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REVIEW

Brain Delivery Strategies for Biomacromolecular Drugs: Intranasal Administration

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Abstract: Macromolecular Drugs (including monoclonal antibodies, recombinant proteins, and nucleic acid therapies) have become a cornerstone strategy for intervening in complex pathological mechanisms such as cancer, autoimmune diseases, and genetic disorders due to their high specificity for disease targets and low off-target toxicity. However, compared to traditional small-molecule drugs, the high molecular weight (>10 kDa) and structural complexity of macromolecular drugs result in extremely low transmembrane permeability. This is particularly challenging in the treatment of central nervous system (CNS) diseases, where the blood-brain barrier (BBB) imposes stringent selectivity, further limiting drug delivery efficiency. This review focuses on the breakthrough strategy of nose-to-brain (NtB) drug delivery. On one hand, the NtB pathway bypasses the BBB, enabling direct CNS drug delivery. On the other hand, nanocarrier technology can synergistically achieve systemic delivery and brain-targeted transport. Based on the latest research advances, this article systematically examines the feasibility of delivering macromolecular drugs via NtB administration. We comprehensively summarize relevant delivery carriers and discuss the potential advantages of intranasal-brain delivery for CNS disease treatment. Notably, while significant progress has been made in this field, further exploration is still needed regarding the mechanisms of NtB delivery and challenges in clinical translation.

Keywords: macromolecular drugs, BBB, central nervous system disorders, nanocarriers, intranasal administration

Introduction

At this stage, the hot topic in the field of pharmaceutical technology is how to improve the bioavailability of drugs and achieve a more convenient and faster treatment method based on a balance between toxicity and therapeutic effect of drugs.[1] As a result, a number of biomolecular drugs prepared from biomaterials, including proteins, monoclonal antibodies, peptides, nucleic acids, vaccines, etc., have gained widespread interest because of their highly effective specificity.[2] Macromolecular drugs are commonly employed in the diagnosis and treatment of tumors, immune disorders, cardiovascular diseases, and particularly central nervous system (CNS) diseases. Biomolecular drugs are often used in the diagnosis and treatment of tumors, immune diseases and cardiovascular diseases. Today, biomolecular drugs have become one of the most promising directions in drug development.[3] To date, a variety of delivery methods for macromolecular drugs exist, such as oral, injection, intranasal, etc., and a variety of drug dosage forms are available. The compilation of macromolecular drugs that have entered clinical trials is summarized in Table 1.

Although macromolecular drugs have made great strides and are playing an increasingly important role in the treatment of disease, there are still many difficulties and obstacles to their in vivo delivery.[41] For example, large molecule drugs are very unstable, easily degraded by proteases in vivo, difficult to isolate and purify, complex in form, immunogenic and difficult to cross the barrier in vivo.[42] The blood-brain barrier (BBB) and blood-cerebrospinal fluid barrier (BCSFB) play crucial roles in segregating the CNS from the peripheral system by preventing the entry of foreign substances, including toxins and bioactive

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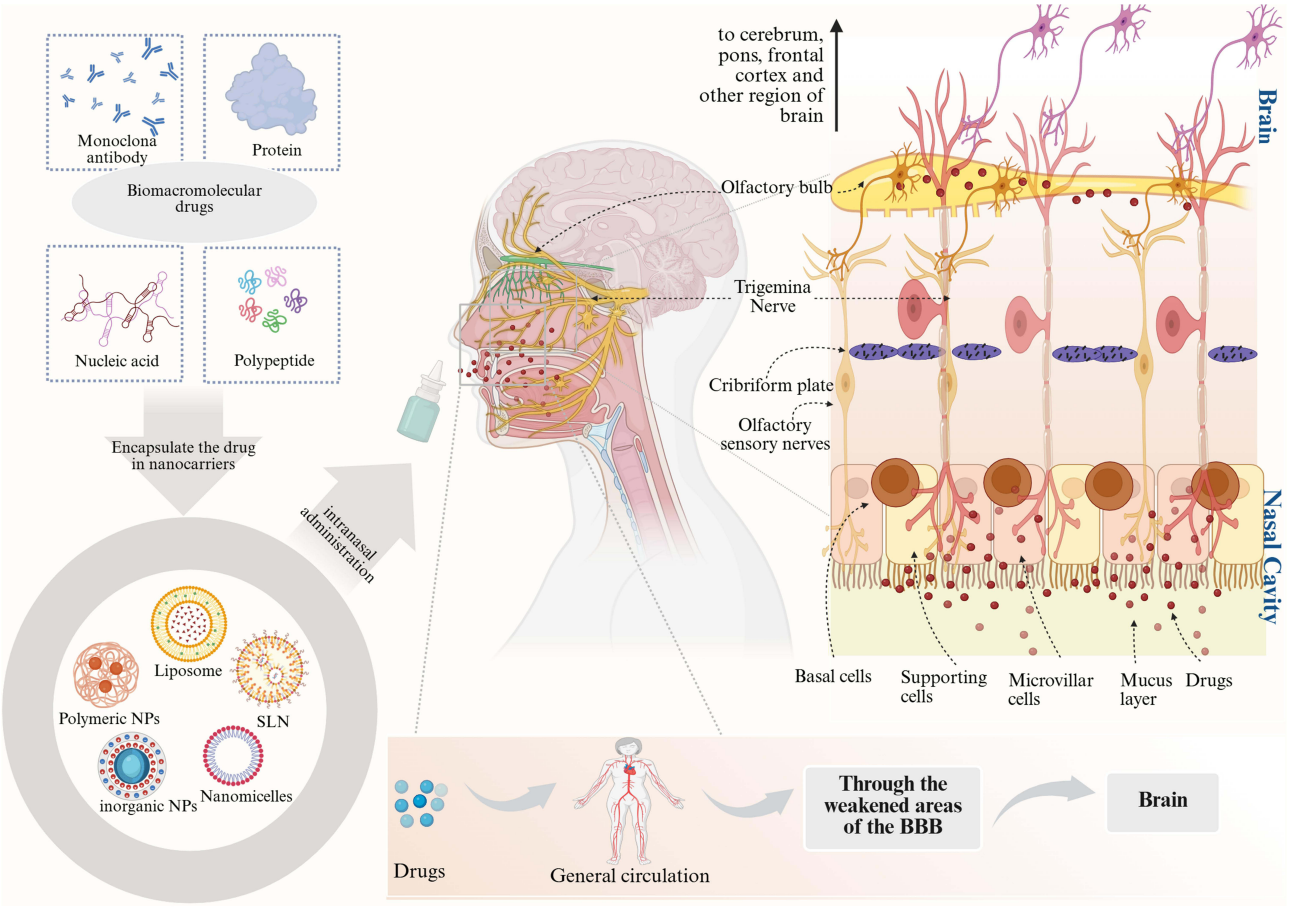
Graphical Abstract



drugs.[43] Generally, small molecules with molecular weights below 500 Da can traverse the BBB via paracellular or transcellular pathways.[44] However, approximately 98% of macromolecules fail to cross this barrier, creating significant challenges for targeted CNS delivery of biologics such as monoclonal antibodies and nucleic acid-based therapeutics. Invasive techniques such as intracerebral injection may be unsuitable for chronic patients requiring long-term treatment, particularly elderly populations.[45] Consequently, strategies bypassing the BBB for targeted drug delivery have become critically important. Notably, intranasal administration has emerged as a highly promising alternative approach, offering a non-invasive NtB delivery route.[46] Some studies have suggested that nasal administration may be an effective way to address the low bioavailability of large molecule biopharmaceuticals.[47–49] In addition, the use of nanomaterials to load macromolecular drugs inside the nasal cavity would further improve drug absorption.[50–52] In this review we will discuss the advantages of nasal delivery of macromolecules and the use of nanocarriers in the nasal delivery of macromolecules for the treatment of CNS diseases.

Barriers to the Delivery of Biomacromolecular Drugs in vivo

The Gastrointestinal Barrier

Oral administration is the most common and convenient route for drug delivery in daily medical practice. However, the gastrointestinal tract (GIT) presents a significant barrier to the effective delivery of certain biomacromolecular drugs.[53] Since the first attempts to administer insulin orally in humans in the last century, the oral administration of large molecules has not been promising.[54] Although a number of biomolecule drugs have made it to market, their bioavailability remains low.[55] The gastrointestinal system, comprising the mouth, esophagus, stomach, small intestine, and colon, harbors a complex milieu of

Table 1 Biomolecule Drugs Already on the Market, Includes Three Modes of Administration and Different Pharmacological Effects

Administration Route	Drug Name (Trade Name)	Category	Indications	Ref.
Injection administration	Trastuzumab (Herceptin)	Monoclonal Antibodies	HER2-positive cancer	[4–7]
	Adalimumab (Humira)		Autoimmune diseases such as rheumatoid arthritis and psoriasis	[8–10]
	Pembrolizumab (Keytruda)		Used for the treatment of multiple types of cancers	[11–13]
	Rituximab (MabThera)		Hematological malignancies autoimmune disorders	[14,15]
	Bevacizumab (Avastin)		Used for the treatment of multiple types of cancers	[16–19]
	Nivolumab (Opdivo)			[20–23]
	Infliximab (Remicade)		Crohn's disease Ulcerative colitis	[24,25]
	Ranibizumab (Lucentis)		Age-related macular degeneration (AMD)	[26]
	Aflibercept (Eylea)		AMD	[27]
	Lecanemab (Leqembi)		Early Alzheimer's Disease(EAD)	[28]
	Omalizumab (Xolair)		Idiopathic angioedema Food Allergies	[29,30]
	Denosumab (Xgeva)		Osteoporosis Bone Metastases from Solid Tumors	[31,32]
	Interferon (Pegasys)	Recombinant protein	Hepatitis	[33]
	Insulin (Humalog, Lantus)		Diabetes	[34]
	Imiglucerase (Cerezyme)	Enzyme replacement therapy	Gaucher's disease	[35]
	Agalsidase (Fabrazyme)		Fabry disease	[36]
Oral administration	Semaglutide (Rybelsus)	Peptides	Type 2 diabetes mellitus(T2DM) Obesity	[37,38]
Intranasal administration	Insulin (Afrezza)	Protein	Diabetes	[39]
	Pulmozyme	DNase	Cystic fibrosis	[40]

tens of thousands of microorganisms and various enzymes. This environment poses significant hurdles to the successful delivery of macromolecules orally. The presence of digestive enzymes and low pH in the stomach can degrade biomolecules, while the mucosal epithelium of the intestine presents a formidable barrier to their absorption[56] (Figure 1). Additionally, the GI tract's immune system and the presence of efflux transporters further limit the bioavailability of orally administered biomolecules.

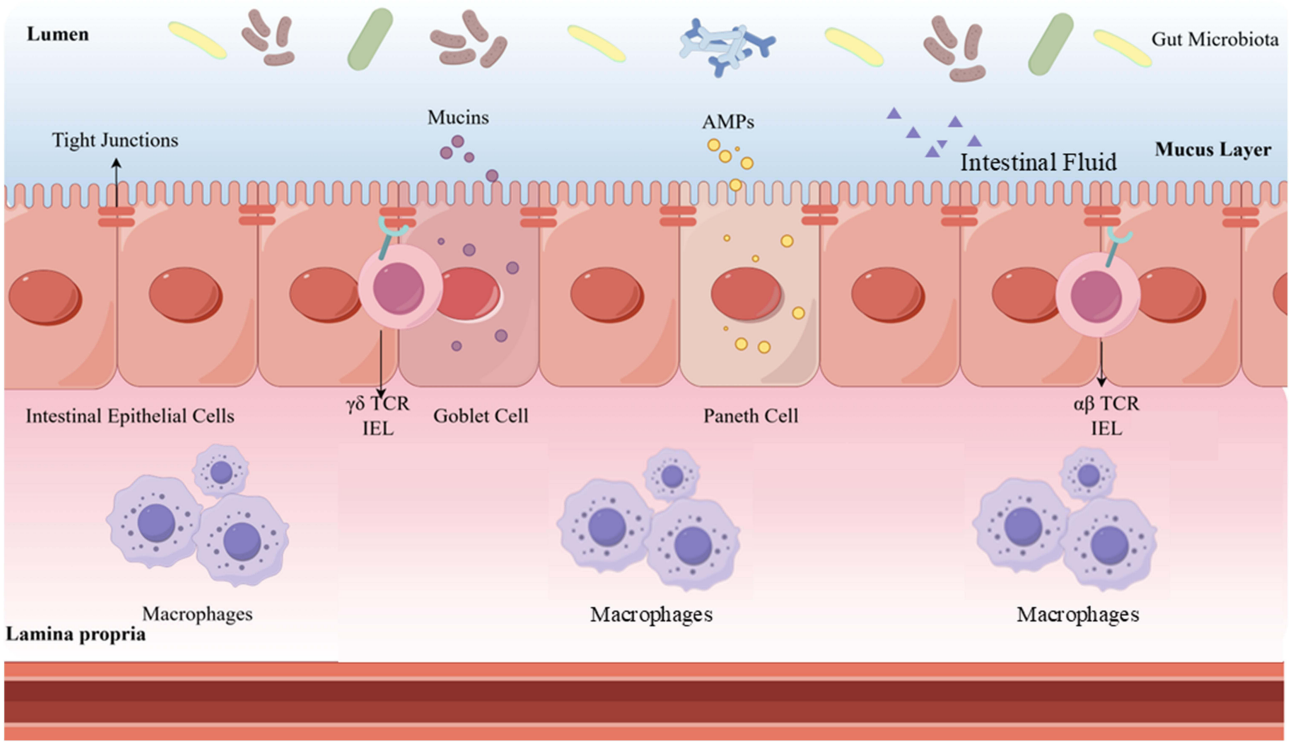


Figure 1 Schematic diagram of the intestinal barrier.The intestinal microflora constitutes a biological barrier through competitive rejection and production of antimicrobial substances; the intestinal mucosal epithelium, which is intact and closely connected to each other, constitutes a mechanical barrier; the intestinal mucosal epithelium secretes mucus and digestive juices to constitute a chemical barrier; and the intestinal mucosal lymphoid tissues and immune cells constitute an immune barrier. Created by Figdraw.

The most significant difficulty encountered in the oral administration of macromolecules is the problem of stability; drugs are easily degraded by acidic and alkaline environments and by metabolic enzymes abundant in the GIT. To ensure the stability of the drug, it is essential to know the pH of the GIT, which varies throughout the digestive tract during the digestion of the drug[57] (Figure 2). The range spans roughly 1 to 8, and changing pH values can cause structural changes in biomolecule drugs (α-helix, β-folding, etc)., as well as ionisation of some amino acids, resulting in a substantial decrease in the stability of the drug.[58] In particular, high acidity in the stomach leads to protein defolding, exposing more motifs that can be recognised

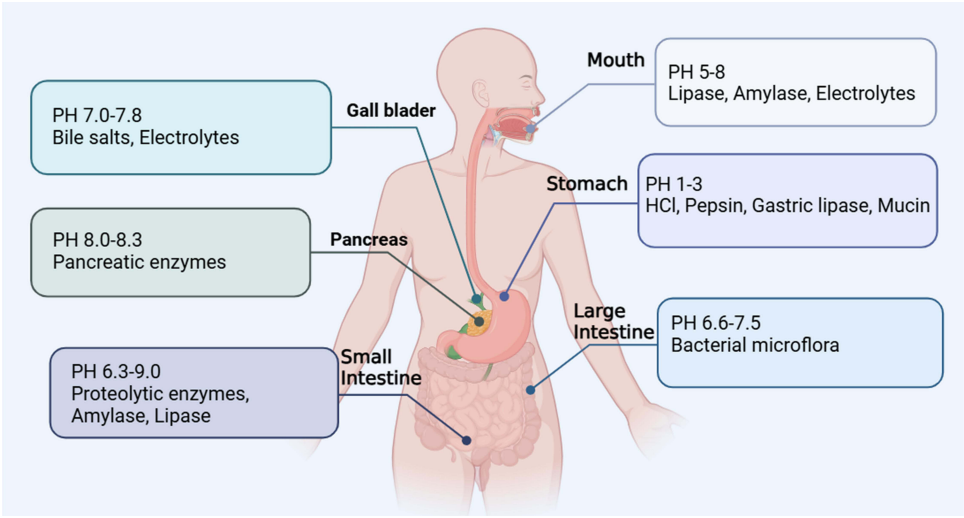


Figure 2 Schematic representation of the different pH values of the digestive tract. Created in BioRender. Wu, H. (2025) https://BioRender.com/wb4kzlh.

by degradative enzymes.[55] A variety of digestive enzymes in the GIT, such as pepsin, chymotrypsin, trypsin and bile salts, cleave proteins and nucleic acids into fragments causing degradation of macromolecular drugs. Even if these impediments are safely circumvented, the mucosal layer covering the entire GIT prevents the entry of large particulate matters.[59,60]

The Blood-Brain Barrier

Injectable administration of biomolecules, while effectively bypassing the challenges posed by the GIT, faces a significant barrier in the form of the BBB. This barrier is highly selective, restricting the passage of most biomolecules into the brain. Therefore, despite their therapeutic potential, many biomolecules administered via injection are unable to reach the brain in sufficient quantities to exert their desired effects. The BBB was first discovered back in the 20th century, Paul Ehrlich and his students, while staining animal organs by injecting water-soluble dyes into the peripheral circulation, found that staining failed in the brain and cerebrospinal fluid, and then injected dyes directly into the cerebrospinal fluid only to find that only the brain and spinal cord were stained.[61] It was not until the invention of the scanning electron microscope (SEM) that the membrane barrier was truly observed.[62] The BBB is situated at the microvascular level within the brain and comprises five essential components that together form a sophisticated barrier[63] (Figure 3). These components include pericytes, astrocytes, neurons, basement membranes, and connecting complexes. Functioning as a dynamic gateway, this neurovascular unit exerts dual regulatory effects: establishing physicochemical exclusion of neurotoxic compounds through transendothelial resistance modulation, while orchestrating carrier-mediated translocation of neurotrophic factors. Of particular significance is the astroglial compartment, whose perivascular endfeet not only provide structural reinforcement but also dynamically regulate barrier permeability via calcium-dependent signaling cascades. One of their key functions is to provide nutrients and metabolic support to

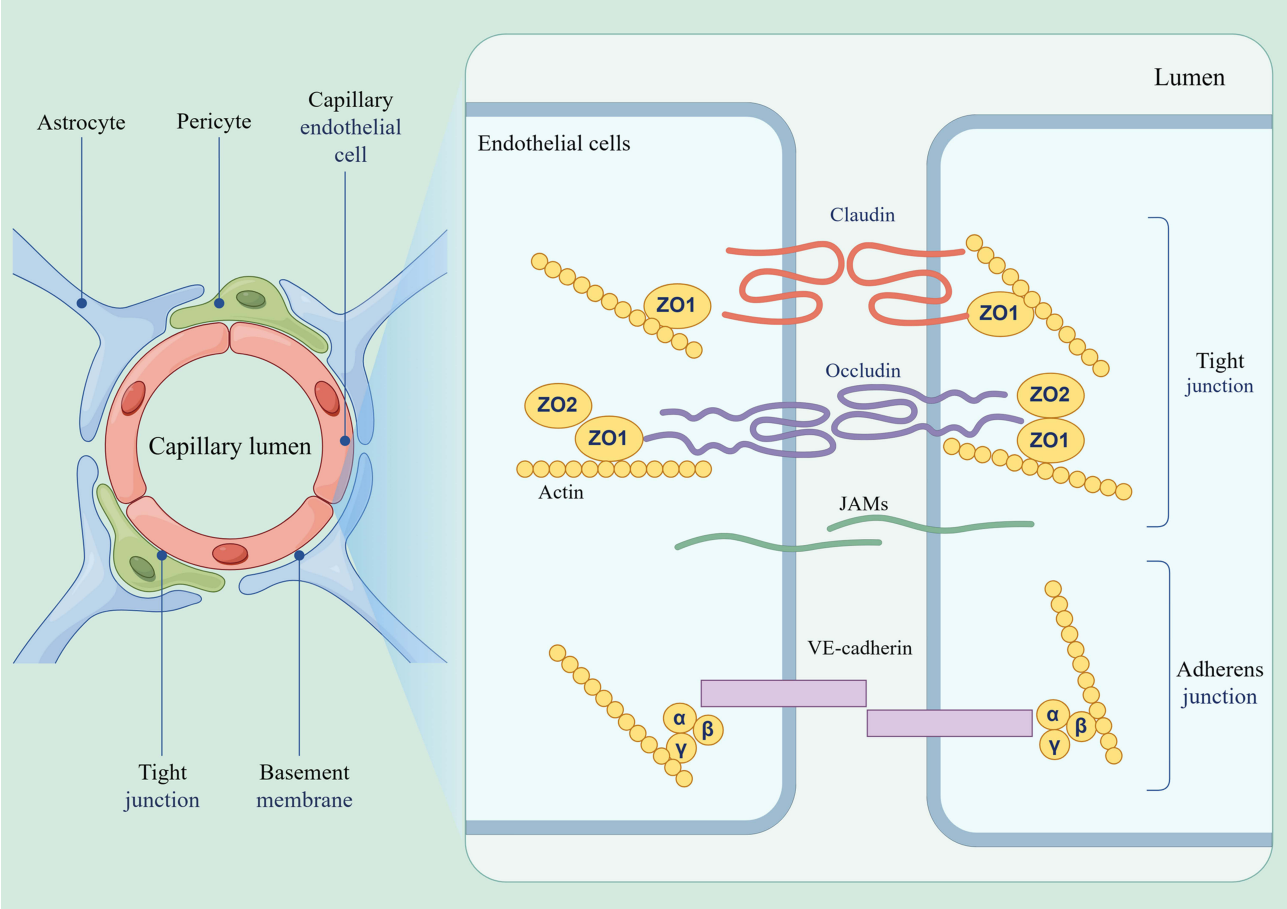


Figure 3 Components of the blood-brain barrier and its internal structure. Created by Figdraw.

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neurons, ensuring their proper functioning and health. These star-shaped glial cells provide essential support to neurons and help regulate the microenvironment of the brain.[61] Additionally, astrocytes are involved in the regulation of the extracellular environment, helping to maintain the balance of ions and neurotransmitters. By actively participating in the BBB, astrocytes contribute to protecting the brain from potentially harmful substances circulating in the bloodstream, thus preserving the delicate neural environment and safeguarding against damage. More importantly, the efflux transport system of the BBB represents another critical mechanism limiting drug penetration into the CNS, primarily mediated by the ATP-binding cassette (ABC) transporter superfamily. These transporters utilize energy derived from ATP hydrolysis to actively pump xenobiotics (eg, therapeutic drugs and toxins) from brain parenchyma back into the bloodstream, thereby maintaining homeostasis of the cerebral microenvironment.[64–66]

The operational principle of this neuroprotective system inherently restricts macromolecular translocation across the blood-CNS interface. Functioning as a dynamic filtration barrier, the BBB establishes stringent molecular sieving through polarized efflux transporters and tight junction complexes. Structural analyses reveal that transcellular permeation is thermodynamically favored only for low-mass lipophilic compounds,[67] creating substantial pharmacokinetic challenges for most neurotherapeutics requiring cerebral bioavailability. The selective permeability of the BBB poses a major pharmacological challenge for CNS-targeted drug development, as the majority of therapeutic compounds fail to achieve sufficient penetration. Consequently, overcoming the BBB remains one of the most critical hurdles in the development of efficacious neurological therapies. Direct CNS delivery methods, including intracerebral, intracerebroventricular, and intrathecal injections or infusions, can circumvent the BBB and facilitate drug distribution within the brain parenchyma. However, these invasive techniques necessitate administration by specialized medical personnel and are associated with elevated risks of infection. Moreover, they are clinically impractical for chronic treatments requiring sustained drug delivery.

The Potential Solution

Drug delivery systems (DDS) enhance drug efficacy by incorporating therapeutic agents with optimized carriers (eg, nanoparticles, NPs).[68] The fundamental principle of DDS involves the strategic combination of drugs with tailored carrier materials. Critical parameters for effective delivery systems comprise:[1] attaining therapeutic concentrations at target sites, and[2] maintaining controlled, sustained release profiles within designated timeframes.[69] Recent advancements in nanotechnology have established NPs as promising drug carriers, demonstrating unique advantages derived from their nanoscale dimensions:[1] Enhanced surface properties enabling superior drug loading capacity,[2] Improved barrier penetration facilitating efficient transport across biological membranes. These distinctive characteristics underscore the significant potential of NPs in biomedical applications.[70] In recent decades, researchers have developed various innovative approaches to enhance drug delivery to the brain. Compared to conventional methods that directly compromise BBB integrity, biologically-inspired engineering of drug carriers enables precise targeting of specific BBB receptors for non-invasive brain delivery.[71] Growing evidence supports the feasibility of NtB delivery, with numerous macromolecular peptides and proteins demonstrating superior efficacy via intranasal administration compared to intravenous injection.[72] This creates a pivotal opportunity for macromolecular NtB delivery. Research demonstrates that peptide or protein drugs administered intranasally can elicit distinct therapeutic effects. Notably, multiple clinical studies have confirmed that intranasal insulin improves cognitive function in patients with Alzheimer's (AD) and Parkinson's diseases (PD).[73,74] The NtB route offers unique advantages:[1] ease of administration;[2] pharmacokinetic superiority;[3] central targeting specificity;[41] formulation versatility. These characteristics make it particularly suitable for delivering macromolecular therapeutics like proteins and peptides, as will be elaborated in subsequent sections.

Physiology of the Nasal Cavity and Nasal Drug Delivery

Human Nasal Anatomy

The nasal structures of humans and rats are different, with the rat's nasal cavity being more complex, so only the human nasal structure will be briefly described here. Specific differences are presented in Table 2. The nose is one of the smallest organs in the human body, with a length of about 12–14 cm, a volume of 13 mL and a total surface area of up to 160 cm^2.[75] The nasal cavity spans from the external nares to the nasopharynx, featuring three bony projections (superior, middle, and inferior

Table 2 Differences in the Structure of the Nasal Cavity Between Man and Other Experimental Animals

Species	Mean Nasal Surface Area (cm^2)	Mean Nasal Cavity Volume (mL)	Conchae Structure
Mouse	2.8	0.03	Double scroll
Rat	14	0.4	Double scroll
Rabbit	61	6	Branched conchae
Human	160	14	Single scroll

conchae) that define its lateral architecture. A midline septal partition creates bilateral chambers, comprising three functional zones: vestibular, respiratory, and olfactory regions.[76] The nasal vestibule occupies the anterior aspect of the nasal cavity, characterized by limited surface area and low permeability. Its dense mucus secretion and vibrissae filtration system constitute the primary immunological barrier against airborne pathogens.[77]

Olfactory Region

The olfactory region occupies the superior nasal cavity, positioned dorsal to the superior concha, and comprises approximately 10% of the total human nasal epithelial surface area.[75] This region consists of pseudostratified columnar epithelium lining the superior nasal cavity, primarily mediating olfactory signal transduction.[78] The olfactory region contains olfactory sensory neurons (OSNs), the sole primary neurons in this area. These neurons feature ciliated dendritic terminals that project through the mucus layer, establishing direct contact with the external environment.[79] The olfactory cilia of OSNs contain specialized olfactory receptors. Odorant molecules readily interact with these receptors within the olfactory epithelium's mucus layer, initiating olfactory transduction. The olfactory epithelium additionally comprises multiple cell types, including sustentacular cells, basal cells, and microvillar cells.[80] They have irregular microvilli and the secreted serous can be used as solvents for odor molecules.

Respiratory Region

In contrast, the respiratory region constitutes the predominant surface area within the nasal cavity, encompassing approximately 80–90% of the total nasal mucosa. This region exhibits a tripartite anatomical organization:[81] the superior turbinate, the middle turbinate and the inferior turbinate, which cause turbulence through the nasal passage, increasing contact between the mucosa and the inhaled air. The nasal mucosa can remove particles, microbes and allergens, warm and humidify the air inhaled.[82] This region comprises a stratified organization of epithelial cells, basement membrane, and lamina propria. The respiratory epithelium features approximately 300 microvilli per cell, with extensive vascularization that enhances surface area and facilitates systemic drug absorption.[83] The respiratory epithelium (ciliated pseudostratified columnar epithelium) comprises four principal cellular components: goblet cells, ciliated and non-ciliated columnar cells, and basal cells. Notably, basal cells are exclusively localized to the basement membrane, functioning as defensive elements that mediate epithelial repair.[84] Goblet cells are responsible for secreting mucin and closely connect with the other two kinds of cells between epithelial cells to prevent hydrophilic particles from spreading freely through the paracellular transport pathway.[85] The lamina propria, situated superior to the respiratory epithelium, facilitates drug absorption through its rich vascular and neural networks. Notably, trigeminal nerve innervation extends throughout the nasal epithelial lining.

The Nasal-CNS Neural Pathways

Advantages of Nasal Delivery

Nasal drug delivery provides numerous advantages compared to other administration routes. The nasal mucosa boasts a large surface area, which, coupled with its rich vascularization, enables efficient drug absorption. This route also offers rapid systemic delivery due to the abundant blood vessels in the submucosal layer, leading to faster drug onset compared to oral

administration.[86,87] Topical administration of drugs through the nasal route is highly effective. Nasal sprays and drops are well-established for treating inflammation or congestion. Specifically, hydrophobic or low molecular weight drugs are particularly suitable for topical nasal applications due to their ability to easily penetrate the nasal mucosa and achieve therapeutic concentrations locally.

Additionally, direct site administration of drugs can necessitate lower doses than systemic administration, which not only reduces the risk of side effects but also provides faster relief of disease symptoms. Topical nasal delivery significantly reduces sedative effects commonly observed with oral antihistamines, thereby improving therapeutic adherence. This route offers dual pharmacokinetic advantages: circumvention of hepatic first-pass metabolism prevents gastrointestinal and hepatic complications, while minimizing systemic drug exposure. Furthermore, low molecular weight lipophilic agents readily undergo transcellular absorption, achieving systemic distribution via vascular or lymphatic pathways.[88]

BBB presents a formidable obstacle for most neurotherapeutics, severely limiting drug penetration into the CNS. Intranasal delivery circumvents this barrier through two principal pathways: the olfactory and trigeminal routes. Notably, following respiratory deposition, select compounds undergo axonal transport via trigeminal nerve branches, facilitating direct delivery to brainstem and other CNS regions through receptor-mediated endocytotic mechanisms.[89] A greater proportion of drugs are delivered to the brain via the olfactory region, and the olfactory pathway has three different modes of transport: Drugs can be internalised in or transported within neurons; can be transported out of cells through gaps between cells, (especially along pathways near the olfactory nerve); can be transported across cells through the basal epithelium.[90] For CNS administration, from the nasal cavity to the brain is the simplest and easiest way to achieve[91] (Figure 4).

The Olfactory Pathway

The olfactory pathway comprises specialized cellular components, notably OSNs accompanied by sustentacular and progenitor basal cells.[77] Olfactory receptor neurons are unique in that they originate from the nasal olfactory epithelium and extend specialized hair-like structures called cilia into the mucus lining the nasal cavity. OSNs transduce airborne odorant molecules into neural impulses, which propagate axonally to the olfactory bulb (OB) for central odor processing. Sustentacular cells maintain neuronal structural integrity and metabolic homeostasis, while resident basal stem cells ensure lifelong neurogenesis. Pharmacologic agents undergo transneuronal transport via this pathway, migrating from nasal epithelium to OB. From there, it progresses to the olfactory cortex, which is responsible for processing olfactory information. Finally, the drug enters the CNS, specifically reaching the cerebrum and cerebellum. This unique pathway offers a direct route for drugs to access the brain, bypassing the BBB and potentially enhancing therapeutic effects for CNS disorders.[93] However, this method has the disadvantage of a relatively slow transduction time due to the complex process of neuronal signaling and transmission. Additionally, drugs may also be transported outside the nerve pathway. For example, drugs can traverse the

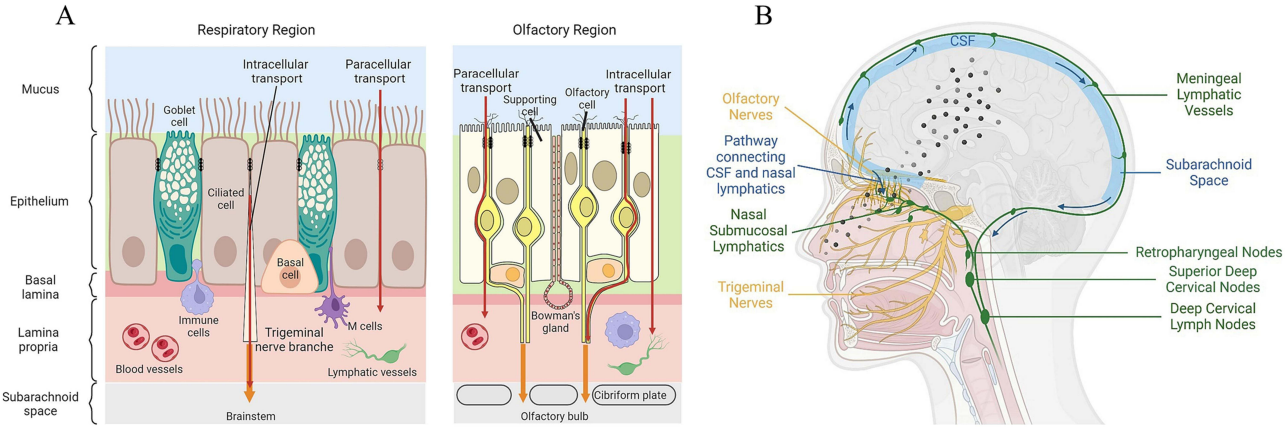

Figure 4 Diagram of the uptake mechanism of the nasal epithelium for NtB delivery and schematic diagram of the NtB delivery pathway. (**A**) Schematic diagram of the anatomy of the nasal epithelium and the main pathways across this barrier. (**B**) Anatomical diagram of the NtB delivery pathway, mainly including the trigeminal nerve pathway and the olfactory nerve pathway. Reprinted from Adv Drug Deliv Rev, 207, Chen Y, Zhang C, Huang Y, et al. Intranasal drug delivery: the interaction between nanoparticles and the nose-to-brain pathway, 115196, Copyright 2024, with permission from Elsevier.[92]

olfactory mucosa through various mechanisms, including diffusion through the intercellular spaces of the epithelial cells or by being carried along with the supporting cells as they migrate toward the surface of the epithelium.[94]

The Trigeminal Pathway

The trigeminal nerve, representing the most extensive cranial neural pathway, comprises three principal divisions: ophthalmic, maxillary, and mandibular. These axonal projections synapse at the trigeminal ganglion—a pivotal relay nucleus mediating connectivity between peripheral sensory inputs and central brainstem nuclei.[95] The maxillary and ophthalmic divisions of the trigeminal nerve form direct neuroanatomical conduits between nasal mucosa and the CNS. This pathway mediates both somatosensory transduction and potential neurotherapeutic delivery, bypassing conventional BBB restrictions.[96] The drug can travel along the respiratory epithelium, gaining access to the trigeminal nerve and ultimately reaching the brainstem. This route presents a unique opportunity for drugs to bypass the BBB and directly target the CNS.[97] An animal study investigated the potential of intranasally administered insulin-like growth factor-I (IGF-I) to enter the CNS and its related transport mechanisms.[98] The results showed that after intranasal and intravenous administration in different groups of rats, the concentration of [125I]-IGF-I in central nervous tissues was significantly higher with intranasal delivery compared to intravenous injection. Specifically, in the OB, the intranasal concentration (3.43±0.53 nM) was approximately 880 times higher than the intravenous concentration (0.0039±0.0002 nM), demonstrating that intranasal administration can effectively bypass the BBB to deliver IGF-I to the CNS.[98] Furthermore, the investigation demonstrated that intranasal IGF-I predominantly accesses the CNS via dual neural pathways: the olfactory and trigeminal systems.[98] These results empirically validate this pathway's utility for CNS-targeted therapeutic delivery.

The Systemic Pathway

After intranasal administration, drugs are absorbed by the nasal mucosal capillaries and enter systemic circulation, distributing throughout the body.[99] However, to reach the CNS, drugs must cross the highly selective BBB,[99] which presents a significant challenge as it restricts the passage of many neurotherapeutic molecules.[100] Consequently, this reduces treatment efficacy and limits the quantity of drugs that can effectively reach the brainstem.[99]

Drug Absorption Barrier

Nevertheless, multiple physiological variables within the nasal cavity modulate drug delivery efficacy. Nasal hemodynamics, enzymatic degradation, mucociliary clearance efficiency, and mucosal integrity collectively determine the pharmacokinetic profile of intranasally administered therapeutics.[101] The extensive vascularization of the nasal cavity serves dual physiological functions: thermohumidification of inspired air and mucosal perfusion. This robust circulatory network simultaneously enables efficient systemic drug absorption through enhanced vascular permeability and first-pass metabolism avoidance.[102] Enhanced vascular perfusion facilitates systemic drug absorption and distribution, while nasal mucosal enzymes may compromise pharmaceutical stability.

For instance, aminopeptidases and proteases can degrade peptides and proteins, reducing the effectiveness of these drugs when administered nasally.[103] Furthermore, the nasal mucosa contains endopeptidases like serine and cysteine proteases, which cleave internal peptide bonds, as well as exopeptidases such as aminopeptidases and carboxypeptidases, which respectively cleave N-terminal and C-terminal peptides.[104] These enzymatic activities can degrade peptides and proteins, leading to decreased bioavailability of drugs administered nasally.

The nasal mucus undergoes complete renewal every 10–15 minutes, propelled by ciliary action at 5–6 mm/min to facilitate the clearance of airborne particulates and pathogens.[105,106] Consequently, intranasal drugs exhibit brief residence times, necessitating rapid absorption. Hydrophilic compounds demonstrate particularly slow transmucosal penetration due to mucosal solubility, resulting in accelerated ciliary clearance. Notably, mucociliary clearance efficiency displays regional heterogeneity across nasal subsites.[107] There are fewer cilia in the first half of the nasal cavity, so active drugs can stay here longer. Continuous nasal administration is also a challenge in the cold season. Due to the change of climate, the physiological environment in the nose will also change, so the conditions of drug absorption will change, and it will also affect the effect of drug absorption.[108] In addition, this problem can also be exacerbated by irritation of the nasal mucosa by some other diseases.

Delivery of Macromolecular Drugs by Intranasal Administration

Systemic Drug Delivery

Protein and polypeptide drugs encounter challenges with oral administration due to degradation by gastric acid and barriers in the intestines. Although these therapeutics can be delivered parenterally (intravenously or subcutaneously), hepatic first-pass metabolism persists, significantly reducing systemic bioavailability prior to circulation.[109] Nasal administration offers a more direct route, bypassing the first-pass effect and allowing for rapid drug onset, making it a preferable choice for these types of drugs.[109] The cell-penetrating peptides (CPPs) have shown promise in delivering a variety of bio-pharmaceuticals,[110] which presents a novel approach for intranasal administration of peptides and proteins, offering potential advantages in drug delivery and therapy.[110,111] Research findings indicate that insulin is delivered intranasally using CPPs, it can be absorbed by the nasal mucosa and enter the systemic circulation. This administration method leads to a significant decrease in blood glucose levels in normal mice, suggesting its potential effectiveness in managing glucose levels through non-invasive means.[112] In addition, Nastech Pharmaceutical has developed a rapidly acting intranasal insulin formulation. This new type of intranasal insulin not only has a bioavailability between 17% and 28%, but also has a comparable effect to subcutaneous insulin aspart in controlling postprandial blood glucose levels and is better than conventional treatments. Moreover, after this intranasal insulin enters the human body, it only takes 30 minutes to reach its peak concentration, which is much faster than insulin aspart (90 minutes), indicating that it can take effect more quickly.[113] Various strategies can enhance drug delivery through the nasal route. These include the use of absorption enhancers to improve drug uptake, employing nano-transport systems such as NPs and microspheres for targeted delivery, and incorporating compounds like cyclodextrins and chitosan (CS) to enhance drug stability and bioavailability.[78]

Nasal Brain-Targeted Delivery for the Treatment of Central Nervous System Diseases

An important feature of intranasal administration is the ability to enable drugs to reach the brain directly through the nasal cavity, a phenomenon known as NtB drug delivery. This pathway takes advantage of the anatomical proximity between the nasal mucosa and the brain.[114] By utilizing this pathway, drugs can bypass the blood-brain barrier and enter the brain directly, potentially enhancing the therapeutic effects for nervous system diseases[100] (Figure 5).

Healthcare statistics reveal a rapid increase in the prevalence of CNS disorders worldwide.[115] Conditions like PD, AD, and other neurodegenerative disorders are becoming more prevalent.[116] While current therapeutic strategies have improved patient survival rates, they still face significant challenges in effectively treating and managing these complex disorder.[116] The primary obstacle in treating most CNS disorders is the necessity for drugs to effectively penetrate the BBB to achieve therapeutic levels.[117] Research suggests that approximately 98% of low molecular weight active substances and nearly 100% of large molecules are unable to cross the BBB, resulting in notably low bioavailability at the target site. This significant challenge underscores the urgent need for innovative drug delivery approaches to surmount the BBB and improve treatment outcomes for CNS disorders.[118] Nasal brain administration is a painless, non-invasive method of drug delivery compared to other delivery methods.[119] This route bypasses the BBB, enabling direct cerebral drug delivery. Furthermore, nasal administration avoids first-pass metabolism, typically requiring doses 2–10 times lower than oral regimens.

AD

AD, the predominant form of global dementia,[120] is pathologically characterized by β-amyloid (Aβ) plaque accumulation and neurofibrillary tangles (NFTs) composed of hyperphosphorylated tau proteins.[121] Currently, the treatment of AD primarily relies on pharmacological interventions.[122] Nevertheless, AD therapeutic development encounters substantial obstacles, including dose-limiting toxicity, inadequate BBB penetration to achieve therapeutic drug levels, and prohibitive developmental costs and resource requirements.[122] Small-molecule drugs, such as acetylcholinesterase (AChE) inhibitors and N-methyl-D-aspartate (NMDA) receptor antagonists, have been commercialized and widely used for treatment. However, they often induce gastrointestinal side effects that compromise therapeutic efficacy.[123] Recently developed monoclonal antibodies, such as lecanemab, donanemab, and aducanumab, have shown encouraging clinical trial evidence—achieving >60% clearance of Aβ deposits after 18 months of treatment.[124] Immunotherapy may represent the most advanced therapeutic strategy for AD.[125] However, biologics such as vaccines and antibodies, which are currently administered peripherally, have limited brain penetration, resulting in inefficient drug delivery.[125] Nanocarriers

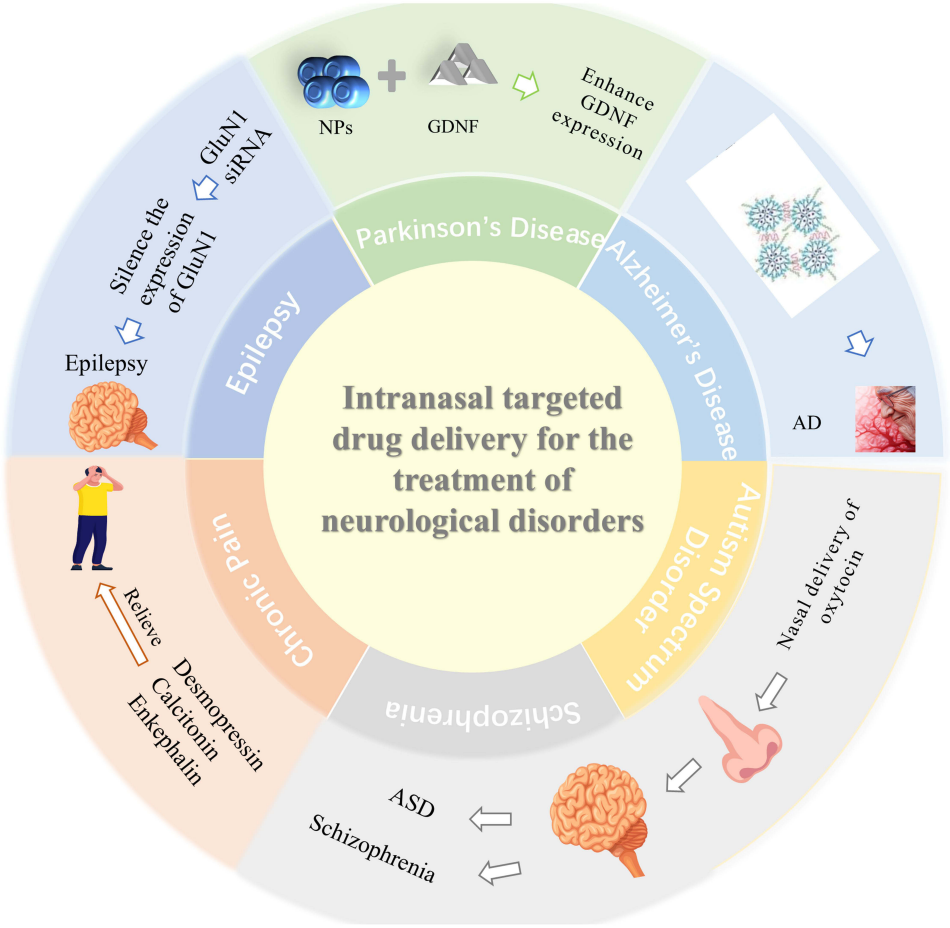

Figure 5 Schematic diagram of intranasal targeted drug delivery for the treatment of various neurological disorders.

administered intranasally play a crucial role in enhancing drug concentration and bioavailability,[122] offering a highly promising alternative therapeutic approach.[123] Gaikwad S et al developed a monoclonal antibody, TTCM2, loaded into micelles (TTCM2-ms). Intranasal delivery of TTCM2-ms effectively targeted pathological tau in mouse brains, clearing pathological tau in aged mice after a single dose, increasing synaptic protein levels, and improving cognition.[126] Additionally, Yang et al developed a multifunctional nanocarrier (Rapa@DAK/siRNA) for AD treatment. This system was constructed by modifying dendrigraft poly-L-lysines (DGLs) with Aleuria aurantia lectin (AAL) and Aβ-binding peptides (KLVFF). Following intranasal administration, it successfully co-delivered small interfering RNA targeting β-site amyloid precursor protein cleaving enzyme-1 (BACE1 siRNA) and rapamycin to the brain. The intranasal route enabled drug delivery via the NtB pathway, with AAL enhancing brain uptake efficiency and KLVFF facilitating Aβ binding and inhibition. The dual release of these agents reduced BACE1 expression, enhanced autophagy, and decreased Aβ deposition, ultimately improving cognition in transgenic AD mice[127] (Figure 6). This combined therapy, integrating gene therapy (siRNA) and pharmacological treatment (rapamycin), may exert synergistic effects through distinct mechanisms of action. It not only provides an effective intranasal delivery strategy for AD treatment but also offers a novel approach for comprehensive disease management.

PD

PD represents the second most prevalent neurodegenerative disorder worldwide and a predominant etiology of neurological impairment.[128] Its core pathological features include the misfolding and aggregation of α-synuclein, forming Lewy bodies and Lewy neurites—neuronal inclusions that lead to cell loss in brain regions such as the substantia nigra and trigger prion-like cell-to-cell propagation.[128] The primary pharmacological treatments for PD rely on small-molecule drugs, including levodopa,

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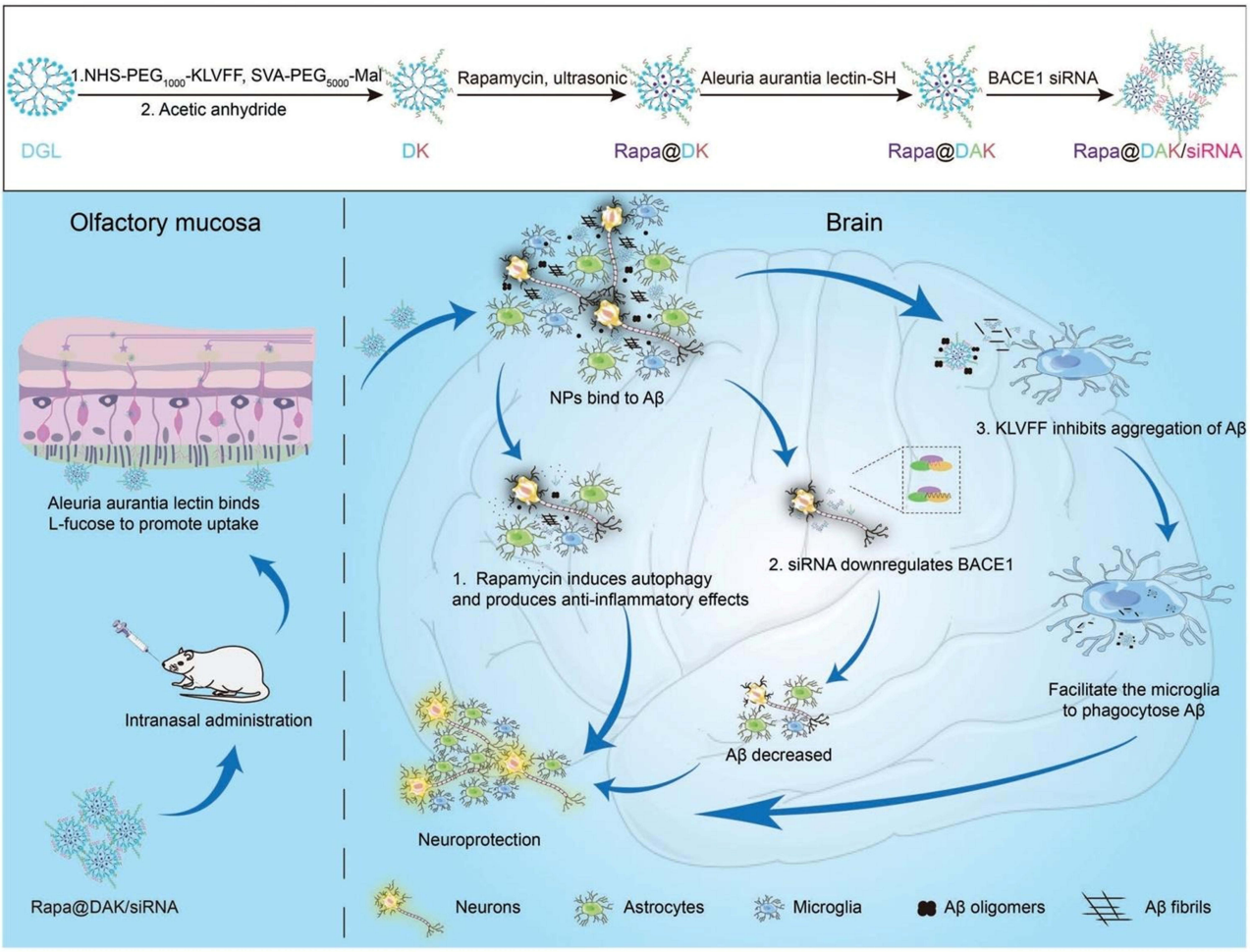

Figure 6 Schematic diagram of Rapa@DAK/siRNA for intranasal administration in the treatment of AD and the possible mechanism of neuroprotection. Reprinted with permission from Yang X, Yang W, Xia X, et al. Intranasal delivery of BACE1 siRNA and rapamycin by dual targets modified nanoparticles for Alzheimer's disease therapy. Small. 2022;18(30):e2203182. © 2022 Wiley-VCH GmbH.[127]

anticholinergics, and antiglutamatergic agents, typically administered orally or via injection.[129] However, these approaches increase systemic exposure risks, often causing diverse complications, and fail to halt disease progression, significantly limiting their therapeutic efficacy.[129] Thus, there is an urgent need to explore novel therapeutics that enhance targeting precision, minimize adverse effects, and delay disease progression. Glial cell-derived neurotrophic factor (GDNF) exhibits potent neurotrophic effects on various neurons, particularly dopaminergic neurons (DANs),[130] making it a promising candidate for alleviating PD symptoms. However, BBB remains a major obstacle hindering the therapeutic efficacy of such macromolecular drugs.[131] An animal study investigated the therapeutic effects of intranasally administered GDNF-loaded extracellular vesicles (EVs) derived from genetically engineered macrophages in PD.[131] In wire-hang and rotarod tests, EV-GDNF treated PD mice showed approximately 4 times longer endurance than saline-treated controls after 12 months of treatment, reaching levels comparable to wild-type (WT) mice, demonstrating effective preservation of motor function. EV-GDNF also significantly improved hyperactive behaviors and anxiety-like symptoms in PD mice ($p<0.05$).[131] This study suggests a promising new intranasal delivery strategy for PD treatment.

Epilepsy

Epilepsy is a common neurological disorder affecting approximately 65 million people worldwide. Its primary clinical manifestation is recurrent and persistent epileptic seizures.[132] Since the 19th century, over 30 antiseizure medications (ASMs) have been developed for epilepsy treatment.[133] However, these drugs are ineffective against drug-resistant epilepsy and fail to modify disease progression.[133] There is an urgent need to develop novel therapeutics with improved tolerability, safety, and

disease-modifying potential.[134] RNA-based drugs represent a promising approach, as they can be designed to target non-coding RNAs and modulate entire disease pathways. Additionally, they can be customized to correct genetic mutations. While these drugs are typically delivered via intrathecal injection for targeted CNS action,[133] intranasal administration offers a less invasive alternative with potentially superior therapeutic outcomes.[135] A study evaluated the silencing efficacy of intranasally administered siRNA nanoparticle systems targeting the GluN1 subunit in a rat epilepsy model.[136] Results showed that GluN1 subunit expression in the hippocampus of the siRNA-treated group significantly decreased (0.45-fold change). The latency of the first tonic-clonic seizure in the siRNA-treated group was notably prolonged at 14 days compared to the control group ($p = 0.0001$), with no statistical difference between the two groups at 21 days. The experiment indicated that the intranasal administration route, featuring easy operation, good patient tolerance, relative safety and continuous usability, offers a new perspective for treating temporal lobe epilepsy (TLE).[136]

Other Neurological Disorders

Autism spectrum disorder (ASD) is a complex neurodevelopmental disorder with a variety of symptoms and potential causes. 5-hydroxytryptamine and risperidone are medications that can help control certain symptoms of ASD, but they do not address all aspects of the condition. Currently, there is no medication that can completely treat autism.[137] Recent studies have highlighted oxytocin as a neurotransmitter of significant interest for potential ASD treatment.[138] Intranasal oxytocin delivery has emerged as a prominent research focus, with multiple clinical trials demonstrating its therapeutic potential for ASD treatment in recent years.[139] Oxytocin receptors regulating emotional and social cognition are predominantly expressed in the frontal cortex, which exhibits anatomical proximity to the OB. Consequently, increased oxytocin concentrations in the OB enhance therapeutic efficacy for ASD.[138] The administration time is shorter and the concentration of the drug in the brain is higher compared to intravenous administration. At the same time, intranasal administration of oxytocin can also induce changes in brain function in response to social stimuli.[140,141] Patients with schizophrenia have low oxytocin levels, and oxytocin treatment can reduce psychotic symptoms and improve emotional recognition in schizophrenic patients. In schizophrenic patients, oxytocin decreased amygdala activity in response to emotional faces, whereas in healthy controls, oxytocin increased amygdala activity. Oxytocin nasal spray may be effective in altering neural activity in schizophrenia patients with dysfunction related to emotion processing.[142] Transnasal oxytocin can also relieve chronic pain, as Tzabazis A et al have demonstrated by showing that intranasal oxytocin can significantly inhibit the response of specific brainstem regions to head and facial pain stimuli.[143] In addition to oxytocin, peptides such as desmopressin, calcitonin and enkephalin can also be administered in a transnasal manner to relieve chronic pain.[119,144,145]

The nasal-brain targeted drug delivery route provides an effective and feasible solution for treating CNS diseases, offering hope for the cure of some diseases that are otherwise difficult to treat.

Important Nanocarriers for Nasal Drug Delivery

Building upon the effectiveness of the nasal-brain pathway, the choice of drug carrier is crucial. When traditional formulations are used for nasal-brain drug delivery, issues often arise due to their physicochemical properties, such as low bioavailability, hydrophobicity or lipophilicity, ionization, and extensive metabolism.[146] Intranasal nano-carrier-based delivery represents one of the most promising approaches for transporting macromolecular drugs to the CNS. This system offers multiple advantages including high drug-loading capacity, enhanced delivery efficiency, low toxicity, minimal immunogenicity, improved drug absorption, increased bioavailability, and superior brain targeting specificity. Furthermore, the versatile nature of these carriers allows for structural modifications to optimize performance.[92] These advantages allow macromolecular drugs to overcome physiological barriers and achieve targeted delivery. However, nano-carriers present limitations, including the constrained drug-loading capacity and poor storage/delivery stability of lipid-based nano-carriers (LBNs) due to potential intraliposomal coagulation and crystallization, which may cause premature drug release.[147] To address these limitations, researchers have developed effective solutions. CS, a naturally occurring polysaccharide polymer, offers multiple advantages including hydrophilicity, non-toxicity, biocompatibility, and biodegradability.[148] Various CS-based nano-carriers have been engineered for intranasal macromolecular drug delivery to the brain.[149–152] The benefits of CS nano-carriers have been extensively reviewed.[68] Polyethylene glycol (PEG)-modified nano-carriers have been extensively developed. PEGylation alters the physicochemical properties of nano-carriers by reducing surface charge density and enhancing stability.[101] More importantly,

PEG modification enables NPs to evade mononuclear phagocyte system uptake, thereby improving targeted delivery efficiency in vivo.[127] To further enhance nano-carrier delivery and targeting efficacy, researchers have employed CPPs and CPP-modified nano-carriers for NtB delivery.[153–155] CPPs enable the transformation from passive delivery systems to active penetrating systems. This review summarizes key nano-carriers for intranasal macromolecular drug delivery (Table 3), including representative studies demonstrating their potential to overcome physiological barriers and achieve effective brain targeting (Figure 7).

Table 3 Summary of Nanocarriers for Delivery of Macromolecular Drugs in the Past Decade

Delivery System/ Carrier	Biomacromolecule Drugs/ Active Compounds	Delivery Efficiency	Yr. of Study, Authors	Ref.
PEGylated Liposomes	H102 Peptide	A 2.92-fold increase in H102 hippocampal distribution	2015, Zheng X, Shao X, Zhang C, et al	[156]
CS-NLC	GDNF	70% cumulative release over 144 h	2016, Gartziandia O, Herrán E, Ruiz-Ortega JA, et al	[149]
CS NPs	Gal-1 siRNA	Fluorescence signal in OB/tumor at 4 h	2016, Van Woensel M, Wauthoz N, Rosière R, et al	[150]
NL	bFGF	N/A	2016, Zhao YZ, Lin M, Lin Q, et al	[157]
Cationic Nanoemulsion	TNF-α siRNA	6-hour delivery efficiency was 1.38% ID	2016, Yadav S, Gandham SK, Panicucci R, et al	[158]
CS-RVG-9R-SLNs	BACE1 siRNA	N/A	2017, Rassu G, Soddu E, Posadino AM, et al	[159]
PEI	R_8-Aβ(25–35)	17% of the daily dose of 9 nmol peptide	2017, Cheng YS, Chen ZT, Liao TY, et al	[160]
PVP-based NG	Insulin	N/A	2017, Picone P, Sabatino MA, Ditta LA, et al	[161]
L-penetratin	Exendin-4	N/A	2018, Kamei N, Okada N, Ikeda T, et al	[153]
PLGA NPs	Bevacizumab	~1.44% at 7 days post-dose	2019, Sousa F, Dhaliwal HK, Gattacceca F, et al	[162]
ENCPs	miR-132	N/A	2019, Samaridou E, Walgrave H, Salta E, et al	[163]
polyGIONs	miR-100 antimiR-21	Fluorescence signal in brain at 24–48 h	2019, Sukumar UK, Bose RJC, Malhotra M, et al	[164]
PEG-PCL-Tat	siTNF-α	N/A	2019, Kanazawa T, Kurano T, Ibaraki H, et al	[155]
CS-based NPs	Anti-HTT siRNA	Achieve ≥50% knockdown of HTT mRNA	2020, Sava V, Fihurka O, Khvorova A, et al	[151]
RVG29-PEG-PLGA NPs	miR-124	Relative accumulation increased 3–4 fold	2020, Hao R, Sun B, Yang L, et al	[165]
PLGA NPs NLC NPs	Anti-TRAIL monoclonal antibody	N/A	2022, Musumeci T, Di Benedetto G, Carbone C, et al	[166]
CTI	Insulin	N/A	2022, Nojoki F, Ebrahimi-Hosseinzadeh B, Hatamian-Zarmi A, et al	[152]
Rapa@DAK	BACE1 siRNA	N/A	2022, Yang X, Yang W, Xia X, et al	[127]
89WP-CLS/R8	siRNA, sic-Myc	Relative accumulation increased 4-fold	2022, Hu Y, Jiang K, Wang D, et al	[154]
HA/DP7-C nanomicelles	VEGF siRNA PLK1 siRNA	Fluorescence signal in brain at 2 h	2022, Yang Y, Zhang X, Wu S, et al	[167]

(*Continued*)

Table 3 (Continued).

Delivery System/ Carrier	Biomacromolecule Drugs/ Active Compounds	Delivery Efficiency	Yr. of Study, Authors	Ref.
Lesion-Recognizing NPs	BACE1 siRNA caspase-3 siRNA	Fluorescence signal in brain at 6 h	2023, Li J, Peng H, Zhang W, et al	[168]
Liposomes	BACE1 siRNA	N/A	2024, Lee D, Shen AM, Garbuzenko OB, et al	[169]
BMSCs-Exos	Direct nasal delivery	N/A	2025, Wu J, Li A, Shi Y, et al	[170]
Lactobacillus plantarum WCFS1	Leptin α – MSH BDNF	~40% in vitro	2025, Shen H, Aggarwal N, Cui B, et al	[171]

Abbreviations: PEG, Polyethylene Glycol; CS-NLC, Chitosan-coated Nanostructured Lipid Carrier; GDNF, Glial cell-Derived Neurotrophic Factor; Gal-1, Galectin-1; NL, Nanoliposomes; bFGF, basic Fibroblast Growth Factor; TNF-α, Tumor Necrosis Factor-alpha; ID, Injected Dose; RVG-9R, the 9 arginine residues of the rabies virus glycoprotein peptide; SLNs, solid lipid nanoparticles; PEI, Polyethylenimine; R8, Octaarginine; PVP-based NG, Poly(N-Vinyl Pyrrolidone)-based Nanogels; PLGA NPs, Poly(D,L-lactic-co-glycolic acid) Nanoparticles; ENCPs, Enveloped Nanocomplexes; polyGIONs, polyfunctional Gold-iron Oxide Nanoparticles; PCL, Polycaprolactone; Tat, Transactivator of Transcription; HTT, Huntington's Disease; RVG29, Rabies Virus Glycoprotein; TRAIL, Tumor necrosis factor (TNF)-Related Apoptosis Inducing Ligand; CTI, Chitosan-Transfersulin; Rapa@DAK, PEGylated dendrigraft poly-l-lysines (DGL) nanoparticles modified with Aleuria aurantia lectin (AAL) and β amyloid (Aβ)-binding peptide (KLVFF); BACE1 siRNA, β-site precursor protein (APP) cleaving enzyme-1; 89WP, N9W-penetratin; HA, Hyaluronic Acid; DP7-C, Cholesterol to the N-terminus of antimicrobial peptide DP7; VEGF, Vascular Endothelial Growth Factor; PLK1, Polo - like Kinase 1; BMSCs-Exos, Bone Marrow mesenchymal Stem Cells Exosome; α – MSH, alpha - Melanocyte - Stimulating Hormone; BDNF, Brain - Derived Neurotrophic Factor.

Lipid-Based Nanocarriers (LBNs)

In 1965, Bangham AD et al first reported the spontaneous formation of phospholipid bilayers in aqueous solution, forming lamellar liquid crystals with water layers separating each bilayer.[173] This discovery established the theoretical foundation for

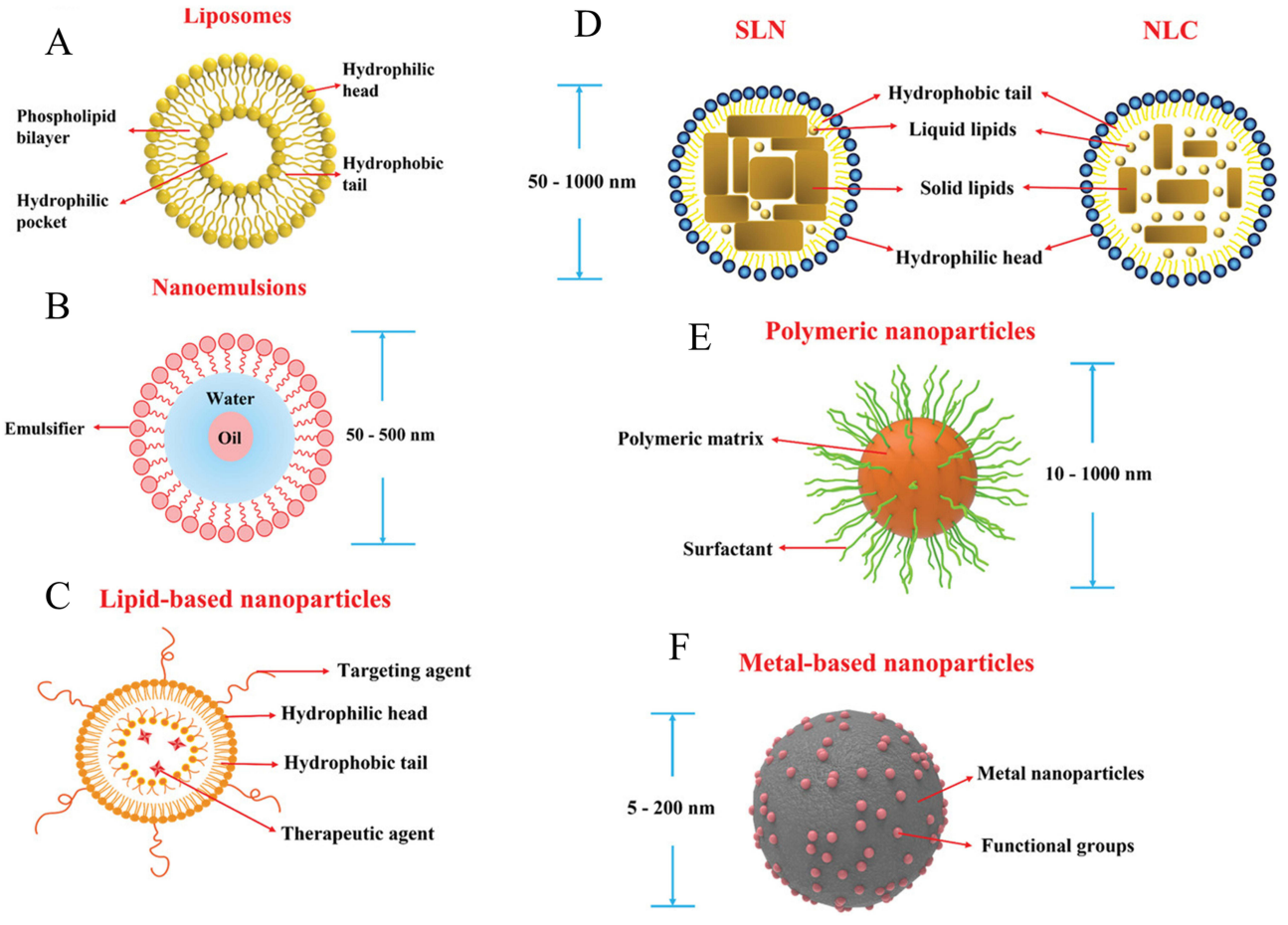

Figure 7 Schematic diagrams of various nanocarriers for nose-to-brain delivery. (**A**) Liposomes; (**B**) Nanoemulsions; (**C**) Lipid-based nanoparticles; (**D**) SLN and NLC; (**E**) Polymeric nanoparticles; (**F**) Metal-based nanoparticles. Reprinted with permission from Zha S, Wong K-L, All AH. Intranasal delivery of functionalized polymeric nanomaterials to the brain. Adv Healthc Mater. 2022;11(11):e2102610. © 2022 Wiley-VCH GmbH.[172]

liposomes as drug carriers. Currently, LBNs represent one of the most widely used DDS. For intranasal macromolecular delivery, major LBNs types include: liposomes,[154,156,157] solid lipid nanoparticles (SLNs),[159] nanostructured lipid carriers (NLCs),[149,166] nanoemulsions,[158] key advantages of LBNs include: (1) high encapsulation efficiency; (2) excellent biocompatibility; (3) strong biomembrane permeability; (4) targeted delivery capability; (5) low toxicity and biodegradability.[172,174]

Liposomes

Liposomes are vesicular structures composed of phospholipids and cholesterol, featuring hydrophilic heads and hydrophobic tails. In aqueous environments, phospholipid molecules spontaneously self-assemble into closed bilayers through hydrophobic interactions, subsequently forming NPs.[172] These characteristics confer excellent biocompatibility while protecting drug activity and enhancing solubility. Zheng X et al prepared PEGylated liposomes encapsulated with β-sheet breaking peptide (H102 peptide), and then evaluated the improvement of AD symptoms in a rat model after intranasal administration. The encapsulation efficiency of the liposomes was 71.35±0.87%, which could significantly protect the H102 peptide from degradation by plasma enzymes (63% remained after 2 hours). After intranasal administration, the area under the plasma concentration-time curve (AUC) of the liposome group in the hippocampus (HI) of rats was 2.92 times that of the H102 solution group. Meanwhile, it could improve the spatial memory impairment of AD model rats and had low toxicity to the nasal mucosa.[156] Another study constructed an 89WP-CLS/R8/siRNA core-shell liposomal complex, featuring an octaarginine (R8) core enveloped by cationic liposomes (CLSs) and surface-modified with Q8W/N9W-penetratin (89WP) for glioblastoma (GBM) targeting (Figure 8A). This lipoplex significantly enhanced siRNA permeability across the nasal mucosa (Figure 8B) and demonstrated a 3-fold increase in tumor

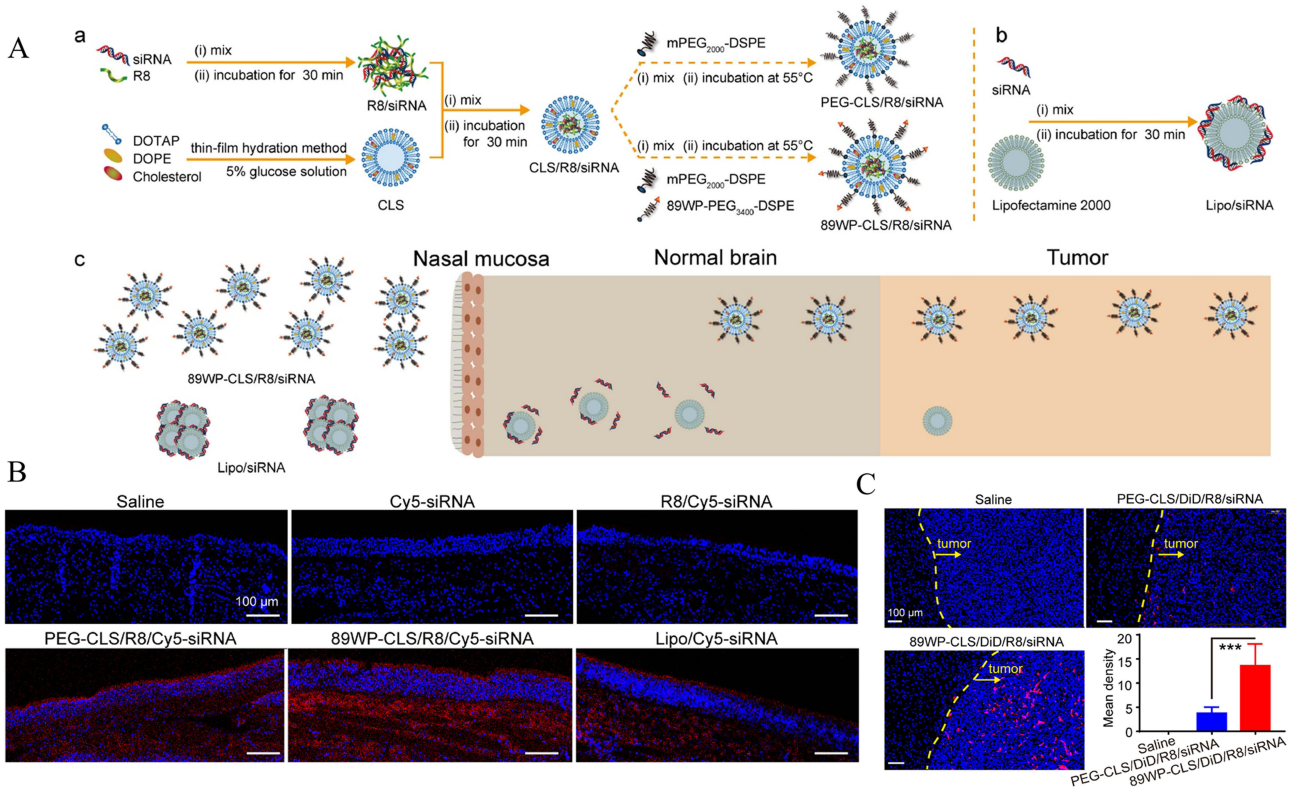

Figure 8 Construction of lipoplexes for targeted treatment of glioblastoma. (**A**) Schematic diagram of the preparation and transportation of lipoplexes. (**B**) Paraffin sections of nasal mucosa treated with siRNA formulations. Cell nuclei are stained blue with 4',6-diamidino-2-phenylindole (DAPI), and siRNA is labeled with Cy5 and appears red. (**C**) Confocal images of the distribution of DiD-labeled lipoplexes in the brains of glioma-bearing mice and the normalized integral optical density (IOD). Cell nuclei are stained blue with DAPI, and the DiD-labeled lipoplexes are red. Reprinted from Acta Biomater, 138, Hu Y, Jiang K, Wang D, et al. Core-shell lipoplexes inducing active macropinocytosis promote intranasal delivery of c-Myc siRNA for treatment of glioblastoma, 478–490, Copyright 2022, with permission from Elsevier.[154]

siRNA accumulation in glioma-bearing mice (Figure 8C). The system potently suppressed c-Myc expression, achieving 57.7% protein-level and 32.3% mRNA-level reductions. These findings establish a novel therapeutic strategy for GBM treatment.[154]

SLN and NLC

SLNs feature a solid lipid core coated with surfactants. Their physiologically compatible solid matrix remains stable at body temperature, enabling controlled drug release.[172] Developed from SLNs, NLCs incorporate both liquid and solid lipids in their core, surrounded by surfactants. This hybrid structure combines the advantages of both lipid phases, demonstrating enhanced drug-loading capacity, improved stability, and tunable release kinetics.[175] Rassu et al developed CS-coated, CPP (RVG-9R)-modified SLNs for BACE-1 siRNA delivery in AD treatment. In Caco-2 cell models, the CS-coated group demonstrated optimal permeability at 60 minutes, significantly enhancing siRNA penetration. The BACE1 siRNA effectively reduced Aβ plaque formation, suggesting potential for AD progression delay.[159] A recent study explored NtB delivery for AD using NLCs loaded with TRAIL-neutralizing monoclonal antibodies (anti-TRAIL mAb), achieving 99% encapsulation efficiency. Following intranasal administration in mice, immunofluorescence analysis revealed significantly elevated NLC levels in the hippocampus. This system offers a promising non-invasive strategy for CNS delivery of macromolecules, particularly antibodies.[166] Further research is needed to evaluate the immunogenicity and toxicity of these nanocarriers.

Polymeric Nanocarriers

Biodegradable polymeric nanocarriers have emerged as one of the most promising strategies for NtB drug delivery. These polymers can spontaneously form nano-sized aggregates (1–1000 nm) under specific environmental or experimental conditions, exhibiting unique physicochemical properties that qualify them as nanobiopolymers.[176] Extensive research has utilized both natural polymers (particularly CS) and synthetic polymers (including PEG, PLGA, and polyethyleneimine) as nanocarriers for macromolecular drug delivery.[127,151,160,162] Notably, these synthetic polymers undergo biodegradation into oligomers and monomers that can be eliminated through normal metabolic pathways.[177] The polymeric nanocarriers demonstrate excellent drug encapsulation and protection capabilities, particularly for stabilizing vulnerable therapeutic agents like proteins and peptides by preventing their premature degradation in vivo.[69,178] Sousa F et al pioneered bevacizumab-loaded PLGA NPs that significantly enhanced cerebral bioavailability via intranasal administration, achieving approximately 3-fold higher brain drug concentrations compared to free bevacizumab. This innovative strategy presents substantial clinical potential for glioblastoma treatment.[162]

Additional Nanocarriers

Other nanocarriers have been developed for macromolecular NtB delivery. Nanoemulsions are composed of two phases, namely water and oil, among which oil-in-water (O/W) nanoemulsions are the predominant type. Lipophilic drugs dissolved in the oil phase can form nanoprecipitates during phase transition to the aqueous phase. These nanoprecipitates exhibit high surface area and rapid dissolution kinetics, thereby enhancing delivery efficiency.[123] Yadav S et al developed cationic nanoemulsions (SNEs) encapsulating anti-TNF-α siRNA, achieving 5-fold higher cerebral siRNA concentrations than free siRNA after intranasal administration. The SNEs significantly reduced systemic siRNA exposure and decreased brain TNF-α expression (523% to 351%, $p<0.05$), demonstrating superior brain targeting. This study provides an innovative therapeutic strategy for neuroinflammatory disorders.[158]

Recent studies have explored nanomicelles for drug delivery. A multifunctional core-shell nanomicelle system (HA/DP7-C) was developed using CCP DP7-C and hyaluronic acid (HA) for NtB siRNA delivery. Following intranasal administration, HA/DP7-C/siRNA complexes rapidly reached the CNS via trigeminal pathways within hours and accumulated at tumor sites. Both in vitro and in vivo studies demonstrated significant inhibition of glioma growth when targeting VEGF or PLK1 siRNA was delivered through this system[167] (Figure 9). This strategy constitutes a robust and biocompatible siRNA delivery system for glioma treatment, especially targeting chemoresistant brain malignancies.

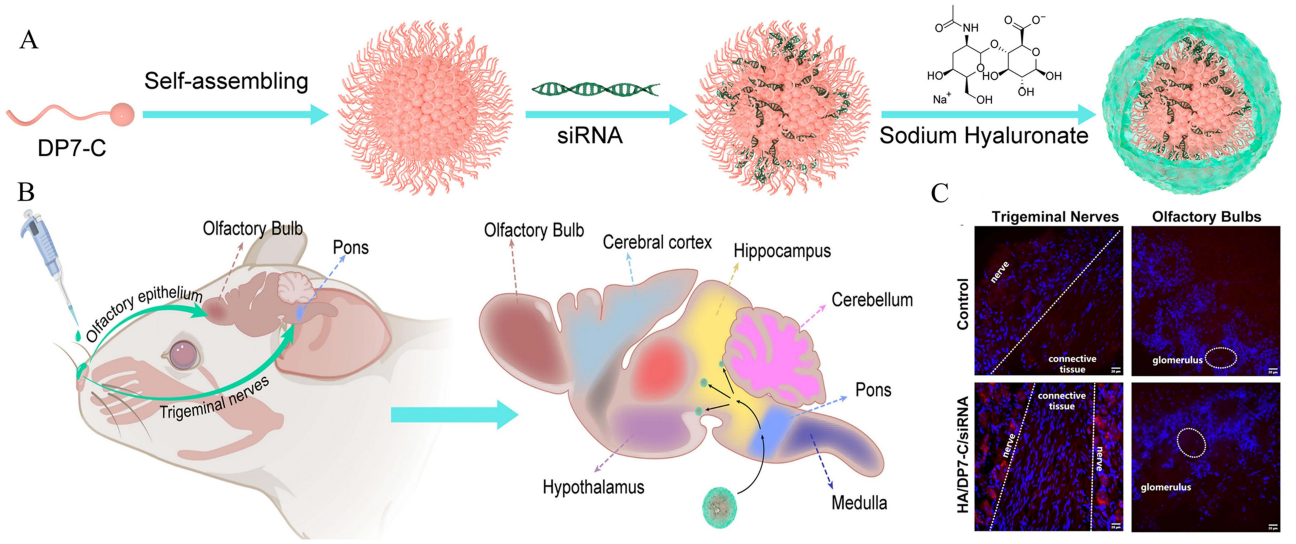

Figure 9 Preparation of nanomicelles for the treatment of glioma. (**A**) Schematic diagram of the preparation process of nanomicelles. (**B**) Schematic diagram of the nose-to-brain delivery pathway of nanomicelles. (**C**) Tissue sections of the trigeminal nerve and olfactory bulb 30 minutes after the intranasal administration of the siRNA formulation. Reprinted from J Control Release, 342, ang Y, Zhang X, Wu S, et al. Enhanced nose-to-brain delivery of siRNA using hyaluronan-enveloped nanomicelles for glioma therapy,66-80, Copyright 2022, with permission from Elsevier.[167]

Recent advances have established bioinspired nanovehicles, including exosomal and intranasal microbial carriers, for facilitating neurotherapeutic macromolecule delivery.[170,171] Engineered Lactobacillus plantarum WCFS1 (Lp), exhibiting natural olfactory epithelium tropism, efficiently mediated brain-targeted payload delivery. In obesity models, intranasal Lp administration induced prolonged anorexigenic effects and enhanced metabolic parameters compared to recombinant leptin, indicating greater therapeutic durability[171] (Figure 10). This innovative approach utilizes endogenous olfactory epithelium-targeting microbiota to circumvent intranasal delivery barriers. Concurrently, inorganic NPs have been engineered for enhanced neurotherapeutic transport.[164]

Summary and Outlook

Intranasal delivery offers a non-invasive, low-risk alternative with adjustable dosing and easy discontinuation, making it preferable for patients unsuitable for or declining surgery. Crucially, it bypasses the BBB, enabling direct CNS delivery of macromolecular biologics (eg, proteins, peptides). This approach provides novel therapeutic strategies for CNS disorders including PD, AD, autism, and schizophrenia.

However, the natural clearance mechanism in the nasal cavity poses challenges to drug delivery. To overcome these obstacles, nanocarriers loaded with therapeutic drugs have emerged as a promising solution. Therefore, continuous research efforts are crucial for developing nanocarriers specifically designed for intranasal administration.[1] Enhance delivery efficiency and precise targeting: Optimize the structure, size, surface properties, and biocompatibility of nanocarriers to maximize drug loading efficiency, stability, and brain targeting ability. By developing co-delivery systems (such as siRNA + chemotherapeutic drugs/immunomodulators), multi-target delivery can be achieved, and tumor drug resistance can be overcome through synergistic treatment.[2] Deepen the delivery mechanism of nasal-to-brain administration: The specific transport mechanisms of NPs in the trigeminal and olfactory nerve pathways can be clarified through in vivo imaging and neural tracing techniques.[3] Conduct preclinical and clinical translational research: Evaluate the long-term nasal mucosal toxicity, immunogenicity, and the risk of neuroinflammation in animal models, as well as the effects of repeated administration on olfactory and trigeminal nerve functions. Meanwhile, optimize the preparation process of NPs to achieve large-scale production and stability, making them convenient for clinical use.[41] Combine multiple treatment methods, such as gene therapy, immunotherapy, and chemotherapeutic drugs.[42] Interdisciplinary integration: Incorporate exosomes or biomimetic NPs to improve biocompatibility and targeting ability. In addition, it can be combined with intranasal drug delivery devices to maximize the deposition of

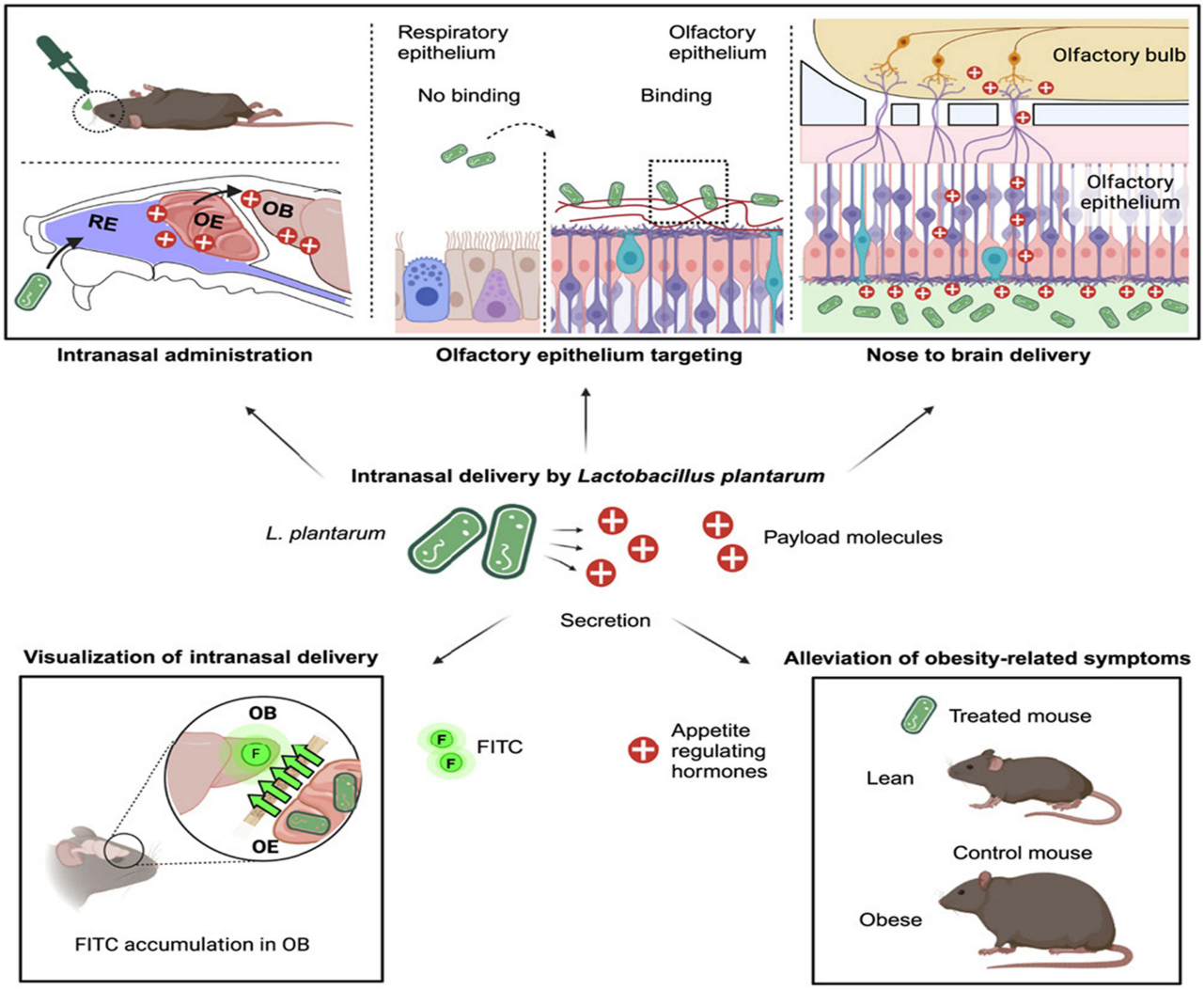

Figure 10 Lactobacillus plantarum WCFS1 (Lp) has a natural affinity for the OE, and it is engineered to serve as a brain-targeted drug delivery carrier. After intranasal administration, Lp can release the payload in the OE and be transported to the brain. Reprinted with permission from.[171]

drugs on the olfactory epithelium, thereby achieving better therapeutic effects. The combination of intranasal administration and optimized nanocarriers provides an important opportunity for advancing treatment strategies for a series of CNS diseases. Continuous research and development in this field have the potential to transform the treatment prospects for patients with these challenging diseases.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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