges pertaining to the maintenance of drugs in the nasal mucosa before entering the brain, necessitating consideration of all the limiting factors during the development of therapeutics for this route. The limited administration volume of formulation, mucus layer, and epithelial barrier, are challenging obstacles that hamper the passage of drugs into the brain through the nose-to-brain route [13,14]. To combat all the obstacles, certain smart intranasal drug delivery systems have been built to address the factors for the effective treatment of various diseases and conditions in the CNS. Advancements in nanotechnological formulations for nose-to-brain delivery offer valuable opportunities for targeted and selective brain delivery which promotes drug accumulation in the CNS through increased nasal permeation [15,16]. Numerous drug-loaded nanocarriers have been tested successfully to overcome barriers encountered during nose-to-brain drug delivery so as to achieve improved efficacy and reduced systemic side effects [17–19].

Herein, we provide a comprehensive overview of nasal anatomy and discuss the intricate pathways involved in nose-to-brain transport. By enhancing our understanding of potential physiological barriers to effective nasal delivery, we provide a detailed summary of the barriers associated with nose-to-brain drug delivery in treating neurological diseases. Refraining from previous reviews that predominantly concentrate on diverse nanocarriers, our unique contribution lies in highlighting recent advancements in key nanotechnology-based studies that facilitate nasal drug delivery into the brain by overcoming mucosal and epithelial barriers while increasing drug accumulation at brain lesions. Furthermore, after an extensive discussion on the advantages and challenges of nose-to-brain drug delivery, we summarize both completed and ongoing clinical trials and studies investigating intranasal treatments for brain diseases. We believe that this comprehensive analysis will contribute to a deeper understanding of nose-to-brain drug delivery mechanisms and inspire future research aimed at improving treatment strategies for brain diseases.

2. Pathways of nose-to-brain transport

2.1. Anatomy of the nasal cavity

To investigate the nose-to-brain drug delivery pathways, it is imperative to gain a comprehensive understanding of the intricate anatomy of the nose. The nasal cavity, responsible for the humidification and warming of inspired air as well as dust adsorption, is the major structure of the nose. It is supported by bone and cartilage and lined with mucous membranes. Vertically divided into left and right cavities by the nasal septum, the total area of both cavities measures approximately 150–160 cm^2 [20]. Each cavity can be further categorized into three distinct regions: vestibule, respiratory region, and olfactory region [21,22]. The vestibular area is covered by squamous epithelium containing sweat and sebaceous glands with limited surface area for drug absorption [8]. The respiratory region consists of basal cells, goblet cells, non-ciliated columnar cells, and ciliated cells, collectively known as the ciliated pseudostratified columnar epithelium. The ciliated and columnar cells in this region possess numerous microvilli that greatly increase the surface area of the respiratory region to approximately 130 cm^2. Additionally, this region is highly vascularized, further enhancing its capacity for drug absorption into the bloodstream and systemic circulation [13,21]. Importantly, innervation of the respiratory area by the trigeminal nerves provides a direct pathway for drugs to enter the CNS through the nasal cavity. The olfactory region in humans constitutes a minor fraction (approximately 10 cm^2) of the total surface area of the nasal epithelium. It consists of a pseudostratified columnar epithelium located in the upper part of the nasal cavity and plays a crucial role in regulating the sense of smell [22,23]. Positioned beneath the cribriform plate of the skull, this area connects the nasal mucosa directly to the brain. Olfactory receptor neurons within this area are bipolar neurons responsible for transmitting information from epithelial cells to the olfactory bulb [13,22,24]. Drugs can travel through axons via olfactory filaments formed by the olfactory nerve and pass through sieve plates to reach the olfactory bulb in the cerebral cortex before reaching the CNS.

2.2. Nose-to-brain transport pathways

The entry of drugs into the brain via the nasal cavity can be divided into direct path and indirect path. In the direct pathway, drug molecules can bypass the BBB by entering the CNS through either the olfactory or trigeminal nerves in the nasal cavity. This process may take place either by intracellular or extracellular pathways, i.e., paracellular pathway and transcellular pathway. While, in the indirect pathway, drug molecules

Table 1
Commercially available nasal preparations for the treatment of brain disease.

Drug	Active ingredient	Indication	Time to market	Company
OPVEE	Nalmefene hydrochloride	For the emergency treatment of opioid overdose	2023-05-22	Indivior Inc.
Dexmedetomidine Hydrochloride Nasal Spray	Dexmedetomidine hydrochloride	For the preoperative sedation/anti-anxiety	2023-03-15	Shanghai Hengrui Pharmaceutical Co., Ltd.
ZAVZPRET	Zavegepant hydrochloride	Migraine with or without aura	2023-03-09	Pfizer Inc.
VALTOCO	Diazepam	Acute treatment of intermittent, stereotypic episodes of frequent seizure activity	2020-01-10	Neurelis Inc.
NAYZILAM	Midazolam	Acute treatment of intermittent, stereotypic episodes of frequent seizure activity	2019-05-17	UCB Inc.
SPRAVATO	Esketamine hydrochloride	Depression	2019-03-05	Janssen-Cilag International NV
ONZETRA Xsail	Sumatriptan succinate	Acute treatment of migraine with or without aura	2016-01-27	Currax™ Pharmaceuticals LLC
Instanyl	Fentanyl	Moderate to severe pain	2009-07-20	Takeda Pharma A/S
Zomig Nasal	Zolmitriptan	Acute treatment of migraine with or without aura	2002-7-08	Grünenthal GmbH
BUTORPHANOL NASAL SPRAY	Butorphanol tartrate	Moderate to severe pain	2000-08-01	AA PHARMA INC.
IMIGRANE 20 mg/0,1 ml, solution pour pulvérisation nasale	Sumatriptan	Migraine with or without aura	1997-06-10	Laboratoire GLAXOSMITHKLINE
MIGRANAL NASAL SPRAY 4MG/ML	Dihydroergotamine mesylate	Migraine with or without aura	1996-11-5	SteriMax Inc.
NICOTROL	Nicotine	For the relief of tobacco withdrawal symptoms	1996-03-22	Pfizer Inc.

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are absorbed into systemic circulation through capillaries present in the nasal mucosa and subsequently gain access to CNS by crossing BBB (Fig. 1).

Drugs can be transported directly through the olfactory nerve, via the olfactory bulb into the olfactory cortex, and then into the CNS. There are two major ways that substances can be transmitted via olfactory nerve fibers, namely intracellular and extracellular pathways, the latter of which can be further divided into paracellular transport and transcellular transport. The intracellular transport pathway, also known as the intra-neuronal pathway of drug transport, is a little bit slow for drug transport from the nasal cavity to the CNS, taking hours or even days for drugs to reach their target. In this way, drugs are transferred from olfactory epithelial cells to olfactory sensory neurons by endocytosis, and delivered to the olfactory cortex through olfactory nerve cells [13]. In addition, drugs can be transported to the brain through the extracellular route, which is faster. In this pathway, drugs can be transported by transcellular transport and paracellular transport. Drugs can cross the olfactory mucosa and enter the CNS either by passing through supporting cells (transcellular transport) or alongside them (paracellular transport). In both cases, drugs pass through the lamina propria [15]. Similar to the olfactory pathway, substances can also be transported via trigeminal nerve fibers through intracellular and extracellular routes. Drugs are either transferred from respiratory epithelial cells to peripheral trigeminal neurons through endocytosis, subsequently reaching the brain stem and entering the CNS via the trigeminal nerve, or they can be absorbed from the respiratory epithelium into the brain stem, where they gain access to ventricles and further penetrate the brain [14,15].

The indirect pathway is also called the systemic pathway, in which drug molecules can be absorbed by nasal submucosal capillaries and enter the systemic circulation rapidly. Compared to other mucous membranes in our body, the nasal mucosa exhibits faster absorption and helps avoid first-pass metabolism [14]. However, drugs entering the blood circulation must cross the BBB or blood-cerebrospinal fluid (CSF) barrier to reach the CNS. The ability of drugs to penetrate BBB via passive diffusion is influenced by their physicochemical properties, with lipophilicity being a crucial factor. Drugs that reach the lamina propria through the nasal epithelium but escape local absorption into the bloodstream and drainage within lymphatic vessels to the deep cervical lymph nodes may also enter the CSF and then enter the CNS [23].

3. Barriers of nose-to-brain drug delivery in treating neurological diseases

The precise mechanisms underlying the transport of drugs from the nasal cavity to various regions of the CNS are under investigation. Scientists have studied the intranasal pathway of PEGylated Fe_3O_4 nanoparticles (NPs) into the brain, where they found NPs initially traverse the nasal mucosa and enter both the perineural space of the trigeminal nerve and olfactory nerve. Subsequently, these NPs flow into the subarachnoid space along with CSF, with further dispersion to other CNS areas from these initial (Fig. 2) [25]. Hereby, intranasal administration of psychopharmacological agents into the brain for the treatment of brain disorders encompasses at least three sequential stages [23]. Upon entering the nasal cavity, drugs initially come into contact with the mucus layer and undergo removal by cilia in the superficial mucosal layer. Overcoming challenges related to rapid mucus traversal, minimizing cilia clearance, and prolonging drug retention time in the nasal cavity are crucial for successful delivery to the brain. In quick succession, drugs that effectively traverse the mucus layer reach epithelial cells and enter the brain through intra−/extracellular pathways. Another significant challenge lies in efficiently crossing the epithelial barrier during nasal drug delivery. Once inside the brain, drugs exert their therapeutic effects on specific sites and targets. Enhancing drug targeting and retention at lesion sites while minimizing side effects represents a critical hurdle to overcome at this stage. Overall, nasal drug delivery systems for brain disorders encounter three major barriers, namely the nasal mucus barrier, the nasal epithelial barrier, and the brain lesion site “barrier”. A thorough understanding of these barriers is essential in devising strategies that overcome these barriers to maximize delivery efficiency.

3.1. Nasal mucus barrier

Nasal mucociliary clearance, the most crucial physiological defense mechanism within the nasal cavity, constitutes the primary barrier

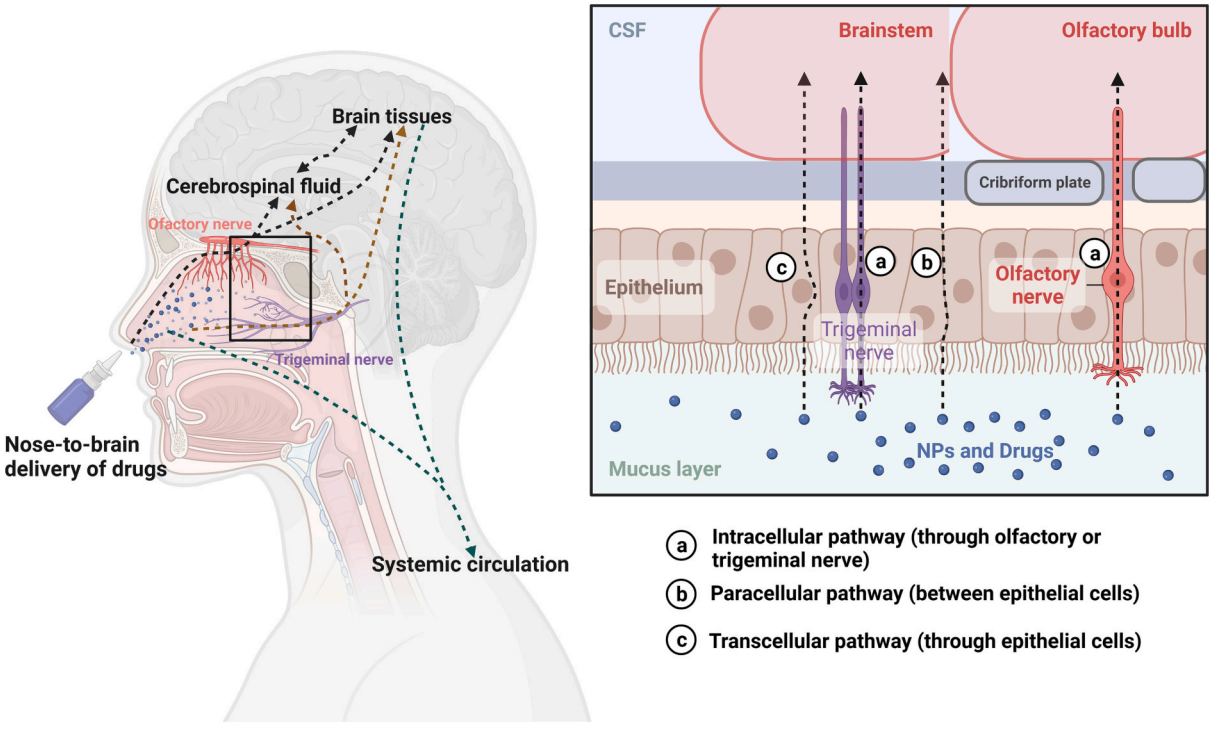

Fig. 1. Schematic representation of the different pathways to the brain following intranasal administration.

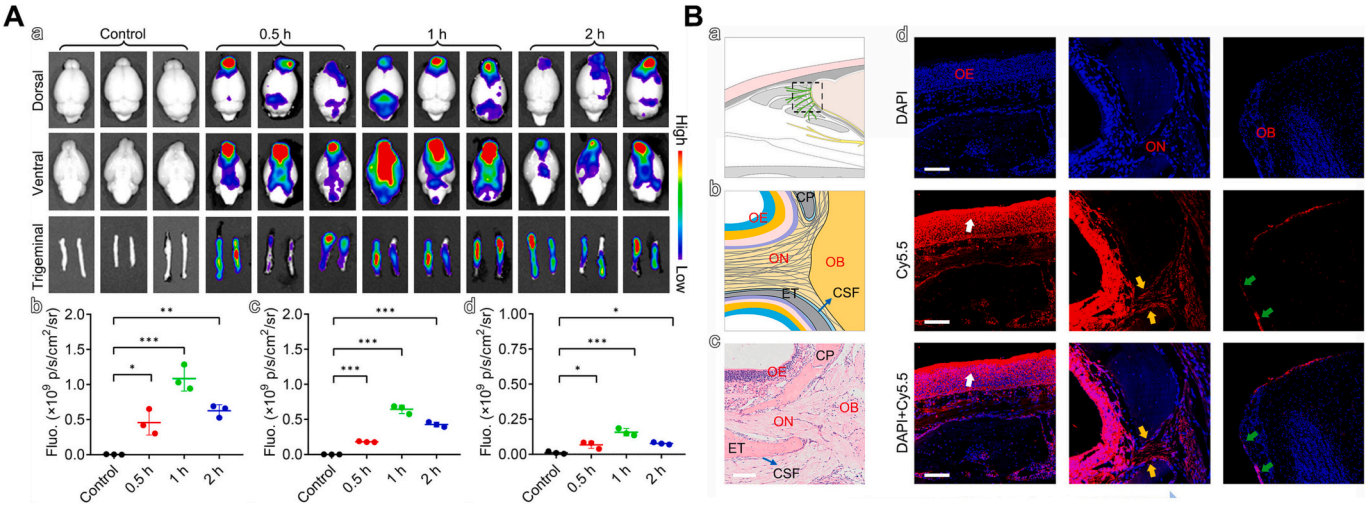

Fig. 2. The intranasal pathway and major barriers for NPs to enter the CNS. (A) Distribution of Fe_3O_4@PEG-Cy5.5 NPs based on fluorescence imaging. (B) Pathway for intranasally delivered NPs to enter the brain. (OE: olfactory epithelium; ON: olfactory nerve; CP: cribriform plate; ET: ethmoturbinate; OB: olfactory bulb; CSF: cerebrospinal fluid). The white, orange, and green arrows were used to indicate the actual positions of olfactory mucosa, olfactory nerve, and olfactory bulb, respectively. Upon entering the nasal cavity, NPs initially encounter the mucus barrier. Subsequently, NPs that effectively traverse the mucus layer meet the epithelial barrier. Nano-systems exert therapeutic effects on specific lesion sites and targets. Once inside the brain, overcoming the brain lesion "barrier" becomes imperative. Reproduced with permission. [25] Copyright 2023, American Chemical Society. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

influencing nasal drug delivery. The nasal mucociliary clearance system encompasses epithelial cilia and mucus secreted by goblet cells. The mucus itself consists of two distinct phases: a more viscous gel-layer positioned atop to ensnare inhaled particles and foreign pathogens, while beneath lies a less viscous sol-layer that intimately interacts with the cilia of the epithelium. This sol-layer serves to lubricate airway surfaces and facilitate effective ciliary movement for the efficient removal of mucus [26]. Under normal conditions, the mucus undergoes pulsation in a manner that facilitates coordinated movement of cilia within the sol-phase, transmitting momentum to the gel-phase through metachronous and synchronous motion with cilia. This mechanism enables efficient transportation of mucus towards the drainage site, thereby facilitating the elimination of inhaled particles or irritants from the nasal cavity [27]. The mucus layer, characterized by reticular viscoelastic gelatinous structures, consists of cross-linked tangles of protein fibers derived from the mucin family. Serving as both structural and functional constituents within the mucus layer [28,29], mucins contain two subgroups, namely secretory mucins and cell membrane-associated mucins. Secretory mucins determine the viscosity of mucus and are the structural basis for the formation of intricate gel networks [30,31]. The chain molecules of these secreted mucins are linked by disulfide bonds and further stabilized by intermolecular non-glycosylation and non-covalent interactions such as Van der Waals forces, hydrogen bonding, hydrophobic interactions, and electrostatic interactions to form a hydrated mucin network. After intranasal administration, the drug initially undergoes clearance by the nasal mucociliary system, a process that diminishes drug uptake and restricts brain bioavailability. Because of the rapid renewal of mucus, the design of mucoadhesive NPs can increase their retention time within the mucus and increase their potential for brain transportation. However, within a certain timeframe, NPs will be eliminated if they fail to penetrate the mucus layer. Therefore, while the adhesion strategy partially prolongs NPs' residence time in the mucosa, it also necessitates timely penetration of the mucus barrier before clearance. The key considerations in designing nose-to-brain drug delivery involve carriers' capacity to traverse the mucus layer efficiently while adhering to it, thereby reducing mucociliary clearance for optimal nose-to-brain transport. Consequently, optimizing the interaction of the system with mucus to transiently prolong drug retention in the nasal cavity, and augmenting mucus permeability on top of this are anticipated to enhance brain entry efficiency.

3.2. Nasal epithelial barrier

Another major challenge of nose-to-brain drug transport is the obstruction by the nasal epithelial barrier. Transport across the olfactory or respiratory epithelial barriers occurs either by intracellular or extracellular pathways. In mice and squirrel monkeys, intranasally delivered native horseradish peroxidase has been shown to pass through open intercellular clefts extracellularly, in addition to intracellular uptake, to reach the olfactory bulb of the CNS [32]. The primary determinant of a given NP's paracellular permeability is the presence of tight junction at the epithelial barrier. Drugs in the lamina propria subsequently enter the brain by passive diffusion or receptor-mediated endocytosis to complete transcellular transport, which is the major pathway for lipid-soluble molecules. The nasal delivery of NPs into the brain involves one or a combination of the above pathways. The intracellular pathway relies on cell-NP affinity and cellular internalization rate, whereas the extracellular pathway is closely related to the presence of epithelial tight junctions, extracellular spaces, or interstitial spaces between cells. Enhancing NPs' ability to efficiently cross barriers between epithelial cells or neurons is key for improving nasal drug delivery efficacy into the brain.

3.3. Brain lesion site "barrier"

Once the intranasally administered substances reach the olfactory bulb or brainstem via the olfactory or trigeminal nerves, they then transfer to adjacent brain tissue or CSF for eventual distribution to other distal regions of the brain. To fully harness therapeutic effects, drugs need to be transported to focal sites, thus underscoring the significance of intelligent targeted drug delivery systems, which, through rational design, can facilitate drug accumulation at brain lesions and ultimately optimize therapeutic benefits and minimize side effects. Considering the characteristic pathological features of diseases such as AD, where toxic amyloid beta (Aβ) protein and Tau protein serve as both focal site markers and drug therapy targets, targeted delivery systems can be designed to reduce toxicity towards normal tissues [33]. Lesion

targeting can also be achieved by exploiting surface receptors up-regulated by microglia, astrocytes, and other cells under pathological conditions [34]. In addition, based on the heterogeneous brain microenvironment of different diseases such as inflammatory or acidic microenvironment, the nano-delivery system with focal responsive release can be designed to enhance efficacy while minimizing toxicity [35].

4. Nanotechnology-based strategies for enhanced nose-to-brain delivery

The earliest clinical studies compared the drug administration via nasal and intravenous routes. The clinical trial involving 15 healthy men who received both intranasal and intravenous arginine-vasopressin revealed an augmentation in brain wave activity following intranasal administration [36]. Similarly, another clinical study involving 12 healthy adults receiving both intranasal and intravenous angiotensin II reported comparable findings [37], with nasal administration demonstrating a more rapid and direct CNS action, thus garnering increasing attention. Recently, nanomedicines have gradually emerged as one of the most promising drug delivery platforms for CNS therapeutics due to their functional attributes features associated with the nanoscale and material composition [38–40]. Despite the challenges encountered, nasal administration of nanotechnology-based systems remains the most auspicious alternative for effectively delivering therapeutic agents to the CNS. Several studies have shown that the nose-to-brain route exhibits superior efficiency for NPs than for solutions [41,42]. By addressing the three major barriers of nose-to-brain delivery for neurological diseases, nanotechnology can significantly enhance transport by transiently prolonging drug retention in the nasal cavity and augmenting mucus permeability to overcome the mucus barrier, improving intracellular and extracellular transport to efficiently cross barriers between epithelial cells or neurons, and increasing brain focal accumulation via receptor-mediated focal targeting as well as pathologic responsive drug release (See Fig. 5).

4.1. Transporting across the nasal mucus barriers

Most mucin glycoconjugates exhibit strong negative charges due to their high sialic acid and sulfate content, which stabilizes the system [43,44]. This means that positively charged NPs are more likely to interact with nasal mucus via electrostatic adsorption. Similarly, targeting the hydrophobic non-glycosylated regions of mucins using hydrophobic interactions increases their interaction with hydrophobic NPs. The mucus layer prevents exogenous agents from directly contacting the epithelial cells, acting as a protective mechanism, but accelerates the rapid clearance of drugs from the body via nose-to-brain delivery. The interaction between NPs and the mucosal barrier cannot be ignored when designing nose-to-brain drug delivery systems. Specific optimization for nasal formulations is required to design NPs with appropriate mucosal adhesion or penetration properties, which are essential for overcoming the mucus barrier and achieving enhanced nose-to-brain delivery.

4.1.1. Increased mucus adhesion

Considering the aforementioned, mucoadhesion appears to hold promise as a viable approach for overcoming nasal mucus barriers. Mucoadhesion aims to lengthen the residence time of drugs at mucosal sites via increasing interaction with mucin in order to increase the likelihood of transport into the brain. Three main mechanisms can be employed to enhance mucus adhesion based on mucin properties: electrostatic adsorption, covalent binding, and weak interactions between NPs and the mucus.

Electrostatic adsorption is the most contemplated strategy. Due to the highly negative charge of mucins, positively charged carriers are prone to interact via electrostatic bonds with negatively-charged mucins in mucus, increasing the residence time of drugs in the nasal cavity. Solid polymeric NPs exhibit exceptional mucoadhesive properties owing to their easily engineered positively charged surface to confer the ability that bond with highly negatively charged mucins [8]. Chitosan is one of the most extensively used cationic polymers in nasal drug delivery and achieved remarkable success. Based on the assembly of chitosan and graphene quantum dots as smart components, *Mostafavi* et al. developed chitosan/quantum dots NPs as ultrasmall nanoplatforms using the microfluidic technique. The incorporation of chitosan acted as a smart mucoadhesive polymer that prolonged the residence time of NPs in the nasal cavity and prevented their clearance before absorbance, which greatly increased the efficiency of the brain target for AD therapy [45]. *Sultana* et al. developed chitosan-coated poly(lactic-*co*-glycolic acid) (PLGA) NPs for carmustine delivery using a double emulsion solvent evaporation technique for the treatment of glioblastoma via nasal route. The cationic charge over the NPs, attributed to chitosan, facilitated interaction with sialic acid on the nasal mucosa and transiently opened tight junctions. Consequently, these factors collectively enhanced drug penetration across the nasal mucosa and significantly increased drug accumulation in the brain following nasal administration [46]. Another research reported the role of coated chitosan in biodegradable PLGA NPs for enhanced nasal mucosa adhesion for antiepileptic hormone brain delivery [47]. Other nanomaterials, such as hydrogels [18,48], cationic liposomes [49], micelles [50], etc., are frequently engineered as carriers to increase mucosal electrostatic adhesion for nasal delivery. The prolonged retention of cationic PLGA NPs in comparison to the other four types of NPs indeed underscores the robust electrostatic interactions between cationic NPs and anionic sialic acid and glycosaminoglycans present in the mucin [51].

Moreover, since mucins are rich in cysteine residues, NPs containing thiol groups are capable of forming covalent bonds with free sulfhydryl groups to achieve mucosal adhesion, for instance, thiolated chitosan micelles [52], thiolated carboxymethyl β-cyclodextrin [53], thiolated microspheres [54] were used as controlled drug delivery carriers with improved mucoadhesive properties. For example, thiolated chitosan hydrogel was selected in a study for incorporation with liposome for intranasal delivery of donepezil HCl, an anti-Alzheimer drug, in rabbits. The intranasal delivery of donepezil HCl through thiolated chitosan hydrogel resulted in a 107% increase in the mean brain content of the drug compared to the free form, which suggested that thiolation of transnasal vehicles holds promise as a nasal delivery device to improve brain drug bioavailability [55].

Additionally, weak interactions, which means that hydrogen bonding, van der Waals bonding, and hydrophobic interaction, also strengthen the mucosal adhesion. Highly glycosylated surfaces of mucins, as well as glycoproteins on the surface of epithelial cells, enhance mucosal adhesion and promote NP internalization by the binding force between specific glycosylated surfaces and lectins. Lectin-mediated mucoadhesion provides specific biological interactions to enhance mucin adhesion. In our previous study, a multifunctional nanocarrier (Rapa@DAK/siRNA) was constructed for AD treatment based on Aleuria aurantia lectin and Aβ-binding peptide modified PEGylated dendrigraft poly-l-lysines via intranasal administration (Fig. 3). After administration, aleuria aurantia lectin, specifically binding to L-fucose located in the olfactory epithelium, endowed Rapa@DAK/siRNA with high brain entry efficiency to achieve high small interfering RNA of β-site precursor protein cleaving enzyme-1 (BACE-1) and rapamycin co-delivery into the brain. The multifunctional nanocarrier was verified to provide an effective intranasal avenue for combination therapy of AD [19]. To improve nose-to-brain drug delivery and reduce immunogenicity, odorranalectin was conjugated to poly(ethylene glycol)–poly(lactic-*co*-glycolic acid) (PEG–PLGA) NPs and its biorecognitive activity was verified by haemagglutination tests. With the specific binding ability of L-fucose located on the olfactory epithelium of nasal mucosa, odorranalectin modification increased the brain delivery of NPs and augmented the therapeutic effects on Parkinson's disease [56]. What's

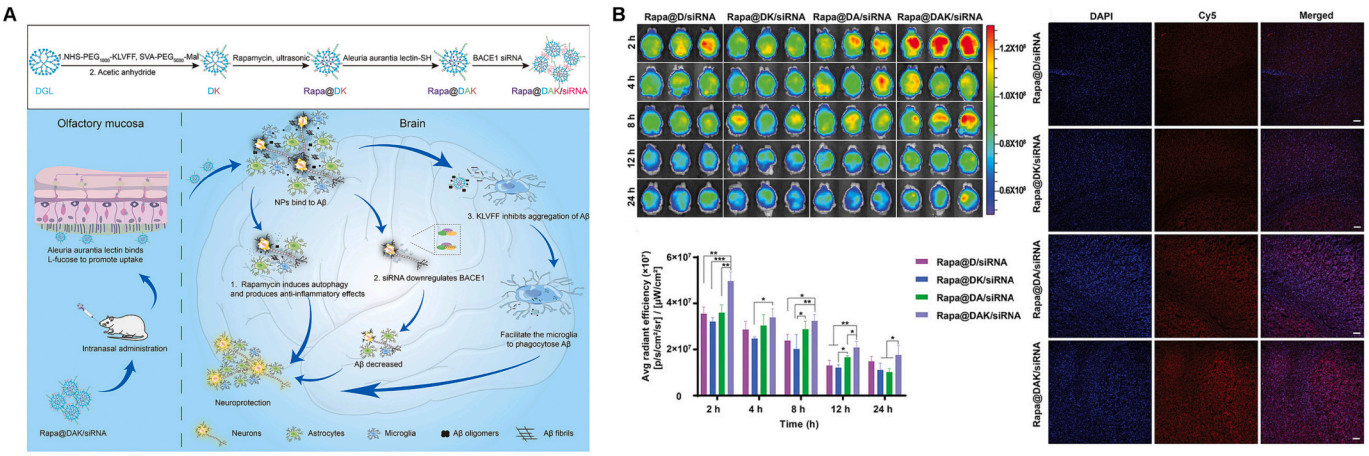

Fig. 3. Intranasal delivery of BACE1 siRNA and rapamycin by dual targets modified NPs for Alzheimer's disease therapy. (A) Scheme of Aleuria aurantia lectin and Aβ-binding peptide modified DGL NPs for nasal administration. (B) The accumulation of NPs in the brain. Reproduced with permission. [19] Copyright 2022, Wiley-VCH.

more, the ulex europeus agglutinin [57] and wheat germ agglutinin [58,59], which respectively bind with L-fucose residues and *N*-acetyl-d-glucosamine as well as sialic acid abundantly present in the nasal cavity, are other commonly employed lectins in adhesion reinforcement for nose-to-brain drug delivery systems.

4.1.2. *Enhanced mucus penetration*

Due to the rapid removal and renewal of mucus, which inevitably shortens their retention time, mucoadhesive NPs and certain drugs, such as nucleic acids and peptides, will be removed if they fail to reach the epithelial surface. Also, enzymatic degradation or exposure to different microenvironments can also contribute to their removal. Hence, it is critical for NPs to effectively penetrate the lower epithelium before being washed away from the administration site, even though good adhesion is still required to prolong the residence of NPs in nasal mucus for further NP uptake. To address this limitation, extensive research has been dedicated towards achieving rapid NP penetration across the mucus layer and maximally avoiding the interference caused by continuous mucus turnover during nasal administration.

Regarding the NPs themselves, three crucial factors influencing mucus penetration can be summarized as particle size, hydrophilicity, and surface charge. The first consideration is particle size. Mucins cross-link with each other to form a mucus layer with a mesh structure, whose mesh pores range from ~200 nm. NPs with larger particle sizes are not able to be rapidly transported through the mucus barrier [60]. Secondly, hydrophobic areas increase the opportunity of interaction with hydrophobic regions of mucins. NPs featuring hydrophilic surfaces aid in reducing interactions with mucins and facilitate their penetration [61]. Finally, NP surface charge plays a pivotal role in mucus penetration. Due to the abundance of negatively charged groups in the mucin fibers, positively charged NPs inevitably become immobilized within the mucus through electrostatic binding, prolonging the retention time in the mucus. Although this reduces NP removal, at the same time, excessive negative charges also cause NPs to be trapped in the mucus due to unwanted repulsion and prevent their further transport into the brain. Henceforth, the simultaneous maintenance of particle size and moderate surface properties are essential for rapid mucus diffusion.

Given the rapid mucus transport capacity of certain viruses to infect mucosal tissues, mucus-penetrating NPs can be engineered by drawing inspiration from nature. For example, in addition to their diminutive size and simplistic structure, viruses with high barrier permeability tend to have few exposed hydrophobic sites so that they can reduce interactions with the hydrophobic regions of mucin fibers [61]. Nanomaterials on hydrophilic surfaces are frequently employed to reduce interactions with mucins and facilitate their penetration. Poly(ethylene glycol) (PEG) has emerged as the most popular hydrophilic polymers for modifying NPs [62]. The molecular weight [63,64], density [65], and the ratio of hydrophilic and hydrophobic units [66] of its coating will affect the diffusion of NPs in mucus and necessitate optimization and screening for specific applications. Despite increased permeability conferred by a hydrophilic shell, NPs with sufficient muco-inert coating would show undesirable cellular internalization and transport. Thus, in certain cases, nanoplatforms are modified to achieve an optimal "hydrophilicity/hydrophobicity balance" on their surface to maximize the mucus penetration effect.

Similarly, careful consideration is also given to the surface charge of NPs to design NPs with superior mucus penetration capabilities. Prior to this, in order to understand the impact of different surface charges of NPs on their delivery from the nose to the brain, fluorescently labeled liposomes with varying surface charges and PEG modification were prepared using fluorescent dye-labeled liposomes, followed by *ex vivo* imaging analysis for observing their brain distribution (Fig. 4). At the same time, radioisotope (RI)–labeled liposomes were prepared for quantitative analysis. The results showed that positively charged NPs tended to be distributed in the forebrain and olfactory bulb, and negatively charged NPs showed high distribution in the hindbrain under the same modifications. Conversely, neutral liposomes displayed distribution throughout the entire brain and spinal cord, and higher fluorescence intensity was observed than charged liposomes. For neutral liposomes, the presence or absence of modifications affected their stability in tissues, which in turn affected cellular uptake. All in all, neutral liposomes with modifications are more suitable as drug carriers for nasal delivery into the brain [67]. Inspired by mucus-penetrating viruses, whose distinguishing feature is the distribution of equal amounts of positive and negative charges on their surfaces, appearing electrically neutral [68], researchers designed NPs with balanced positive and negative charges to avoid the effects of electrostatic interactions with mucin. Amphiphilic ionic polymers show promising applications in penetrating mucus barriers. *Chen* et al. established a nanoplatform with various surface modifications, including PEG, poly(vinyl alcohol) (PVA), pluronic F127 (F127), and polydopamine (PDA), and systematically evaluated the mucus penetrability of these different NPs. Unmodified and PVA-modified PLGA NPs showed poor mucus penetrating ability, while the PEG and F127-modified NPs exhibited relatively satisfactory mucus penetrability but showed low epithelial cell uptake efficiency. In contrast, the zwitterionic surface feature of PLGA-PDA NPs facilitated rapid mucus penetration and enhanced cellular uptake, highlighting the sequential penetration of both mucus and epithelial barriers by zwitterionic modified NPs as a promising strategy to overcome mucosal barriers [69]. In recent years, the charge-reversal strategy has also been

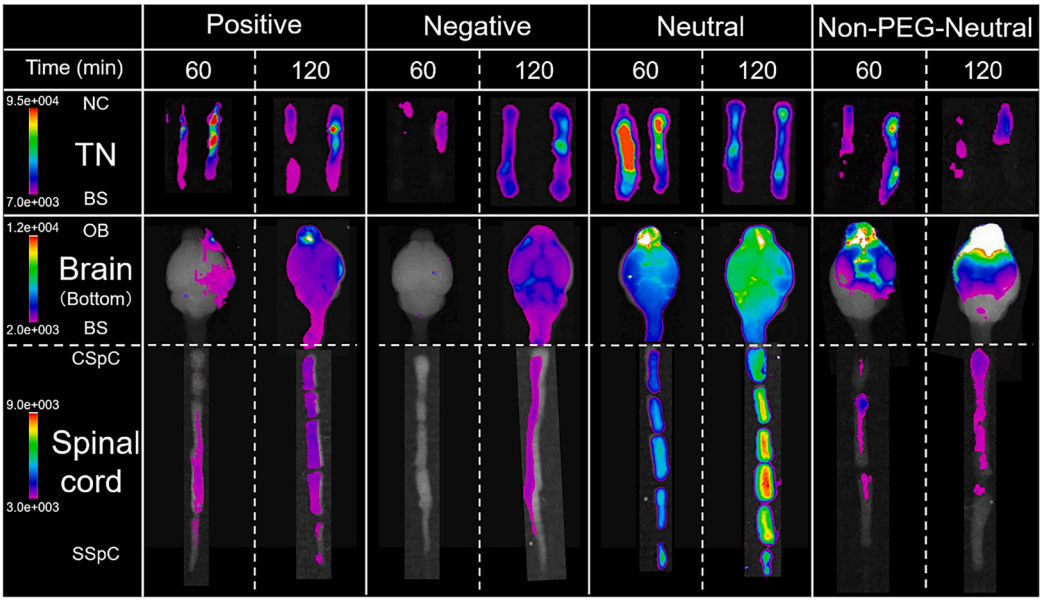

Fig. 4. Fluorescence imaging of trigeminal nerve, brain, and spinal cord after intranasal administration of fluorescently labeled liposomes. Reproduced with permission. [67] Copyright 2022, Elsevier.

explored for smart nanomedicine [70]. By design, initial NPs have a positive zeta potential enabling adhesion of the mucus layer. Peptides containing hydrophobic amino acids conjugated on their surfaces undergo cleavage upon interaction, resulting in a neutral or negative zeta potential that facilitates their mucus penetration. This design will hopefully be used for nasal delivery to quickly overcome the mucus barrier into the brain.

In addition to modification of the NPs themselves, mucus penetration can be accelerated by mucus modulation via mucus-modulating agents to improve NP delivery. Mucolytic agents are incorporated prior to or in conjunction with the NPs to augment their nose-to-brain transport. When cysteine and papain are attached to the NP surface, they can disrupt the peptide bonds of mucins, a combination that has been shown to increase their mucus permeability [71]. *N*-acetylcysteine, commonly employed, has been shown to facilitate nasal absorption of drugs due to its ability to cleave disulfide bonds between mucins [72].

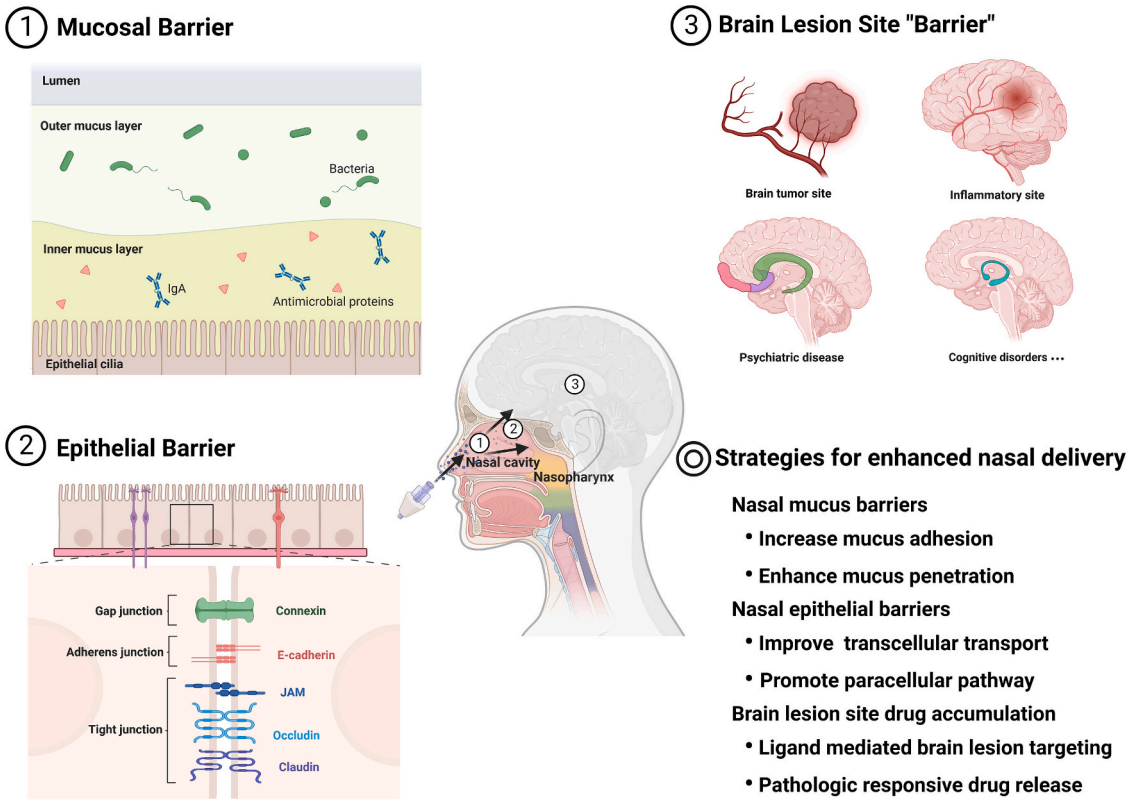

Fig. 5. Summary of nose-to-brain drug delivery barriers and the nanotechnology-based strategies for enhanced nose-to-brain drug delivery.

4.2. Overcoming the nasal epithelial barriers

After successfully crossing the mucus barrier, drugs reach the epithelial cells and transport across another barrier presented by the olfactory or respiratory epithelia occur either by intracellular or extracellular pathways. Enhancing the transcellular efficiency, whether by augmenting intracellular transport or enhancing cellular uptake, as well as facilitating the paracellular pathway via modulating cellular junctions, would promote NPs crossing the epithelial barrier and facilitating their intranasal transport into the brain.

4.2.1. Enhancement of transcellular transport

One of the most important pathways for nose-to-brain transport is transcellular transport via olfactory and respiratory epithelium, encompassing axons of the olfactory and trigeminal nerves as well as basal and Sertoli cells. Facilitating drug uptake by these cells can significantly improve the efficiency of nose-to-brain entry. The cell membrane, composed mainly of lipids and proteins, is a selective permeability barrier that regulates the entry into and out of substances. The phospholipids enriched in cell membranes are structures with polar head groups and nonpolar fatty acid tails and self-assemble into a bilayer structure with a hydrophobic hydrocarbon core. Substances enter cells either by active transport or passive diffusion across the lipid bilayer [73–75]. Strategies to enhance cellular uptake to facilitate transcellular transport can be achieved by designing delivery systems that transiently disrupt cell membranes or exploit the machinery responsible for regulating transport across cell membranes, such as receptor-mediated endocytosis.

The most prevalent approach to enhance cellular uptake involves perturbing cellular membranes transiently through the utilization of cell-penetrating peptides (CPPs). CPPs, the protein-transduction domains, are short peptides capable of entering biological cells by a variety of mechanisms [76,77]. Arginine-rich cationic CPPs are able to form hydrogen bonds with carboxylic acids and phosphates on cell membranes, thereby enhancing transcellular transport via mediating endocytosis of NPs through macropinocytosis. Co-administration of CPPs with carrier systems, along with covalent modification of CPPs on the surface of NPs, can both significantly enhance the transcellular transport of NPs. Co-administration of CPPs with carrier systems represents a straightforward method to augment transmembrane transport. Our previous study found that co-administration of CPPs and NPs increased the number of NPs transported through the nasal cavity to the brain following intranasal administration [78]. *Takeda-Morishita* et al. coadministered the CNS-related insulin and CPP to mice via intranasal rote. As a result, insulin coadministered with CPP reached distal regions of the brain, including the cerebral cortex, cerebellum, and brain stem. This demonstrated nasal delivery of pharmaceuticals to the brain can be facilitated by increasing cellular uptake of drugs by the supporting and neuronal cells [79]. Unlike the co-administration approach, the system of which is separate, the covalent strategies, where penetrating peptides were directly linked to NPs, have also been widely developed for nasal delivery [80]. Researchers enveloped CPP DP7-C with hyaluronic acid (HA) and developed a multifunctional core-shell structure nanomicelles HA/DP7-C for nose-to-brain delivery of siRNA for glioma therapy. *In vivo* experiments indicated that siRNA was effectively delivered to the CNS by HA/DP7-C through the trigeminal nerve pathway within hours after intranasal administration. The DP7-C used as the siRNA delivery carrier improved the efficiency of siRNA delivery from the nose to the brain and prolonged the survival time of tumor-bearing mice [81]. *Lee* et al. conjugated resveratrol (RSV) to an amphiphilic α-helical leucine (L)- and lysine (K)-rich CPP (LK) and intranasally delivered it to nasal epithelial cells to treat chronic rhinosinusitis with nasal polyps. The RSV conjugates penetrated the nasal epithelium and efficiently inhibited epithelial-mesenchymal transition, nasal polyp formation, and related inflammation in mice. With the ability to overcome the tight nasal epithelial barrier, this CPP-based delivery system provided a new option for the treatment of localized nasal diseases with minimum systemic side effects [82]. By adding CPP and penetration accelerating sequences into the design, a glucagon-like peptide-2 derivative can not only be taken up into cells but also be transported out of the cells. As a result, enhanced cellular uptake and promoted endosomal escape mediated by CPP were achieved, enabling direct translocation of glucagon-like peptide-2 from the nose to the brain [83].

Indeed, nasal epithelial cells express a variety of receptors. Strategically designed approaches that selectively bind to these receptors involved in NP transcellular transport can augment the transmembrane translocation of NPs by receptor-mediated endocytosis to overcome the epithelial barrier. Transferrin receptor is ubiquitously expressed in human tissues [84,85]. Previous studies have shown that transferrin is highly expressed in the human nasal cavity, leading to the widespread utilization of transferrin-modified nano-delivery systems for nasal drug delivery due to their ability to exploit endocytosis mediated by the interaction between transferrin and its receptor. Transferrin-decorated chitosan NPs were used to assess the passage of model proteins through the nasal epithelial barrier by *Olivia M. Merkel* and his colleagues. Transferrin-decorated NPs exhibited faster passage through the epithelial cell layer, as well as increased cellular internalization into glioblastoma cells compared with unmodified NPs. Moreover, it was observed that NPs with a higher density of surface targeting ligands displayed greater cellular uptake in human nasal epithelial cell lines [86]. Another frequently used targeting moieties is lactoferrin. Due to high expression levels of the lactoferrin receptor in neurons and nose endothelial cells, modification of lactoferrin may achieve dual targeting effects of the nasal mucosa and brain in the construction of nasal drug delivery systems [87]. For example, *Liu* et al. reported that an enhanced therapeutics accumulation was observed in large regions of rat brain such as the cerebrum, cerebellum, olfactory tract, olfactory bulb, and hippocampus after intranasal administration of lactoferrin-modified NPs, which confirmed the significant role that lactoferrin plays in the nose to brain entry [88]. In addition, the combined construction of nasal drug delivery NPs by the increased mucosal adhesion via *N*-trimethylated chitosan and the lactoferrin-mediated enhancement of transcellular transport achieved even stronger nose-to-brain entry efficiency, presenting a promising strategy against AD [89].

4.2.2. Promotion of paracellular pathway

Epithelial junctions, including tight junctions, adherens junctions, and desmosomes along with gap junctions, are arranged on lateral surface of epithelial cells and engage in crosstalk through protein-protein interaction and signaling cascades, all of which contribute to the establishment and maintenance of paracellular barrier [90]. Among them, tight junctions composed of three primary constituents of transmembrane proteins namely claudin (CLDN), occludin (OCLN), and junctional adhesion molecules (JAMs), as well as adherens junctions represented by *E*-adhesins, are the main barriers for drug transport through paracellular pathway [91,92]. Tight junction modulators acting on these components promote drug transport into the brain via paracellular pathway and have been used in the development of formulations for nasal delivery.

Tight junction modulation encompasses non-specific modulators, such as surfactants, chitosan, bile salts, fatty acids, and specific modulators target specific components, such as the regulators targeting cytoskeleton, enzyme, occluding, claudin, etc. [90]. For the treatment of viral infections, intranasal mRNA vaccination offers a flexible and convenient approach. However, effective delivery of antigens to nasal-associated lymphoid tissues remains challenging due to the limitations of the nasal epithelial barrier. To address this issue, a potent intranasal mRNA vaccination system based on polymer for HIV-1 treatment was synthesized containing cationic cyclodextrin-polyethylenimine 2 k conjugate (CP 2 k) complexed with anionic mRNA encoding HIV gp120. As a result, by reversibly opening tight junctions in the nasal epithelium, CP 2 k contained in the delivery system not only facilitated the

paracellular delivery of mRNA but also minimized the absorption of toxins present in the nasal cavity [93]. In June 2023, a New Drug Application for Diazepam Nasal Spray was approved by China's National Medicinal Products Administration (NMPA) for the acute treatment of patients with epilepsy aged 6 years and older. The n-dodecyl-beta-D-maltoside (DDM), a nonionic surfactant and absorption enhancement agent used in the formulation, promotes the transmucosal bioavailability of drugs. The results showed that diazepam nasal spray is effective in treating seizure clusters [94]. DDM has also been utilized to enhance the nasal absorption of nalmefene hydrochloride [95]. The carbomer-based gel can extend the residence time of the drug delivery system in the nasal cavity to further enhance paracellular transport efficiency for the treatment of insomnia [96]. Targeted modulation of specific proteins involved in tight junctions has also undergone extensive investigation in recent years [97,98], and this strategy allows for reversible tight junction opening and facilitating drug paracellular transport to increase nose-to-brain delivery. Rational design, material syntheses, and combinatorial libraries have proven invaluable in yielding reagents that enhance paracellular pathways via precise tight junction targeting to increase nose-to-brain drug delivery, offering researchers with a range of material-based choices with distinct advantages depending on the application. Nevertheless, since the epithelial barrier is a defense barrier against microorganisms and harmful pathogens, when applying tight junction modulators, the impact on the epithelial barrier after administration should be addressed in a comprehensive manner to improve the efficacy of nasal drug delivery while ensuring safety. Rats are predominantly employed in the current research models for nasal drug delivery. Although nasal administration of nanosystems targeted to the brain has demonstrated enhanced efficacy in treating brain diseases, it is important to consider that humans possess a relatively smaller area of olfactory epithelium compared to rats, which could potentially impact drug absorption through the olfactory epithelium [99]. Therefore, prior to initiating clinical studies, it is necessary to evaluate the effectiveness of intranasal formulations in animal models that closely resemble the structure of the human nasal cavity.

4.3. Improving drug accumulation in brain lesions

For the treatment of specific brain diseases, a suitable nose-to-brain delivery system, whether a modified drug or an NP carrier, should ideally have two functionalities—One to surmount nasal mucosal and epithelial barriers for brain entry, and another to target and penetrate the pathologically affected regions. NPs need to be precisely distributed to the main lesion sites after intranasal administration, such as brain tumors site, brain injury site, hippocampus, damaged neurons, dysfunctional microglia in AD, etc. to exert therapeutic effect so as to achieve precise treatment.

4.3.1. Ligand-mediated brain lesion targeting

Utilizing receptors that are highly expressed on the cell surface at the lesion site enables specific cell targeting and represents a promising strategy to enhance drug accumulation specifically at brain lesion sites. C-X-C chemokine receptor type 4 (CXCR4) is an alpha chemokine receptor specific for stromal-derived factor-1, which is overexpressed in tumor cells like glioblastoma [100]. CXCR4 serves as a targetable functional receptor for glioblastoma therapy. *Ramasamy Paulmurugan* and his colleagues adopted nasal delivery of miRNA-loaded CXCR4-engineered extracellular vesicles (eEVs) in orthotopic glioblastoma mouse models and observed the pattern of eEVs trafficking across the nasal epithelia into the intracranial compartment. The further enhanced specific glioblastoma targeting of EVs by modifying their surfaces using the CXCR4 manifested selective tropism towards glioblastoma cells to deliver their miRNA cargo. The accumulation of delivered miRNAs sensitized glioblastoma cells to temozolomide, resulting in prominent tumor regression and improved overall survival of mice [101]. Similar to stromal-derived factor-1, ephrin type-A receptor 3 (EphA3) is frequently overexpressed in tumor-initiating cells of glioblastoma but not in normal cells [102]. Thus, the EphA3 antibody, a low-toxicity non-fucosylated IgG1j monoclonal antibody, can further enhance glioma targeting via its specific interactions with EphA3 receptor. The NP systems that were modified with EphA3 antibody and loaded temozolomide for targeted GBM therapy via intranasal administration increased drug accumulation in the glioma site and enhanced treatment efficacy [103,104]. Exosomes are used as drug carriers for targeted therapy owing to the presence of specific receptors on their surface. Exosomes derived from mesenchymal stem cells were found to be able to accumulate in neurons in pathological areas of the brain after nasal administration, indicating an active targeting effect of exosomes as carriers for nasal drug delivery [105,106]. A clinical trial was conducted recently to evaluate the safety and efficacy of allogenic human adipose mesenchymal stromal cells-derived exosomes (ahaMSCs-Exos) in patients with mild to moderate AD (NCT04388982). Notably, no adverse events were reported during the study period. In the medium-dose arm, there was a decrease of 2.33 (1.19) in AD Assessment Scale-Cognitive section (ADAS-cog) scores and an increase of 2.38 (0.58) in the basic version of Montreal Cognitive Assessment scores at week 12 compared to baseline levels, indicating improved cognitive function. Furthermore, ADAS-cog scores continued to decrease by 3.98 points until week 36 in the medium-dose arm. Although no significant differences were observed in altered amyloid or tau deposition among the three arms, it is noteworthy that hippocampal volume exhibited less shrinkage to some extent in the medium-dose arm. These results indicate intranasal administration of ahaMSCs-Exos is safe and well tolerated, and larger-scale clinical trials are expected to be implemented to ascertain its efficacy [107].

Based on the characteristics of the disease lesion, targeting toxic proteins mediated by ligands can achieve both aiding drug delivery systems in localizing at target regions and exerting therapeutic effects through toxic substances removal. For example, in AD pathology, cerebral Aβ accumulation has been identified as the central event, triggering the following tau deposition, neuroinflammation, neuron and synaptic loss, and cognitive decline [108–110]. Investigators have constructed a series of intelligent nano-delivery systems targeting toxic Aβ for nasal drug delivery in AD treatment [19,111]. The design of dual-targeting NPs with the decoration of transcriptional activator protein and monosialotetrahexosylganglioside facilitated both NPs translocation across nasal epithelial cells and NPs binding to Aβ after entering the brain, which greatly improved NP retention at targetable AD brain lesions [111].

In addition to these prevalent brain disorders, the utilization of nose-to-brain delivery for precise brain lesion targeting is progressively demonstrating advantages in some rare diseases, specifically LSDs. The majority of LSDs arise from deficiencies in lysosomal enzymes, and this observation underpins the fundamental basis for most currently approved therapies involving enzyme-replacement therapy (ERT) [112]. Conventional ERT effectively mitigates lysosomal storage and disease pathogenesis in peripheral organs, but its efficacy in halting disease progression within the brain is limited due to low expression of receptors on BBB endothelial cells and parenchymal cells, as well as poor transport across the BBB. *Wolf* and colleagues have provided the first evidence that intranasal administration enabled therapeutic levels of a lysosomal enzyme to bypass the BBB [113]. For more precise lysosomal targeting, *Tong* et al. described a method that enhances the delivery of recombinant enzymes to the brain lysosome via nasal administration. In their study, intranasally administered iduronidase exhibited rapid brain penetration. The carrier utilized a guanidinylated form of neomycin (GNeo), which harnesses the high-affinity of GNeo to cell-surface heparan sulfate proteoglycans and their ability to internalize macromolecular cargo through micropinocytosis, resulting in sufficient enzyme delivery to lysosomes upon entry into the brain. These findings showed conjugation with GNeo enhanced the efficacy of intranasal ERT in the brain [114]. By modulating the structural characteristics of

guanidinylated glycosides or the linkers connecting glycosides and cargoes, we can further engineer transporter proteins with additional desirable attributes to achieve precise delivery in various organelles via nose-to-brain delivery. This advancement is anticipated to be instrumental in developing targeted therapeutics for a broader range of rare diseases.

4.3.2. Pathologic responsive drug release

While the aforementioned targeting approach involves drug molecules or NPs with disease-specific targeting ligands, other nasal drug systems can be triggered by brain environmental stimuli to achieve localized drug release and accumulation in brain lesions. In most neurodegenerative diseases, disruptions in brain physiology create an abnormal local environment that can be harnessed for environmentally responsive drug delivery. NPs can be engineered to respond to unique cellular conditions associated with brain pathology environment, including low pH, high metal ion level, hypoxia, inflammation, redox, to increase the release and accumulation of drugs in brain lesions following nasal administration.

In terms of pH, the acidic environments generated by inflammatory and tumor sites can be taken advantage of by incorporating pH-responsive components into the drug system. The incorporation of acid-cleavable bonds and acid-sensitive materials can be attributed to the hydrolysis of acid-labile bonds or protonation of ionizable groups. The acid-cleavable bonds display accelerated hydrolysis in low pH environments, while the pH-responsive amine-bearing polymers exhibit increased solubility under an acid environment [115]. In a "nano-courier" system designed for delivery of acetylcholine and melatonin by complement component 5a (C5a)-targeted aptamers, amino-modified aC5a aptamers were covalently crosslinked with poly (acrylic acid) of nanospheres by pH-sensitive amide bonds and both acetylcholine and melatonin were controllably released into the ischemic focus triggered by low pH in the ischemic regions, effectively attenuating reperfusion injury of ischemic stroke [116]. These response bonds are expected to be progressively developed for nasal drug delivery systems in the future to increase drug accumulation at the lesion site. Redox states occur as a lot of neurological disorders, especially in the hippocampus during AD [117]. As a result of oxidative stress, redox-triggered drug systems have been shown to enable site-specific brain drug release without perturbing homeostasis [118]. In addition to the inflammatory microenvironment, an imbalance in metal ion homeostasis is an integral factor in AD pathology process. The abnormally high concentration of metal ions in the AD brain not only stabilizes neurotoxic Aβ plaques but also catalyzes reactive oxygen species formation and exacerbates neuroinflammation [119,120]. Recognizing the important role of zinc ions in AD pathogenesis, *Liu* et al. first attempted to make use of the carboxylated pillar [5]arene supramolecular vesicles to alleviate zinc ion burden and achieve drug release at the lesion site. In their work, intelligent resveratrol-loaded supramolecular NPs with zinc ion responsive release capability were established to alleviate Aβ formation, oxidative stress, and microglial dysfunction. Through intranasal administration, resveratrol-loaded NPs not only modulated zinc ion-dependent Aβ aggregation but also realized zinc environment-responsive cargo release and further reprogramed dysfunctional microglia, which prevented spontaneous neuroinflammation and alleviated cytotoxicity [121]. Recently, mounting evidence has demonstrated the merit of bioresponsive delivery systems in the treatment of brain disorders [122–124]. In particular, these biomaterials sensitive to diverse biochemical signals hold promise as environment-responsive delivery systems for targeted nasal delivery. By precisely regulating cargo kinetics at specific sites of interest, bioresponsive carriers are expected to enhance therapeutic efficacy significantly while concurrently mitigating adverse effects.

5. Advantages and challenges of nose-to-brain drug delivery

As a non-invasive, effective, and alternative route of drug administration bypassing the BBB, intranasal administration has gained increasing attention in the treatment of brain disease. Some distinctive advantages of intranasal administration can be highlighted: (1) The nose-to-brain route allows for BBB avoidance through neuronal transport, including olfactory and trigeminal nerves, resulting in higher CNS bioavailability while reducing drug dosage and minimizing peripheral toxicity. (2) In comparison to traditional oral administration, intranasal administration circumvents hepatic first-pass metabolism and gastrointestinal barriers, making it particularly suitable for acid- and enzyme-intolerant drugs, especially biopharmaceuticals such as proteins and peptides. (3) For acute illnesses requiring prompt treatment, the rapid onset of action associated with intranasal administration is appealing. Research has demonstrated that ^{125}I-insulin achieves complete brain distribution within 30 min after nasal administration [125]. (4) Intranasal administration offers unparalleled advantages in terms of clinical applications. Its non-invasive route of cerebral drug delivery, combined with its ease of administration, high patient compliance, and potential for self-medication, make it a patient-friendly and clinically significant route of drug delivery, which is particularly convenient for patients undergoing long-term therapy as well as those with gastrointestinal disorders and dysphagia.

Despite the numerous advantages of intranasal administration, the fact remains that its development also encounters some challenges: (1) The limited nasal cavity size and absorption area impose constraints on the volume of drug formulation that can be administered, which significantly curtail the applicability of delivery. Of particular concern is the olfactory region, which not only possesses a small surface area (~5–10 cm^2) but is also situated in the upper posterior part of the nasal cavity. Consequently, precise targeting of this region determines both dosage and efficacy when delivering drugs to the brain. (2) The mucociliary clearance prevents toxins and other foreign particles from entering the body, resulting in poor drug retention after nasal administration. Overcoming mucosal barrier represents an initial challenge for successful nasal drug delivery. (3) The animal model used poses limitations during the transition from the laboratory to the clinic. Rodents are commonly employed as test subjects in current preclinical studies; however, despite broad similarities between rodents and human nasal structures, there exists a significant disparity in terms of olfactory epithelium proportion. Laboratory rats possess olfactory epithelium occupying 50% of their nasal surface area compared to just 10% in humans [126]. This substantial difference may lead to less favorable outcomes in actual clinical trials than those obtained in preclinical studies. (4) Nasal mucosal toxicity is a key parameter that must be taken into consideration in the development of nasal formulations. As the olfactory organ and part of the respiratory system, the physiological condition of the nose has a great impact on the quality of life. Most pharmaceutical substances and polymers/excipients, especially organic solvents and surfactants, are more or less likely to exert some toxic effects, irritation, or damage to the nasal mucosa, which need to be examined [13]. In this case, it is crucial to make full use of the advantages and maximize the disadvantages in order to facilitate the clinical translation of nasal preparations.

6. Clinical trials and on-going studies with nasal nano-formulations

Since the initial patenting of nose-to-brain delivery by *William H. Frey II* in 1989, marking the first step towards clinical studies on this approach, over a dozen formulations for nose-to-brain delivery have been developed and approved for market [13]. Additionally, numerous drugs are currently undergoing clinical trials, as summarized in Tables 1 and 2. These clinical trials are conducted on a broad spectrum of brain disorders. For example, the current clinical trial is conducted to assess the safety, tolerability, and efficacy of intranasal APH-1105 in adults diagnosed with mild to moderate AD (NCT03806478). Most clinical trials used absorption enhancers to improve nasal blood absorption and

Table 2
Clinical trials of nasal preparations for the treatment of brain diseases in the last five years.

Drug	Disease	Title	Phase	State	NCT number
Human Insulin	COVID-19-related smell loss	Intranasal Insulin for COVID-19-related Smell Loss	Phase 3	Completed	NCT05461365
	Mild cognitive impairment; Cognitive impairment	SNIFF Multi-Device Study 2	Phase 2	In progress	NCT04199767
	Psychosis	Effects of Intranasal Insulin on Neuroimaging Markers and Cognition in Patients with Psychotic Disorders	Phase 2	Recruiting	NCT03943537
Oxytocin	Prader-Willi syndrome	Effect of Intranasal Oxytocin on Dysphagia in Children and Adolescents With Prader-Willi Syndrome	Phase 2/ Phase 3	Completed	NCT05298085
	PTSD	Brief Cognitive Behavioral Conjoint Therapy for PTSD With Adjunctive Intranasal Oxytocin	Phase 2	Completed	NCT05207436
	Prader-Willi syndrome	Oxytocin Treatment in Neonates and Infants With Prader-Willi Syndrome	Phase 3	Completed	NCT04283578
	Agnosia	Effect of Oxytocin Nasal Inhalation on Empathy Analgesia	Phase 4	Not yet recruiting	NCT05823441
	Chronic migraine	A Study to Evaluate the Efficacy and Safety of TNX-1900 in Patients With Chronic Migraine	Phase 2	Recruiting	NCT05679908
	Binge-eating disorder	A Study of the Effects of Oxytocin in Adults With Obesity and Binge-eating Disorder	Phase 2	Recruiting	NCT05664516
Prednisolone	Smell loss	Preparation and Characterization Intranasal Film Loaded With Steroid as a Local Treatment of Anosmia in Compare to Insulin Intranasal Film	Phase 1/ Phase 2	Completed	NCT05328414
Mometasone Furoate	Sleep-disordered breathing	Intranasal Steroid as Medical Therapy For Sleep-disordered Breathing in Children	Phase 4	Recruiting	NCT05382494
	COVID-19-related anosmia	Corticosteroid Nasal Spray in COVID-19 Anosmia	Phase 3	Completed	NCT04484493
Glucagon	Hypopituitarism	Stimulation Test With Intranasal Glucagon for Corticotroph, Somatotroph, and Antidiuretic Axes	Phase 4	Completed	NCT05206149
Theophylline	Covid-19-related anosmia	Smell in COVID-19 and Efficacy of Nasal Theophylline	Phase 2	Completed	NCT04789499
	Smell disorder	Smell Changes & Efficacy of Nasal Theophylline	Phase 2	Completed	NCT03990766
PH-94B	Social anxiety disorder	PH94B Nasal Spray for Anxiety Induced by a Public Speaking Challenge	Phase 3	Completed	NCT04754802
	Adjustment disorder with anxious mood	PH94B in the Treatment of Adjustment Disorder With Anxiety	Phase 2	Completed	NCT04404192
M2 Macrophage Soluble Factors	Speech disorders in children	Intranasal Inhalations of M2 Macrophage Soluble Factors in Children With Developmental Speech Disorders	Phase 1/ Phase 2	Completed	NCT04689282
B-244	Migraine	Study to Determine Safety and Efficacy of B244 in Subjects With Episodic Migraine	Phase 2	Completed	NCT03488563
Ropivacaine Hydrochloride Hydrate	Migraine	Sphenopalatine Ganglion Blocks RCT	Phase 4	Completed	NCT03666663
Carbetocin	Prader-Willi syndrome	Phase 3 Study of Intranasal Carbetocin (LV-101) in Patients With Prader-Willi Syndrome	Phase 3	Completed	NCT03649477
Olanzapine	Acute agitation	Safety and Tolerability of INP105 (Olanzapine by I231 POD® Device) Nasal Spray in Healthy Volunteers - SNAP 101	Phase1	Completed	NCT03624322
Induced Pluripotent Stem Cell-Derived Exosomes (GD-iEXo-002)	Refractory focal epilepsy	Induced Pluripotent Stem Cell-Derived Exosomes Nasal Drops for the Treatment of Refractory Focal Epilepsy	Early Phase 1	Recruiting	NCT05886205
Human FGF-1	Parkinson's disease	Intranasal Human FGF-1 for Subjects With Parkinson's Disease	Phase 1	Not yet recruiting	NCT05493462
Ivermectin	Anosmia	Role of Ivermectin Nanosuspension as Nasal Spray in Treatment of Persistent Post covid19 Anosmia	Phase 2/ Phase 3	Recruiting	NCT04951362
APH-1105	Dementia; Alzheimer's disease	Study of APH-1105 in Patients With Mild to Moderate Alzheimer's Disease	Phase 2	Not yet recruiting	NCT03806478

https://clinicaltrials.gov.

thus increase the efficiency of brain penetration, such as DDM. In some clinical trials, customized nasal drug delivery devices were employed to facilitate drug delivery. Compared with the immense clinical application prospect and pharmaceutical market demand, there remains a scarcity of nasal drugs specifically designed for brain disease treatment. Notably, although several nanotechnology-based nasal formulations are being investigated, none have successfully achieved clinical translation thus far.

In addition to the preparations already on the market and the clinical trials, there are a whole series of interesting ongoing studies that concern the use of this route of drug delivery for the treatment of neurological diseases. Nanosystems have been extensively investigated as viable alternatives to conventional dosage forms for drug delivery owing to their inherent advantages, including enhanced solubility, drug protection, targeted delivery, and controlled release [127–129]. Through the implementation of optimization strategies, such as fine-tuning physical properties and surface chemistry, modification of CPPs and target ligands, coating of EVs, gelation, and utilization of physical equipment assistance, numerous intriguing studies have reported the successful optimization of nanosystems for enhanced nose-to-brain drug delivery in their preliminary stages [130]. These optimized systems encompass a wide range of therapeutic agents including small chemical molecules, peptides, proteins, nucleic acids, and natural products. The carriers employed for this purpose comprise liposomes, nanoemulsions, micelles, dendrimers, and others. A list detailing typical intranasal administration nanosystems and strategies that how nanotechnology helps the successful nose-to-brain drug delivery can be found in Table 3. With an increasing number of researchers capitalizing on the unique advantages and rapid progress of nano-formulations fortunately, there is growing momentum towards developing nasal nanomedicine for brain disease therapy to facilitate the clinical translation of pioneering nanotechnology-based nasal formulations.

7. Conclusion and outlook

Nose-to-brain drug delivery represents a promising strategy to

Table 3
Typical intranasal administration nanosystems studied for brain-targeted delivery against neurological diseases.

Carriers	Drugs	Disease	Strategies	Refs
Liposome	Ligustrazine hydrochloride	Cerebral malaria	Utilize glucose transporter 1 as a target for brain-targeted liposomes	[131]
Nanostructured lipid carriers	Rotigotine	PD	Surface modification by cationic polymer to prolong residence time in the nasal cavity	[132]
Liposome	Basic fibroblast growth factor (bFGF)	Stroke	Novel gelatin-cored nanoliposomes improve nose-to-brain drug delivery	[133]
Liquid crystal	Tranilast	CNS disorders	C_{17} monoglycerol ester is selected to increase NPs stability and drug absorption enhancement	[134]
Nanoemulsions	Vinpocetine	AD	Nanoemulsion extends drug residence time in the nasal mucosa, facilitates drug penetration through the nasal epithelia	[135]
Micelles	Antisense microRNA oligonucleotide	Glioblastoma	T7 peptide is used for targeting delivery and intranasal administration to preserve micelles	[136]
Micelles	Liver X receptors agonist	AD	PEG coating for enhanced solubility and mucosal penetration	[137]
Polymeric NPs	Camptothecin	Glioblastoma	Cell membrane-penetrating peptide modification promotes mucosal penetration	[138]
Polymeric NPs	Tanshinone	Cerebral ischemia	Loading borneol helps across the nasal mucosa	[139]
Dendrimers	BACEI siRNA and rapamycin	AD	Aleuria aurantia lectin binding to L-fucose located in the olfactory epithelium, KLVFF peptide used as Aβ targeting ligands	[19]
β-cyclodextrin NPs	Interferon-β (IFN-β)	Multiple sclerosis	Chitosan provided favorable adhesion to mucosal surfaces to increase nasal absorption	[140]
Inorganic NPs	Tarenflurbil	AD	The small diameter of the nanocarrier is utilized to facilitate the transcellular transport of the drug to the olfactory neurons	[141]
RAGE-antagonist peptide NPs	Oligonucleotides antagomir-21	Glioblastoma	Safe non-toxic carriers for enhanced brain delivery	[142]
Small extracellular vesicles	Brain-derived neurotrophic factor (BDNF)	Cerebral ischemia	sEVs are used to reach the infarct region and exert neuroprotective effects in the ischemic brain through intranasal delivery	[143]
Exosomes	Anti-microRNA oligonucleotide	Stroke	RAGE-antagonist peptide as a specific ligand for targeted delivery to hypoxic cells	[144]
Supramolecular vesicles	Metal chelator and resveratrol	AD	Zinc ion responsive design to realize responsive drug release and enhance brain lesion accumulation	[121]
Cationic liposomal formulations	mRNA	–	Cationic liposomal formulation protects mRNA from susceptible nuclease degradation and reduces nonspecific uptake by peripheral tissues	[49]
Hydrogel	Albiflorin	Depression	Temperature-sensitive in situ hydrogels adhere to the nasal mucosa at body temperature and release icariin in a sustained manner	[145]
Human serum albumin NPs	Quercetin	AD	Minimize systemic exposure to enhance brain accumulation	[146]
Microspheres	Insulin	Diabetes	Utilize thiolated groups to provide high adhesive properties	[54]

overcome the obstacles imposed by the BBB, allowing non-invasive and direct access to selective neural pathways within the brain. This approach increases drug bioavailability while reducing systemic exposure, and consequently elevates therapeutic index. Comparative studies comparing this route with intravenous or oral administration reaffirmed the advantages of rapid onset of action and high brain bioavailability of nasal administration [147,148]. Conventional antidepressants typically necessitate a duration of 4–6 weeks to attain complete efficacy in treating depression by targeting monoaminergic pathways. A clinical trial demonstrated that patients treated with esketamine nasal spray had a 1.54-fold higher likelihood of achieving remission after an 8-week period compared to those receiving quetiapine controls, providing compelling evidence for the short- and long-term effectiveness in managing treatment-resistant depression. Esketamine spray exhibited rapid antidepressant effects through its antagonistic action on *N*-methyl-D-aspartate (NMDA) receptors [149]. Owing to the more efficient transport from the nose to the brain, nanotechnology-based drug delivery systems have garnered the attention from researchers and clinicians for the delivery of various therapeutic agents. The versatile nature of nanoplatforms allows for precise customization of crucial characteristics such as size, shape, surface charge, and chemistry that govern their interaction with the nasal mucosa and cellular cues involved in this transportation process, facilitating improved nose-to-brain delivery. Numerous animal studies have demonstrated the ability of nanobiologics to effectively penetrate the brain through nasal administration, paving the way for a new era of long-term, non-invasive therapeutic approaches for neurological disorders [150,151].

Despite the consensus on the potential and benefits of nasal delivery for targeting the CNS and the relatively solid preclinical proof of concept with a wide range of nano-formulations, this therapeutic approach continues to face key issues, as evidenced by the limited number of ongoing clinical trials. Firstly, the successful development of nasal delivery formulations for brain disorders necessitates a complete understanding of brain distribution patterns, primarily involving drug exchange between parenchyma and CSF. In each specific target site within the brain region, precise knowledge regarding disease pathology and targeting factors is indispensable for designing effective nasal delivery systems. Secondly, for the study of pharmacokinetic responses in humans, the need for a harmonized methodology of evaluating pharmacokinetic parameters, coupled with the elucidation of the mechanisms underlying drug transfer from the nasal cavity to the brain holds vital importance for the development of suitable carriers that can target drugs to specific regions within the brain. Thirdly, as far as the design of nasal drug delivery is concerned, more efficient nanocarrier systems need to be designed for the restricted delivery volume, with a key focus on ensuring the safety of these carriers to avoid potential mucosal toxicity that could impede clinical translation. Of course, multiple aspects related to NP manufacturing such as ease of scale-up and long-term stability are also key parameters to be considered in the formulation. In this sense, synergistic interaction between industry, academia, and regulators is required. Lastly, given the intricate network of intranasal pathways outlined before, it is more difficult to consistently target nose-to-brain locations in the nasal cavity. To ensure reliable spray deposition and optimal bioavailability, consistent delivery angle is imperative. Meanwhile, the disparities in nasal anatomy between commonly used animal models (e.g., rodents) and humans, along with the quest for more appropriate animal models to enhance the correlation between preclinical and clinical outcomes, as well as the development of suitable delivery devices for nasal drug administration, necessitate concerted efforts.

Here, we highlighted the promise of intranasal drug delivery by providing a summary of current applications and their unique advantages over other routes of administration. These advantages underscore the unique opportunity provided by intranasal administration for repurposing existing therapies in novel ways. In particular, with regard to strategies aimed at augmenting intranasal drug delivery to the brain, we summarized the latest advancements in nanotechnology-based nose-to-brain drug delivery in treating brain disorders. We believe that this review will contribute to a clear understanding of nasal drug delivery mechanisms as well as to master research in enhancing nasal drug delivery into the brain for treating brain diseases. Undoubtedly, additional work is needed to elucidate the underlying mechanisms of this route and improve intranasal drug delivery techniques. With respect to future perspectives, new generations of nanocomposites with minimized neurotoxicity, improved drug-tracking capability, and enhanced specificity of these novel therapies against brain diseases are imperative to ensure accuracy and reproducibility for fulfilling the desire of clinical translation.

CRediT authorship contribution statement

Qianqian Huang: Writing – original draft, Visualization, Investigation. **Yongke Chen:** Writing – original draft, Visualization. **Weiwei Zhang:** Writing – original draft. **Xue Xia:** Writing – review & editing. **Hanmei Li:** Writing – review & editing, Conceptualization. **Meng Qin:** Writing – review & editing. **Huile Gao:** Writing – review & editing, Visualization, Supervision, Project administration, Funding acquisition.

Declaration of competing interest

The authors declare no competing interest.

Data availability

No data was used for the research described in the article.

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References

[1] M.O. Owolabi, M. Leonardi, C. Bassetti, J. Jaarsma, T. Hawrot, A.I. Makanjuola, R.K. Dhamija, W. Feng, V. Straub, J. Camaradou, D.W. Dodick, R. Sunna, B. Menon, C. Wright, C. Lynch, A.S. Chadha, M.T. Ferretti, A. De, C.E. Catsman-Berrevoets, M. Gichu, C. Tassorelli, D. Oliver, W. Paulus, R.K. Mohammed, A. Charway-Felli, K. Rostasy, V. Feigin, A. Craven, E. Cunningham, O. Galvin, A. H. Perry, E.L. Fink, P. Baneke, A. Helme, J. Laurson-Doube, M.T. Medina, J. D. Roa, B. Hogl, A. O'Bryan, C. Trenkwalder, J. Wilmshurst, R.O. Akinyemi, J. O. Yaria, D.C. Good, V. Hoemberg, P. Boon, S. Wiebe, J.H. Cross, M. Haas, I. Jabalpurwala, M. Mojasevic, M. DiLuca, P. Barbarino, S. Clarke, S.M. Zuberi, P. Olowoyo, A. Owolabi, N. Oyesiku, P.C. Maly-Sundgren, B. Norrving, S. R. Soekadar, P.A. van Doorn, R. Lewis, T. Solomon, F. Servadei, Global synergistic actions to improve brain health for human development, Nat. Rev. Neurol. 19 (2023) 371–383.
[2] C.W. Lindsley, Global prescription medication statistics: strong growth and CNS well represented, ACS Chem. Neurosci. 6 (2015) (2014) 505–506.
[3] H.J. Liu, P. Xu, Strategies to overcome/penetrate the BBB for systemic nanoparticle delivery to the brain/brain tumor, Adv. Drug Deliv. Rev. 191 (2022) 114619.
[4] E. Nance, S.H. Pun, R. Saigal, D.L.J.N.R.M. Sellers, Drug delivery to the central nervous system, Nat. Rev. Mater. 7 (2022) 314–331.
[5] R. Pandit, L. Chen, J. Gotz, The blood-brain barrier: physiology and strategies for drug delivery, Adv. Drug Deliv. Rev. 165-166 (2020) 1–14.
[6] S.U. Rawal, B.M. Patel, M.M. Patel, New drug delivery systems developed for brain targeting, Drugs 82 (2022) 749–792.
[7] W.A. Banks, From blood-brain barrier to blood-brain interface: new opportunities for CNS drug delivery, Nat. Rev. Drug Discov. 15 (2016) 275–292.
[8] R. Awad, A. Avital, A. Sosnik, Polymeric nanocarriers for nose-to-brain drug delivery in neurodegenerative diseases and neurodevelopmental disorders, Acta Pharm. Sin. B 13 (2023) 1866–1886.
[9] M.L. Formica, D.A. Real, M.L. Picchio, E. Catlin, R.F. Donnelly, A.J. Paredes, On a highway to the brain: a review on nose-to-brain drug delivery using nanoparticles, Appl. Mater. Today 29 (2022).
[10] J. Tang, C. Zeng, T.M. Cox, C. Li, Y.M. Son, I.S. Cheon, Y. Wu, S. Behl, J.J. Taylor, R. Chakaraborty, A.J. Johnson, D.N. Shiavo, J.P. Utz, J.S. Reisenauer, D. E. Midthun, J.J. Mullon, E.S. Edell, M.G. Alameh, L. Borish, W.G. Teague, M. H. Kaplan, D. Weissman, R. Kern, H. Hu, R. Vassallo, S.L. Liu, J. Sun, Respiratory mucosal immunity against SARS-CoV-2 after mRNA vaccination, Sci. Immunol. 7 (2022) eadd4853.
[11] T. Mao, B. Israelow, M.A. Pena-Hernandez, A. Suberi, L. Zhou, S. Luyten, M. Reschke, H. Dong, R.J. Homer, W.M. Saltzman, A. Iwasaki, Unadjuvanted intranasal spike vaccine elicits protective mucosal immunity against sarbecoviruses, Science 378 (2022) eabo2523.
[12] S. Le Guellec, S. Ehrmann, L. Vecellio, In vitro - in vivo correlation of intranasal drug deposition, Adv. Drug Deliv. Rev. 170 (2021) 340–352.
[13] M. Agrawal, S. Saraf, S. Saraf, S.G. Antimisiaris, M.B. Chougule, S.A. Shoyele, A. Alexander, Nose-to-brain drug delivery: an update on clinical challenges and progress towards approval of anti-Alzheimer drugs, J. Control. Release 281 (2018) 139–177.
[14] D.S. Quintana, A.J. Guastella, L.T. Westlye, O.A. Andreassen, The promise and pitfalls of intranasally administering psychopharmacological agents for the treatment of psychiatric disorders, Mol. Psychiatry 21 (2016) 29–38.
[15] C.P. Costa, J.N. Moreira, J.M. Sousa Lobo, A.C. Silva, Intranasal delivery of nanostructured lipid carriers, solid lipid nanoparticles and nanoemulsions: a current overview of in vivo studies, Acta Pharm. Sin. B 11 (2021) 925–940.
[16] P. Saha, H. Kathuria, M.M. Pandey, Intranasal nanotherapeutics for brain targeting and clinical studies in Parkinson's disease, J. Control. Release 358 (2023) 293–318.
[17] J. Garcia-Pardo, F. Novio, F. Nador, I. Cavaliere, S. Suarez-Garcia, S. Lope-Piedrafita, A.P. Candiota, J. Romero-Gimenez, B. Rodriguez-Galvan, J. Bove, M. Vila, J. Lorenzo, D. Ruiz-Molina, Bioinspired theranostic coordination polymer nanoparticles for intranasal dopamine replacement in Parkinson's disease, ACS Nano 15 (2021) 8592–8609.
[18] J.T. Wang, A.C. Rodrigo, A.K. Patterson, K. Hawkins, M.M.S. Aly, J. Sun, K.T. Al Jamal, D.K. Smith, Enhanced delivery of neuroactive drugs via nasal delivery with a self-healing supramolecular gel, Adv. Sci. (Weinh) 8 (2021) e2101058.
[19] X. Yang, W. Yang, X. Xia, T. Lei, Z. Yang, W. Jia, Y. Zhou, G. Cheng, H. Gao, Intranasal delivery of BACE1 siRNA and rapamycin by dual targets modified nanoparticles for Alzheimer's disease therapy, Small 18 (2022) e2203182.
[20] R. Dahl, N. Mygind, Anatomy, physiology and function of the nasal cavities in health and disease, Adv. Drug Deliv. Rev. 29 (1998) 3–12.
[21] F. Erdo, L.A. Bors, D. Farkas, A. Bajza, S. Gizurarson, Evaluation of intranasal delivery route of drug administration for brain targeting, Brain Res. Bull. 143 (2018) 155–170.
[22] K. Selvaraj, K. Gowthamarajan, V. Karri, Nose to brain transport pathways an overview: potential of nanostructured lipid carriers in nose to brain targeting, Artif. Cells Nanomed. Biotechnol. 46 (2018) 2088–2095.
[23] J.J. Lochhead, R.G. Thorne, Intranasal delivery of biologics to the central nervous system, Adv. Drug Deliv. Rev. 64 (2012) 614–628.
[24] D.S. Quintana, G.A. Alvares, I.B. Hickie, A.J. Guastella, Do delivery routes of intranasally administered oxytocin account for observed effects on social cognition and behavior? A two-level model, Neurosci. Biobehav. Rev. 49 (2015) 182–192.
[25] D. Kou, Y. Gao, C. Li, D. Zhou, K. Lu, N. Wang, R. Zhang, Z. Yang, Y. Zhou, L. Chen, J. Ge, J. Zeng, M. Gao, Intranasal pathway for nanoparticles to enter the central nervous system, Nano Lett. 23 (2023) 5381–5390.
[26] F.W. Merkus, J.C. Verhoef, N.G. Schipper, E. Marttin, Nasal mucociliary clearance as a factor in nasal drug delivery, Adv. Drug Deliv. Rev. 29 (1998) 13–38.
[27] R.J. Hewitt, C.M. Lloyd, Regulation of immune responses by the airway epithelial cell landscape, Nat. Rev. Immunol. 21 (2021) 347–362.
[28] J.M. Creeth, Constituents of mucus and their separation, Br. Med. Bull. 34 (1978) 17–24.
[29] F. Taherali, F. Varum, A.W. Basit, A slippery slope: on the origin, role and physiology of mucus, Adv. Drug Deliv. Rev. 124 (2018) 16–33.
[30] R. Bansil, E. Stanley, J.T. LaMont, Mucin biophysics, Annu. Rev. Physiol. 57 (1995) 635–657.
[31] J. Dekker, J.W. Rossen, H.A. Buller, A.W. Einerhand, The MUC family: an obituary, Trends Biochem. Sci. 27 (2002) 126–131.
[32] B.J. Balin, R.D. Broadwell, M. Salcman, M. El-Kalliny, Avenues for entry of peripherally administered protein to the central nervous system in mouse, rat, and squirrel monkey, J. Comp. Neurol. 251 (1986) 260–280.
[33] D.J. Selkoe, Treatments for Alzheimer's disease emerge, Science 373 (2021) 624–626.
[34] F. Leng, P. Edison, Neuroinflammation and microglial activation in Alzheimer disease: where do we go from here? Nat. Rev. Neurol. 17 (2021) 157–172.
[35] S. Ruan, Y. Zhou, X. Jiang, H. Gao, Rethinking CRITID procedure of brain targeting drug delivery: circulation, blood brain barrier recognition, intracellular transport, diseased cell targeting, internalization, and drug release, Adv. Sci. (Weinh) 8 (2021) 2004025.
[36] R. Pietrowsky, C. Struben, M. Molle, H.L. Fehm, J. Born, Brain potential changes after intranasal vs. intravenous administration of vasopressin: evidence for a direct nose-brain pathway for peptide effects in humans, Biol. Psychiatry 39 (1996) 332–340.

[37] I. Derad, K. Willeke, R. Pietrowsky, J. Born, H.L. Fehm, Intranasal angiotensin II directly influences central nervous regulation of blood pressure, Am. J. Hypertens. 11 (1998) 971–977.
[38] S. Hanif, P. Muhammad, R. Chesworth, F.U. Rehman, R.-J. Qian, M. Zheng, B.-Y. Shi, Nanomedicine-based immunotherapy for central nervous system disorders, Acta Pharmacol. Sin. 41 (2020) 936–953.
[39] P.J. Gawne, M. Ferreira, M. Papaluca, J. Grimm, P. Decuzzi, New opportunities and old challenges in the clinical translation of nanotheranostics, Nat. Rev. Mater. (2023) 1–16.
[40] E. Nance, S.H. Pun, R. Saigal, D.L. Sellers, Drug delivery to the central nervous system, Nat. Rev. Mater. 7 (2022) 314–331.
[41] S. Bahadur, K. Pathak, Buffered nanoemulsion for nose to brain delivery of ziprasidone hydrochloride: preformulation and pharmacodynamic evaluation, Curr. Drug Deliv. 9 (2012) 596–607.
[42] A.O. Choi, D.J.P.N. Maysinger, Intranasal fluorescent nanocrystals for longitudinal in vivo evaluation of cerebral microlesions, Pharm. Nanotechnol. 1 (2013) 93–104.
[43] R. Bansil, B.S. Turner, The biology of mucus: composition, synthesis and organization, Adv. Drug Deliv. Rev. 124 (2018) 3–15.
[44] C. Werlang, G. Carcarmo-Oyarce, K. Ribbeck, Engineering mucus to study and influence the microbiome, Nat. Rev. Mater. 4 (2019) 134–145.
[45] F. Mohebichamkhorami, M. Faizi, M. Mahmoudifard, A. Hajikarim-Hamedani, S. S. Mohseni, A. Heidari, Y. Ghane, M. Khoramjouy, M. Khayati, R. Ghasemi, H. Zali, S. Hosseinzadeh, E. Mostafavi, Microfluidic synthesis of ultrasmall chitosan/graphene quantum dots particles for intranasal delivery in Alzheimer's disease treatment, Small 19 (2023) e2207626.
[46] S. Ahmad, I. Khan, J. Pandit, N.A. Emad, S. Bano, K.I. Dar, M.M.A. Rizvi, M. D. Ansari, M. Aqil, Y. Sultana, Brain targeted delivery of carmustine using chitosan coated nanoparticles via nasal route for glioblastoma treatment, Int. J. Biol. Macromol. 221 (2022) 435–445.
[47] S. Kaur, P. Manhas, A. Swami, R. Bhandari, K.K. Sharma, R. Jain, R. Kumar, S. K. Pandey, A. Kuhad, R.K. Sharma, N. Wangoo, Bioengineered PLGA-chitosan nanoparticles for brain targeted intranasal delivery of antiepileptic TRH analogues, Chem. Eng. J. 346 (2018) 630–639.
[48] Y. Tan, Y. Liu, Y. Liu, R. Ma, J. Luo, H. Hong, X. Chen, S. Wang, C. Liu, Y. Zhang, T. Chen, Rational design of thermosensitive hydrogel to deliver nanocrystals with intranasal administration for brain targeting in Parkinson's disease, Research (Wash D C) 2021 (2021) 9812523.
[49] H.K. Dhaliwal, Y. Fan, J. Kim, M.M. Amiji, Intranasal delivery and transfection of mRNA therapeutics in the brain using cationic liposomes, Mol. Pharm. 17 (2020) 1996–2005.
[50] B. Sipos, I. Csoka, M. Budai-Szucs, G. Kozma, D. Berkesi, Z. Konya, G.T. Balogh, G. Katona, Development of dexamethasone-loaded mixed polymeric micelles for nasal delivery, Eur. J. Pharm. Sci. 166 (2021) 105960.
[51] M.Q. Le, R. Carpentier, I. Lantier, C. Ducournau, I. Dimier-Poisson, D. Betbeder, Residence time and uptake of porous and cationic maltodextrin-based nanoparticles in the nasal mucosa: comparison with anionic and cationic nanoparticles, Int. J. Pharm. 550 (2018) 316–324.
[52] A. Mahmood, M. Lanthaler, F. Laffleur, C.W. Huck, A. Bernkop-Schnurch, Thiolated chitosan micelles: highly mucoadhesive drug carriers, Carbohydr. Polym. 167 (2017) 250–258.
[53] M. Prabaharan, S.J.C.P. Gong, Novel thiolated carboxymethyl chitosan-g-β-cyclodextrin as mucoadhesive hydrophobic drug delivery carriers, Carbohydr. Polym. 73 (2008) 117–125.
[54] T. Nema, A. Jain, A. Jain, S. Shilpi, A. Gulbake, P. Hurkat, S.K. Jain, Insulin delivery through nasal route using thiolated microspheres, Drug Deliv. 20 (2013) 210–215.
[55] S. Al Harthi, S.E. Alavi, M.A. Radwan, M.M. El Khatib, I.A. AlSarra, Nasal delivery of donepezil HCl-loaded hydrogels for the treatment of Alzheimer's disease, Sci. Rep. 9 (2019) 9563.
[56] Z. Wen, Z. Yan, K. Hu, Z. Pang, X. Cheng, L. Guo, Q. Zhang, X. Jiang, L. Fang, R. Lai, Odorranalectin-conjugated nanoparticles: preparation, brain delivery and pharmacodynamic study on Parkinson's disease following intranasal administration, J. Control. Release 151 (2011) 131–138.
[57] X. Gao, J. Chen, W. Tao, J. Zhu, Q. Zhang, H. Chen, X. Jiang, UEA I-bearing nanoparticles for brain delivery following intranasal administration, Int. J. Pharm. 340 (2007) 207–215.
[58] X. Gao, W. Tao, W. Lu, Q. Zhang, Y. Zhang, X. Jiang, S. Fu, Lectin-conjugated PEG-PLA nanoparticles: preparation and brain delivery after intranasal administration, Biomaterials 27 (2006) 3482–3490.
[59] Y. Su, B. Sun, X. Gao, X. Dong, L. Fu, Y. Zhang, Z. Li, Y. Wang, H. Jiang, B. Han, Intranasal delivery of targeted nanoparticles loaded with miR-132 to brain for the treatment of neurodegenerative diseases, Front. Pharmacol. 11 (2020) 1165.
[60] P.I. Chater, M.D. Wilcox, J.P. Pearson, Efficacy and safety concerns over the use of mucus modulating agents for drug delivery using nanoscale systems, Adv. Drug Deliv. Rev. 124 (2018) 184–192.
[61] L.M. Ensign, C. Schneider, J.S. Suk, R. Cone, J. Hanes, Mucus penetrating nanoparticles: biophysical tool and method of drug and gene delivery, Adv. Mater. 24 (2012) 3887–3894.
[62] L. Wu, W. Shan, Z. Zhang, Y. Huang, Engineering nanomaterials to overcome the mucosal barrier by modulating surface properties, Adv. Drug Deliv. Rev. 124 (2018) 150–163.
[63] L.M. Ensign, B.C. Tang, Y.Y. Wang, T.A. Tse, T. Hoen, R. Cone, J. Hanes, Mucus-penetrating nanoparticles for vaginal drug delivery protect against herpes simplex virus, Sci. Transl. Med. 4 (2012), 138ra179.
[64] Y.Y. Wang, S.K. Lai, J.S. Suk, A. Pace, R. Cone, J. Hanes, Addressing the PEG mucoadhesivity paradox to engineer nanoparticles that "slip" through the human mucus barrier, Angew. Chem. Int. Ed. Eng. 47 (2008) 9726–9729.
[65] K. Maisel, M. Reddy, Q. Xu, S. Chattopadhyay, R. Cone, L.M. Ensign, J. Hanes, Nanoparticles coated with high molecular weight PEG penetrate mucus and provide uniform vaginal and colorectal distribution in vivo, Nanomedicine (London) 11 (2016) 1337–1343.
[66] A. Popov, E. Enlow, J. Bourassa, H. Chen, Mucus-penetrating nanoparticles made with "mucoadhesive" poly(vinyl alcohol), Nanomedicine 12 (2016) 1863–1871.
[67] T. Kurano, T. Kanazawa, A. Ooba, Y. Masuyama, N. Maruhana, M. Yamada, S. Iioka, H. Ibaraki, Y. Kosuge, H. Kondo, T. Suzuki, Nose-to-brain/spinal cord delivery kinetics of liposomes with different surface properties, J. Control. Release 344 (2022) 225–234.
[68] R.A. Cone, Barrier properties of mucus, Adv. Drug Deliv. Rev. 61 (2009) 75–85.
[69] S.S. Hu, Z.X. Yang, S. Wang, L.P. Wang, Q.Q. He, H. Tang, P. Ji, T. Chen, Zwitterionic polydopamine modified nanoparticles as an efficient nanoplatform to overcome both the mucus and epithelial barriers, Chem. Eng. J. 428 (2022) 132107.
[70] M. Zhang, X. Chen, C. Li, X. Shen, Charge-reversal nanocarriers: an emerging paradigm for smart cancer nanomedicine, J. Control. Release 319 (2020) 46–62.
[71] C. Menzel, A. Bernkop-Schnurch, Enzyme decorated drug carriers: targeted swords to cleave and overcome the mucus barrier, Adv. Drug Deliv. Rev. 124 (2018) 164–174.
[72] T. Matsuyama, T. Morita, Y. Horikiri, H. Yamahara, H. Yoshino, Improved nasal absorption of salmon calcitonin by powdery formulation with N-acetyl-L-cysteine as a mucolytic agent, J. Control. Release 115 (2006) 183–188.
[73] P.D. Dobson, D.B. Kell, Carrier-mediated cellular uptake of pharmaceutical drugs: an exception or the rule? Nat. Rev. Drug Discov. 7 (2008) 205–220.
[74] K. Sugano, M. Kansy, P. Artursson, A. Avdeef, S. Bendels, L. Di, G.F. Ecker, B. Faller, H. Fischer, G. Gerebtzoff, H. Lennernaes, F. Senner, Coexistence of passive and carrier-mediated processes in drug transport, Nat. Rev. Drug Discov. 9 (2010) 597–614.
[75] J. Zimmerberg, K. Gawrisch, The physical chemistry of biological membranes, Nat. Chem. Biol. 2 (2006) 564–567.
[76] G. Guidotti, L. Brambilla, D. Rossi, Cell-penetrating peptides: from basic research to clinics, Trends Pharmacol. Sci. 38 (2017) 406–424.
[77] T. Lin, E. Liu, H. He, M.C. Shin, C. Moon, V.C. Yang, Y. Huang, Nose-to-brain delivery of macromolecules mediated by cell-penetrating peptides, Acta Pharm. Sin. B 6 (2016) 352–358.
[78] X. Yang, X. Chen, T. Lei, L. Qin, Y. Zhou, C. Hu, Q. Liu, H. Gao, The construction of in vitro nasal cavity-mimic M-cell model, design of M cell-targeting nanoparticles and evaluation of mucosal vaccination by nasal administration, Acta Pharm. Sin. B 10 (2020) 1094–1105.
[79] N. Kamei, M. Takeda-Morishita, Brain delivery of insulin boosted by intranasal coadministration with cell-penetrating peptides, J. Control. Release 197 (2015) 105–110.
[80] E. Samaridou, H. Walgrave, E. Salta, D.M. Alvarez, V. Castro-Lopez, M. Loza, M. J. Alonso, Nose-to-brain delivery of enveloped RNA - cell permeating peptide nanocomplexes for the treatment of neurodegenerative diseases, Biomaterials 230 (2020) 119657.
[81] Y. Yang, X. Zhang, S. Wu, R. Zhang, B. Zhou, X. Zhang, L. Tang, Y. Tian, K. Men, L. Yang, Enhanced nose-to-brain delivery of siRNA using hyaluronan-enveloped nanomicelles for glioma therapy, J. Control. Release 342 (2022) 66–80.
[82] Y. Kim, S. Hwang, R. Khalmuratova, S. Kang, M. Lee, Y. Song, J.W. Park, J. Yu, H. W. Shin, Y. Lee, Alpha-helical cell-penetrating peptide-mediated nasal delivery of resveratrol for inhibition of epithelial-to-mesenchymal transition, J. Control. Release 317 (2020) 181–194.
[83] T. Akita, R. Kimura, S. Akaguma, M. Nagai, Y. Nakao, M. Tsugane, H. Suzuki, J. I. Oka, C. Yamashita, Usefulness of cell-penetrating peptides and penetration accelerating sequence for nose-to-brain delivery of glucagon-like peptide-2, J. Control. Release 335 (2021) 575–583.
[84] J.A. Habeshaw, D. Bailey, A.G. Stansfeld, M.F. Greaves, The cellular content of non Hodgkin lymphomas: a comprehensive analysis using monoclonal antibodies and other surface marker techniques, Br. J. Cancer 47 (1983) 327–351.
[85] S. Sato, S. Liu, A. Goto, T. Yoneyama, K. Okita, S. Yamamoto, H. Hirabayashi, S. Iwasaki, H. Kusuhara, Advanced translational PBPK model for transferrin receptor-mediated drug delivery to the brain, J. Control. Release 357 (2023) 379–393.
[86] B. Gabold, F. Adams, S. Brameyer, K. Jung, C.L. Ried, T. Merdan, O.M. Merkel, Transferrin-modified chitosan nanoparticles for targeted nose-to-brain delivery of proteins, Drug Deliv. Transl. Res. 13 (2023) 822–838.
[87] A.O. Elzoghby, M.A. Abdelmoneem, I.A. Hassanin, M.M. Abd Elwakil, M. A. Elnaggar, S. Mokhtar, J.Y. Fang, K.A. Elkhodairy, Lactoferrin, a multi-functional glycoprotein: active therapeutic, drug nanocarrier & targeting ligand, Biomaterials 263 (2020) 120355.
[88] Z. Liu, M. Jiang, T. Kang, D. Miao, G. Gu, Q. Song, L. Yao, Q. Hu, Y. Tu, Z. Pang, H. Chen, X. Jiang, X. Gao, J. Chen, Lactoferrin-modified PEG-co-PCL nanoparticles for enhanced brain delivery of NAP peptide following intranasal administration, Biomaterials 34 (2013) 3870–3881.
[89] Q. Meng, A. Wang, H. Hua, Y. Jiang, Y. Wang, H. Mu, Z. Wu, K. Sun, Intranasal delivery of Huperzine A to the brain using lactoferrin-conjugated N-trimethylated chitosan surface-modified PLGA nanoparticles for treatment of Alzheimer's disease, Int. J. Nanomedicine 13 (2018) 705–718.
[90] J. Brunner, S. Ragupathy, G. Borchard, Target specific tight junction modulators, Adv. Drug Deliv. Rev. 171 (2021) 266–288.

[91] I. Ramirez-Velez, B. Belardi, Storming the gate: new approaches for targeting the dynamic tight junction for improved drug delivery, Adv. Drug Deliv. Rev. 199 (2023) 114905.
[92] C. Zihni, C. Mills, K. Matter, M.S. Balda, Tight junctions: from simple barriers to multifunctional molecular gates, Nat. Rev. Mol. Cell Biol. 17 (2016) 564–580.
[93] M. Li, M. Zhao, Y. Fu, Y. Li, T. Gong, Z. Zhang, X. Sun, Enhanced intranasal delivery of mRNA vaccine by overcoming the nasal epithelial barrier via intra- and paracellular pathways, J. Control. Release 228 (2016) 9–19.
[94] J.W. Wheless, I. Miller, R.E. Hogan, D. Dlugos, V. Biton, G.D. Cascino, M. R. Sperling, K. Liow, B. Vazquez, E.B. Segal, D. Tarquinio, W. Mauney, J. Desai, A. L. Rabinowicz, E. Carrazana, D.S. Group, Final results from a phase 3, long-term, open-label, repeat-dose safety study of diazepam nasal spray for seizure clusters in patients with epilepsy, Epilepsia 62 (2021) 2485–2495.
[95] T. Zhang, M. Li, X. Han, G. Nie, A. Zheng, Effect of different absorption enhancers on the nasal absorption of nalmefene hydrochloride, AAPS PharmSciTech 23 (2022) 143.
[96] P. Yu, X. Zhang, G.H. Cheng, H.Z. Guo, X.E. Shi, X.L. Zhang, J. Zhou, S. Wang, Z. G. Wu, J. Chang, Construction of a new multifunctional insomnia drug delivery system, Chem. Eng. J. 430 (2022) 132633.
[97] N. Shashikanth, M.M. France, R. Xiao, X. Haest, H.E. Rizzo, J. Yeste, J. Reiner, J. R. Turner, Tight junction channel regulation by interclaudin interference, Nat. Commun. 13 (2022) 3780.
[98] A.J. Vecchio, S.S. Rathnayake, R.M. Stroud, Structural basis for *Clostridium perfringens* enterotoxin targeting of claudins at tight junctions in mammalian gut, Proc. Natl. Acad. Sci. U. S. A. 118 (2021).
[99] J. Ali, M. Ali, S. Baboota, J.K. Sahani, C. Ramassamy, L. Dao, Bhavna, Potential of nanoparticulate drug delivery systems by intranasal administration, Curr. Pharm. Des. 16 (2010) 1644–1653.
[100] E. Willems, M. Dedobbeleer, M. Digregorio, A. Lombard, N. Goffart, P. N. Lumapat, J. Lambert, P. Van den Ackerveken, M. Szpakowska, A. Chevigne, F. Scholtes, B. Rogister, Aurora A plays a dual role in migration and survival of human glioblastoma cells according to the CXCL12 concentration, Oncogene 38 (2019) 73–87.
[101] K. Wang, U.S. Kumar, N. Sadeghipour, T.F. Massoud, R. Paulmurugan, A microfluidics-based scalable approach to generate extracellular vesicles with enhanced therapeutic MicroRNA loading for intranasal delivery to mouse glioblastomas, ACS Nano 15 (2021) 18327–18346.
[102] B.W. Day, B.W. Stringer, F. Al-Ejeh, M.J. Ting, J. Wilson, K.S. Ensbey, P. R. Jamieson, Z.C. Bruce, Y.C. Lim, C. Offenhauser, S. Charmsaz, L.T. Cooper, J. K. Ellacott, A. Harding, L. Leveque, P. Inglis, S. Allan, D.G. Walker, M. Lackmann, G. Osborne, K.K. Khanna, B.A. Reynolds, J.D. Lickliter, A.W. Boyd, EphA3 maintains tumorigenicity and is a therapeutic target in glioblastoma multiforme, Cancer Cell 23 (2013) 238–248.
[103] L. Wang, S. Tang, Y. Yu, Y. Lv, A. Wang, X. Yan, N. Li, C. Sha, K. Sun, Y. Li, Intranasal delivery of temozolomide-conjugated gold nanoparticles functionalized with anti-EphA3 for glioblastoma targeting, Mol. Pharm. 18 (2021) 915–927.
[104] S. Wang, Y. Yu, A. Wang, X. Duan, Y. Sun, L. Wang, L. Chu, Y. Lv, N. Cui, X. Fan, C. Sha, L. Xu, K. Sun, Temozolomide hexadecyl ester targeted plga nanoparticles for drug-resistant glioblastoma therapy via intranasal administration, Front. Pharmacol. 13 (2022) 965789.
[105] X. Ma, M. Huang, M. Zheng, C. Dai, Q. Song, Q. Zhang, Q. Li, X. Gu, H. Chen, G. Jiang, Y. Yu, X. Liu, S. Li, G. Wang, H. Chen, L. Lu, X. Gao, ADSCs-derived extracellular vesicles alleviate neuronal damage, promote neurogenesis and rescue memory loss in mice with Alzheimer's disease, J. Control. Release 327 (2020) 688–702.
[106] N. Perets, O. Betzer, R. Shapira, S. Brenstein, A. Angel, T. Sadan, U. Ashery, R. Popovtzer, D. Offen, Golden exosomes selectively target brain pathologies in neurodegenerative and neurodevelopmental disorders, Nano Lett. 19 (2019) 3422–3431.
[107] X. Xie, Q. Song, C. Dai, S. Cui, R. Tang, S. Li, J. Chang, P. Li, J. Wang, J. Li, C. Gao, H. Chen, S. Chen, R. Ren, X. Gao, G. Wang, Clinical safety and efficacy of allogenic human adipose mesenchymal stromal cells-derived exosomes in patients with mild to moderate Alzheimer's disease: a phase I/II clinical trial, Gen. Psychiatry 36 (2023) e101143.
[108] L.L. Cai, C.Y. Yang, W.F. Jia, Y.W. Liu, R. Xie, T. Lei, Z.H. Yang, X.Q. He, R. S. Tong, H.L. Gao, Endo/lysosome-escapable delivery depot for improving BBB transcytosis and neuron targeted therapy of Alzheimer's disease, Adv. Funct. Mater. 30 (2020) 1909999.
[109] X. He, X. Wang, L. Yang, Z. Yang, W. Yu, Y. Wang, R. Liu, M. Chen, H. Gao, Intelligent lesion blood-brain barrier targeting nano-missiles for Alzheimer's disease treatment by anti-neuroinflammation and neuroprotection, Acta Pharm. Sin. B 12 (2022) 1987–1999.
[110] Q. Huang, C. Jiang, X. Xia, Y. Wang, C. Yan, X. Wang, T. Lei, X. Yang, W. Yang, G. Cheng, H. Gao, Pathological BBB crossing melanin-like nanoparticles as metal-ion chelators and neuroinflammation regulators against Alzheimer's disease, Research (Wash D C) 6 (2023) 0180.
[111] H. Yang, W. Mu, D. Wei, Y. Zhang, Y. Duan, J.X. Gao, X.Q. Gong, H.J. Wang, X. L. Wu, H. Tao, J. Chang, A novel targeted and high-efficiency nanosystem for combinational therapy for Alzheimer's disease, Adv. Sci. (Weinh) 7 (2020) 1902906.
[112] F.M. Platt, Emptying the stores: lysosomal diseases and therapeutic strategies, Nat. Rev. Drug Discov. 17 (2018) 133–150.
[113] D.A. Wolf, L.R. Hanson, E.L. Aronovich, Z. Nan, W.C. Low, W.H. Frey 2nd, R. S. McIvor, Lysosomal enzyme can bypass the blood-brain barrier and reach the CNS following intranasal administration, Mol. Genet. Metab. 106 (2012) 131–134.
[114] W. Tong, C.A. Dwyer, B.E. Thacker, C.A. Glass, J.R. Brown, K. Hamill, K. W. Moremen, S. Sarrazin, P. Gordts, L.E. Dozier, G.N. Patrick, Y. Tor, J.D. Esko, Guanidinylated neomycin conjugation enhances intranasal enzyme replacement in the brain, Mol. Ther. 25 (2017) 2743–2752.
[115] Y. Dou, C. Li, L. Li, J. Guo, J. Zhang, Bioresponsive drug delivery systems for the treatment of inflammatory diseases, J. Control. Release 327 (2020) 641–666.
[116] X.Y. Xiao, Y. Gao, S.S. Liu, M.J. Wang, M. Zhong, J.W. Wang, N. Jiang, Q.L. Peng, A "nano-courier" for precise delivery of acetylcholine and melatonin by C5a-targeted aptamers effectively attenuates reperfusion injury of ischemic stroke, Adv. Funct. Mater. 33 (2023) 2213633.
[117] D. Furtado, M. Bjornmalm, S. Ayton, A.I. Bush, K. Kempe, F. Caruso, Overcoming the blood-brain barrier: the role of nanomaterials in treating neurological diseases, Adv. Mater. 30 (2018) e1801362.
[118] T. Lei, Z. Yang, X. Xia, Y. Chen, X. Yang, R. Xie, F. Tong, X. Wang, H. Gao, A nanocleaner specifically penetrates the blood–brain barrier at lesions to clean toxic proteins and regulate inflammation in Alzheimer's disease, Acta Pharm. Sin. B 11 (2021) 4032–4044.
[119] C. Cheignon, M. Tomas, D. Bonnefont-Rousselot, P. Faller, C. Hureau, F. Collin, Oxidative stress and the amyloid beta peptide in Alzheimer's disease, Redox Biol. 14 (2018) 450–464.
[120] Y. Liu, M. Nguyen, A. Robert, B. Meunier, Metal ions in Alzheimer's disease: a key role or not? Acc. Chem. Res. 52 (2019) 2026–2035.
[121] Z. Jia, R. Tang, X. Yuan, H. Zhu, J. Guo, Y. Chen, Y. Yang, B. Liang, S. Lu, D. Cao, J. Liu, Multifunctional supramolecular vesicles as Zn(2+) -triggered microglial modulator alleviates Alzheimer's disease, Small 19 (2023) e2302176.
[122] W.C. Ballance, E.C. Qin, H.J. Chung, M.U. Gillette, H. Kong, Reactive oxygen species-responsive drug delivery systems for the treatment of neurodegenerative diseases, Biomaterials 217 (2019) 119292.
[123] Y. Lu, A.A. Aimetti, R. Langer, Z.J.N.R.M. Gu, Bioresponsive materials, Nat. Rev. Mater. 2 (2016) 1–17.
[124] J. Xu, X. Wang, H. Yin, X. Cao, Q. Hu, W. Lv, Q. Xu, Z. Gu, H. Xin, Sequentially site-specific delivery of thrombolytics and neuroprotectant for enhanced treatment of ischemic stroke, ACS Nano 13 (2019) 8577–8588.
[125] T.S. Salameh, K.M. Bullock, I.A. Hujoel, M.L. Niehoff, T. Wolden-Hanson, J. Kim, J.E. Morley, S.A. Farr, W.A. Banks, Central nervous system delivery of intranasal insulin: mechanisms of uptake and effects on cognition, J. Alzheimers Dis. 47 (2015) 715–728.
[126] R. Crisler, N.A. Johnston, C. Sivula, C.L. Budelsky, Functional anatomy and physiology, in: The Laboratory Rat, Elsevier, 2020, pp. 91–132.
[127] M.I. Priester, T.L.M. Ten Hagen, Image-guided drug delivery in nanosystem-based cancer therapies, Adv. Drug Deliv. Rev. 192 (2023) 114621.
[128] C. Xie, J. Liao, N. Zhang, Y. Sun, Y. Li, L. Xiong, Y. Zhang, X. Liu, W. Su, H.J.C.C. L. Chen, Advanced nano drug delivery systems for neuroprotection against ischemic stroke, Chin. Chem. Lett. (2023) 109149.
[129] R. Liu, C. Luo, Z. Pang, J. Zhang, S. Ruan, M. Wu, L. Wang, T. Sun, N. Li, L.J.C.C. L. Han, Advances of nanoparticles as drug delivery systems for disease diagnosis and treatment, Chin. Chem. Lett. 34 (2023) 107518.
[130] Y. Jiang, X.T. Pan, T. Yu, H. Wang, Intranasal administration nanosystems for brain-targeted drug delivery, Nano Res 16 (2023) 13077–13099.
[131] Y. Tian, Z. Zheng, X. Wang, S. Liu, L. Gu, J. Mu, X. Zheng, Y. Li, S. Shen, Establishment and evaluation of glucose-modified nanocomposite liposomes for the treatment of cerebral malaria, J. Nanobiotechnol. 20 (2022) 318.
[132] A. Zafar, O. Awad Alsaidan, N.K. Alruwaili, S. Sarim Imam, M. Yasir, K. Saad Alharbi, L. Singh, M. Muqtader Ahmed, Formulation of intranasal surface engineered nanostructured lipid carriers of rotigotine: full factorial design optimization, in vitro characterization, and pharmacokinetic evaluation, Int. J. Pharm. 627 (2022) 122232.
[133] Y.Z. Zhao, M. Lin, Q. Lin, W. Yang, X.C. Yu, F.R. Tian, K.L. Mao, J.J. Yang, C.T. Lu, H.L. Wong, Intranasal delivery of bFGF with nanoliposomes enhances in vivo neuroprotection and neural injury recovery in a rodent stroke model, J. Control. Release 224 (2016) 165–175.
[134] G.L. See, F. Arce Jr., S. Dahlizar, A. Okada, M. Fadli, I. Hijikuro, S. Itakura, M. Katakura, H. Todo, K. Sugibayashi, Enhanced nose-to-brain delivery of tranilast using liquid crystal formulations, J. Control. Release 325 (2020) 1–9.
[135] X. Shen, Z. Cui, Y. Wei, Y. Huo, D. Yu, X. Zhang, S. Mao, Exploring the potential to enhance drug distribution in the brain subregion via intranasal delivery of nanoemulsion in combination with borneol as a guider, Asian J. Pharm. Sci. 18 (2023) 100778.
[136] Y. Lee, J. Ha, M. Kim, S. Kang, M. Kang, M. Lee, Antisense-oligonucleotide co-micelles with tumor targeting peptides elicit therapeutic effects by inhibiting microRNA-21 in the glioblastoma animal models, J. Adv. Res. 53 (2023) 249–260.
[137] M.E. Navas Guimaraes, R. Lopez-Blanco, J. Correa, M. Fernandez-Villamarin, M. B. Bistue, P. Martino-Adami, L. Morelli, V. Kumar, M.F. Wempe, A.C. Cuello, E. Fernandez-Megia, M.A. Bruno, Liver X receptor activation with an intranasal polymer therapeutic prevents cognitive decline without altering lipid levels, ACS Nano 15 (2021) 4678–4687.
[138] T. Kanazawa, H. Taki, H. Okada, Nose-to-brain drug delivery system with ligand/cell-penetrating peptide-modified polymeric nano-micelles for intracerebral gliomas, Eur. J. Pharm. Biopharm. 152 (2020) 85–94.
[139] L. Wang, L. Xu, J. Du, X. Zhao, M. Liu, J. Feng, K. Hu, Nose-to-brain delivery of borneol modified tanshinone IIA nanoparticles in prevention of cerebral ischemia/reperfusion injury, Drug Deliv. 28 (2021) 1363–1375.

[140] L.F. Gonzalez, E. Acuna, G. Arellano, P. Morales, P. Sotomayor, F. Oyarzun-Ampuero, R. Naves, Intranasal delivery of interferon-beta-loaded nanoparticles induces control of neuroinflammation in a preclinical model of multiple sclerosis: a promising simple, effective, non-invasive, and low-cost therapy, J. Control. Release 331 (2021) 443–459.
[141] E. Muntimadugu, R. Dhommati, A. Jain, V.G. Challa, M. Shaheen, W. Khan, Intranasal delivery of nanoparticle encapsulated tarenflurbil: a potential brain targeting strategy for Alzheimer's disease, Eur. J. Pharm. Sci. 92 (2016) 224–234.
[142] J. Ha, M. Kim, Y. Lee, M. Lee, Intranasal delivery of self-assembled nanoparticles of therapeutic peptides and antagomirs elicits anti-tumor effects in an intracranial glioblastoma model, Nanoscale 13 (2021) 14745–14759.
[143] X. Zhou, X. Deng, M. Liu, M. He, W. Long, Z. Xu, K. Zhang, T. Liu, K.F. So, Q.L. Fu, L. Zhou, Intranasal delivery of BDNF-loaded small extracellular vesicles for cerebral ischemia therapy, J. Control. Release 357 (2023) 1–19.
[144] M. Kim, Y. Lee, M. Lee, Hypoxia-specific anti-RAGE exosomes for nose-to-brain delivery of anti-miR-181a oligonucleotide in an ischemic stroke model, Nanoscale 13 (2021) 14166–14178.
[145] D. Xu, Y.R. Lu, N. Kou, M.J. Hu, Q.S. Wang, Y.L. Cui, Intranasal delivery of icariin via a nanogel-thermoresponsive hydrogel compound system to improve its antidepressant-like activity, Int. J. Pharm. 586 (2020) 119550.
[146] Y. Dou, D. Zhao, F. Yang, Y. Tang, J. Chang, Natural phyto-antioxidant albumin nanoagents to treat advanced Alzheimer's disease, ACS Appl. Mater. Interfaces 13 (2021) 30373–30382.
[147] S. Gupta, A. Perla, A. Roy, J.G. Vitore, B. K, S. Salave, D. Rana, A. Sharma, R. Rathod, H. Kumar, D. Benival, In vivo evaluation of almotriptan malate formulation through intranasal route for the treatment of migraine: systematic development and pharmacokinetic assessment, AAPS PharmSciTech 24 (2023) 32.
[148] Y. Lu, J.T. Wang, N. Li, X. Zhu, Y. Li, S. Bansal, Y. Wang, K.T. Al-Jamal, Intranasal administration of edaravone nanoparticles improves its stability and brain bioavailability, J. Control. Release 359 (2023) 257–267.
[149] A. Reif, I. Bitter, J. Buyze, K. Cebulla, R. Frey, D.J. Fu, T. Ito, Y. Kambarov, P. M. Llorca, A.J. Oliveira-Maia, T. Messer, S. Mulhern-Haughey, B. Rive, C. von Holt, A.H. Young, Y. Godinov, E.-T. Investigators, Esketamine nasal spray versus quetiapine for treatment-resistant depression, N. Engl. J. Med. 389 (2023) 1298–1309.
[150] S. Han, J.T. Wang, E. Yavuz, A. Zam, N. Rouatbi, R.N. Utami, R. Liam-Or, A. Griffiths, W. Dickson, J. Sosabowski, K.T. Al-Jamal, Spatiotemporal tracking of gold nanorods after intranasal administration for brain targeting, J. Control. Release 357 (2023) 606–619.
[151] S. Zha, K.L. Wong, A.H. All, Intranasal delivery of functionalized polymeric nanomaterials to the brain, Adv. Healthc. Mater. 11 (2022) e2102610.