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REVIEW

Micro/Nanoparticles in the Nose-Brain Axis: Implications for Pathogenesis and Therapeutic Interventions

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Abstract: The nose-brain axis (NBA) is a crucial bidirectional deliverypathway between the nasal cavity and the central nervous system (CNS) that influences both neurophysiology and disease progression. In addition to serving as a route for drug delivery, the NBA plays an active role in neurological disorders by mediating inflammatory responses, microbial interactions, and environmental exposure. Emerging evidence suggests that the NBA may be mechanistically relevant to CNS disorders, particularly within neurodegeneration frameworks such as the Braak and dual-hit hypotheses, which emphasize early olfactory or other peripheral involvements. This review explores how micro/nanoparticles interact with the NBA, not only as therapeutic carriers but also as factors contributing to neuroinflammation and neurodegeneration. Pathogenic micro/nanoparticles, including environmental pollutants and industrial nanoparticles, have been implicated in the exacerbation of CNS disorders by triggering oxidative stress and immune activation in both nasal and brain tissues. Conversely, therapeutic micro/nanoparticles such as biomimetic, synthetic, and cell-derived formulations represent promising strategies for modulating neuroinflammation, enhancing neuroprotection, and restoring CNS function through nasal-targeted interventions. However, substantial gaps remain in the existing understanding of the influences of nasal immune responses, microbiota, and barrier integrity on CNS health through the NBA. Addressing these challenges is critical for leveraging micro-/nanoparticles for the prevention and treatment of CNS diseases.

Keywords: nose-brain axis, micro/nanoparticles, neuroinflammation, neurodegenerative diseases

Introduction

The nose-brain axis (NBA) represents a unique and dynamic connection between the nasal cavity and the central nervous system (CNS), providing a pathway for external agents to access the brain and a platform for bidirectional interactions.[1] Traditionally, research on the NBA has focused primarily on its ability to bypass the blood–brain barrier (BBB) during drug delivery. By exploiting the olfactory and trigeminal nerve pathways, this route facilitates direct transfer of therapeutic agents from the nasal cavity to the brain, offering a promising non-invasive alternative for treating CNS disorders.[2] However, emerging evidence has highlighted the broader biological importance of the NBA as a conduit for organ–organ interactions and systemic health

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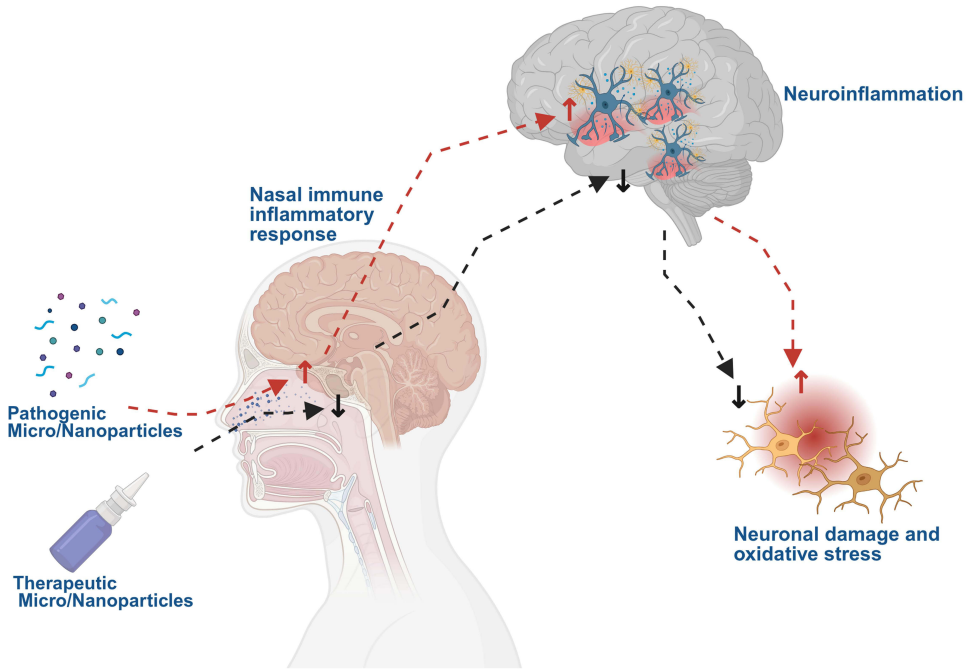
Graphical Abstract



regulation. In addition to drug delivery, this axis mediates bidirectional signaling, linking nasal inflammation, environmental exposure, and infections to CNS pathologies such as neuroinflammation and neurodegeneration.[3]

Recent studies have highlighted the pathological consequences of nasal insults on the brain, emphasizing that infections, environmental toxins, and chronic inflammation in the nasal cavity can trigger or exacerbate CNS damage. For example, pathogens such as *Streptococcus agalactiae* and *Burkholderia pseudomallei* can invade the brain via the olfactory and trigeminal nerves, leading to meningitis and brainstem infections.[4,5] Similarly, acute/chronic inflammatory conditions such as allergic rhinitis (AR) and rhinosinusitis may activate pro-inflammatory cytokines and immune mediators that traverse the nasal-CNS interface, potentially contributing to diseases such as depression, Alzheimer's disease (AD) and Parkinson's disease (PD).[6,7] These findings underscore the importance of the NBA as more than just a passive conduit for drug delivery; it is an active player in CNS health and disease, and is capable of influencing neuroinflammation, neurodegeneration, and overall brain homeostasis.

In addition to its pathological relevance, the NBA has also become the focus of innovation in therapeutic interventions. Advances in nanotechnology have enabled the development of nanoparticles, nanoemulsions, and other formulations designed to optimize drug delivery via this route. These technologies offer distinct advantages, including enhanced drug stability, targeted brain delivery, and reduced systemic side effects.[8] These systems have proven particularly effective in managing conditions such as epilepsy, AD, and schizophrenia.[9] However, the full potential of this axis remains underexplored, particularly the ability to leverage its bidirectional properties to influence both the nasal cavity and brain. For example, therapeutic interventions targeting inflammatory pathways originating in the nasal cavity can alleviate local pathologies and mitigate the systemic effects on the CNS.

Despite these advancements, substantial gaps remain in the existing understanding of the NBA. The molecular mechanisms underlying the bidirectional delivery between the nasal cavity and CNS are poorly understood. For instance, the role of neurotransmitters such as glutamate in mediating neuroinflammatory responses originating in the nasal cavity warrants further investigation. Moreover, the long-term effects of environmental toxins, pathogens, and chronic nasal inflammation on brain

health remain to be fully elucidated.[3] These gaps in knowledge not only hinder the development of effective interventions, but also limit the ability to understand and address the bidirectional effects of nasal diseases and CNS function.

This review systematically elaborates on the physiological and anatomical features of the NBA as well as its associated key neural circuits and pathological mechanisms. Building on this foundation, we introduce the dual role concept of micro/nanoparticles in disease and further explore in detail the specific mechanisms through which these particles exert their actions via the NBA in various disorders. Through a comprehensive discussion of NBA functions, this article emphasizes that under both physiological and pathological conditions, the NBA not only serves as a potential route for treating CNS diseases but also acts as a critical hub for bidirectional delivery between the periphery and the CNS. This understanding contributes to the prevention of CNS diseases that may be induced by micro/nanoparticles. In terms of treatment, drug delivery strategies based on the NBA enable precise targeting while reducing systemic side effects, thereby significantly improving therapeutic outcomes. This review aims to deepen our understanding of the NBA and its potential in transforming the treatment of CNS diseases and managing nasal-related disorders with systemic implications. Regulating NBA-related pathways for treating these diseases is expected to become a highly promising clinical direction in the future.

Search Strategy

We conducted a literature search on PubMed using the following keywords in various combinations: nose-brain axis/pathway, neuroinflammation, micro-/nanoparticles, anatomy, physiology, brain, nose, olfactory nerve, trigeminal nerve, immune, microbial. All possible combinations of these keywords were used, and the abstracts of the retrieved records were evaluated. No time restrictions were applied. Additionally, manual searches of the reference lists from articles meeting the inclusion criteria were performed to identify earlier publications. Secondary literature was obtained from the reference lists of key papers, assessed for relevance, and included accordingly.

Anatomy and Physiology of the Nose and Brain

The intricate anatomical and physiological features of the nasal cavity and the brain form the basis for their dynamic bidirectional delivery, enabling therapeutic applications and pathological interactions. The specific anatomy of the NBA can be seen in Figure 1. The nasal cavity serves as a distinct gateway to the CNS via specialized pathways, including the olfactory and trigeminal nerves. These routes allow the direct transport of molecules, cells, and signals between the nasal cavity and the brain, bypassing the restrictive BBB. However, in addition to facilitating therapeutic drug delivery, this unique connectivity also permits the transmission of environmental toxins, pathogens, and inflammatory mediators from the periphery to the CNS. Conversely, CNS dysfunction can also influence nasal health through the neuroimmune and neuroinflammatory pathways, further confirming that the NBA is a critical focus of investigation. This bidirectional interplay underscores the importance of understanding the structural and functional basis of the NBA to advance scientific insights and clinical interventions.

Anatomy and Physiology of the Nasal Cavity

The nasal cavity, which is anatomically divided into the vestibular, respiratory, and olfactory regions, serves as both a functional filter for inhaled air and a direct interface with the CNS. The olfactory region, located in the superior part of the nasal cavity, is lined with the olfactory epithelium containing olfactory sensory neurons (OSNs). These neurons project axons through the cribriform plate to the olfactory bulb, enabling direct neuronal communication with the brain.[10] In contrast, the respiratory epithelium is composed of ciliated and goblet cells that produce mucus, which traps particulates and pathogens. Although protective, this mucociliary clearance system poses a barrier to drug delivery. To address this issue, nanoparticle-based delivery systems have been engineered to enhance mucoadhesion and enable deeper penetration into the olfactory epithelium.[11] The trigeminal nerve (cranial nerve V) provides sensory innervation to the nasal cavity, and contributes to the perception of irritants and temperature changes. Importantly, its branches extend to the brainstem, offering an alternative route for direct drug transport and a mechanism for transmitting neuroinflammatory signals from the nasal cavity to the CNS.[12]

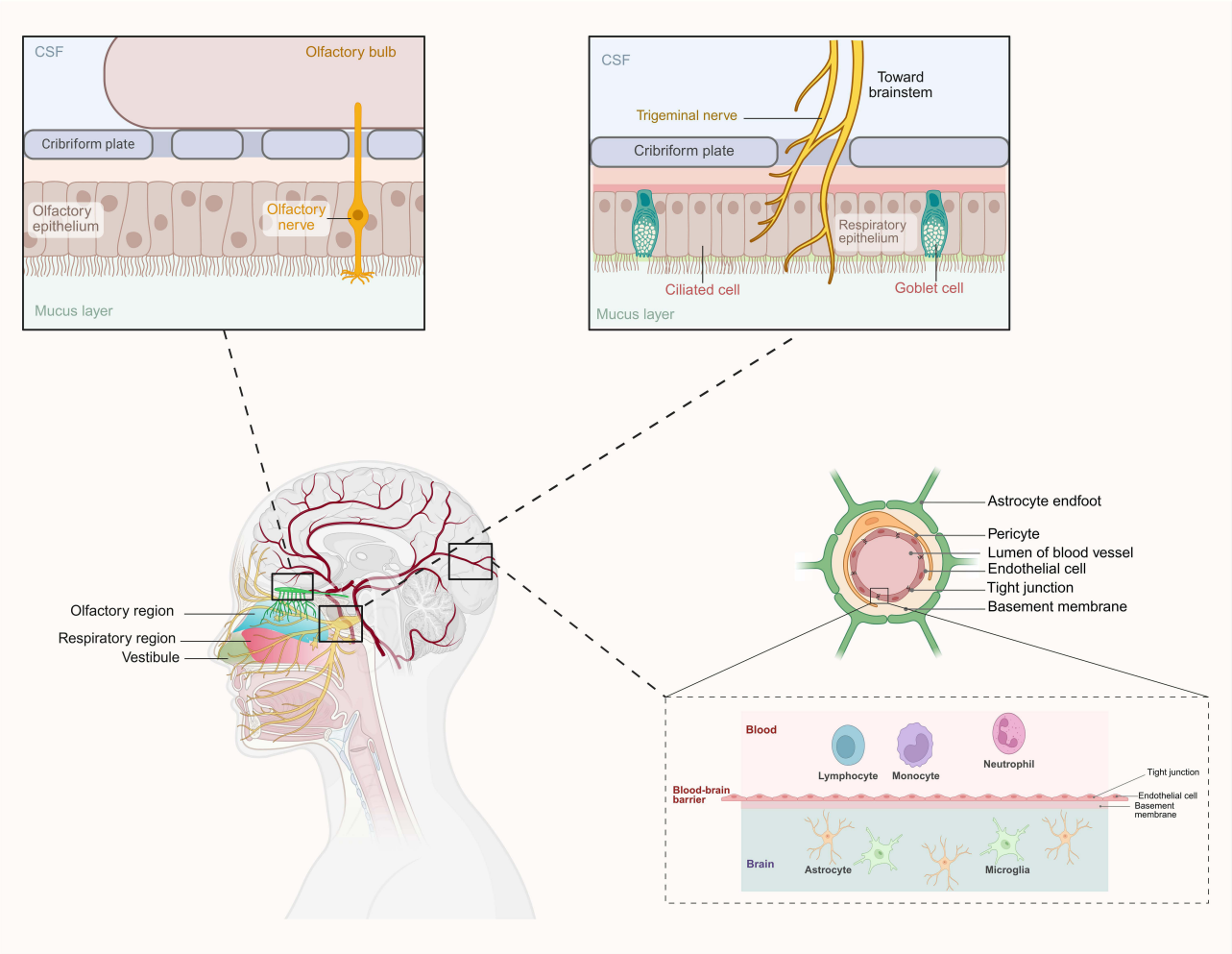


Figure 1 The anatomical schematic of the NBA. The nasal cavity functions as a unique portal to the CNS through specialized neural routes, notably the olfactory and trigeminal nerves. These pathways facilitate the direct transfer of molecules, cells, and neural signals from the nasal epithelium to the brain parenchyma, circumventing the selective permeability of the BBB.
Abbreviations: NBA, nose-brain axis; CNS, central nervous system; BBB, blood-brain barrier.

Environmental toxins, pathogens, and therapeutic agents exploit these neural pathways. For instance, the olfactory route has been implicated in the entry of pathogens such as *Streptococcus pneumoniae*, which can migrate along the olfactory nerve to cause meningitis.[13,14] Similarly, intranasal delivery of drugs via nanoparticulate systems has shown promise in bypassing the BBB to treat CNS disorders such as AD.[15,16]

Anatomy and Physiology of the Brain

The brain is the most complex organ in the CNS, with tightly regulated barriers such as the BBB limiting the entry of substances from the systemic circulation. However, the olfactory bulb, located on the ventral surface of the brain, serves as a direct recipient of signals from the nasal cavity. This anatomical connection creates a unique vulnerability to external insults and provides a potential route for targeted drug delivery.[17] In addition to processing odorant signals, the olfactory bulb also plays a role in neuroinflammation and neurodegeneration. Pathogens and toxins that migrate along the olfactory nerve can induce microglial activation in the bulb, contributing to the inflammatory cascades implicated in neurodegenerative diseases such as PD.[18] In addition to the olfactory pathway, the trigeminal nerve provides an alternative route for interactions between the nasal cavity and brainstem. This nerve is involved in sensory processing and has been implicated in the propagation of neuroinflammatory signals from the periphery to central structures.[18]

The direct neural connections of the NBA bypass the metabolic and enzymatic barriers imposed by the BBB. This is exemplified by intranasal drug-delivery systems, wherein therapeutic agents delivered via the nasal route achieve rapid CNS concentration. Nanoparticles such as those made from polylactic-co-glycolic acid (PLGA) and chitosan have been designed to optimize delivery through these pathways by leveraging their capacity to cross neuronal and perineural interfaces.[19] Understanding the anatomical and physiological interplay between the nasal cavity and brain is critical for advancing therapeutic strategies and mitigating the risks of pathological conditions that exploit this axis.

Mechanisms Linking the NBA

The NBA serves as a pivotal conduit for therapeutic delivery and pathological signaling, leveraging specialized anatomical pathways to facilitate bidirectional delivery between the nasal cavity and CNS. The NBA employs the olfactory and trigeminal nerve pathways as direct ascending conduits. Upon stimulation by allergens, pathogens, or environmental toxins, the nasal mucosa releases pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6). These cytokines disrupt the tight junctions of the nasal epithelium, thereby increasing its permeability. This breakdown allows immune cells and inflammatory mediators, which are normally restricted by the barrier, to accumulate around nerve terminals. Subsequently, these harmful substances and signals can travel directly into the central nervous system along the olfactory and trigeminal nerves via mechanisms such as axonal transport or intercellular transmission, inducing neuronal inflammatory responses and oxidative stress. Concurrently, nasal dysbiosis, characterized by microbial imbalance, exacerbates this inflammatory cascade by disrupting local mucosal immune homeostasis and providing sustained pro-inflammatory stimuli. Furthermore, certain components or metabolites from the dysregulated microbiota may themselves be directly transported upwards along these neural pathways.

Recent evidence has highlighted both extracellular and intracellular mechanisms underlying this transport. Extracellular pathways involve the diffusion of molecules along the olfactory epithelium and mucosal surfaces, enabling their rapid entry into the CNS. Conversely, intracellular transport occurs via axonal migration within sensory neurons, allowing pathogens, nanoparticles, and signaling molecules to bypass the BBB. In addition to these structural mechanisms, emerging evidence has identified the critical roles of neuroimmune signaling and inflammatory mediators in amplifying the effects of nasal insults on brain health. This complex interplay between cellular and molecular mechanisms underscores the importance of the NBA as a central focus for understanding CNS pathology and optimizing therapeutic interventions.

Olfactory Nerve: Direct Transmission Pathway

The olfactory nerve serves as a critical and bidirectional conduit between the nasal cavity and CNS, facilitating the transport of substances and communication of pathological signals. Transport of substances occurs primarily via intracellular and extracellular pathways.[20] Intracellular transport involves the internalization of molecules such as nanoparticles and small molecules by OSNs through endocytosis. These substances are then transported along the axonal microtubule network to the olfactory bulb with the assistance of motor proteins such as dynein and kinesin.[21] Conversely, extracellular transport bypasses cellular internalization, allowing larger molecules and hydrophilic substances to diffuse through the perineural space or traverse the paracellular junctions between olfactory epithelial cells. These pathways enable both therapeutic agents and potentially harmful molecules, such as environmental toxins, to bypass the BBB and directly access the CNS.[22]

Importantly, the olfactory nerve is not merely a one-way conduit; evidence indicates a bidirectional interaction between nasal pathology and CNS health. In neurodegenerative diseases such as PD, the olfactory system is often among the earliest affected regions, with olfactory dysfunction preceding motor symptoms. These findings support the hypothesis that pathological proteins such as alpha-synuclein aggregates may propagate from the nasal epithelium to the CNS via the olfactory nerve.[1] Conversely, nasal health can be influenced by CNS dysfunction. For example, patients with AR, a chronic nasal inflammatory condition, are at increased risk of depression and anxiety, which is likely mediated by neuroimmune and neuroinflammatory pathways that influence brain health.[23]

From a therapeutic perspective, the olfactory nerve has been exploited for direct delivery of neuroprotective agents to the CNS. In neurodegenerative diseases, polymeric nanoparticles such as PLGA, which are functionalized with

mucoadhesive polymers such as chitosan, have shown promise in delivering drugs to the olfactory bulb. For instance, nanoemulsions have been used to rapidly deliver both hydrophilic and hydrophobic drugs to the affected CNS regions in patients with AD and PD.[24] In neuroinflammatory and neuroimmune disorders, nanoparticles loaded with anti-inflammatory agents have been used to reduce CNS inflammation in preclinical models of multiple sclerosis, providing a non-invasive alternative to systemic therapies. Furthermore, diagnostic imaging approaches, such as manganese-enhanced magnetic resonance imaging (MRI), have been used to confirm the rapid transport and distribution of substances delivered intranasally via the olfactory nerve, underscoring the potential of these approaches for monitoring disease progression and evaluating therapeutic outcomes.[25]

The bidirectional role of the olfactory nerve in CNS health and nasal diseases highlights its unique position as both a therapeutic gateway and pathological conduit. Understanding how this pathway mediates reciprocal interactions, such as the influence of neurodegeneration on olfactory function and that of nasal inflammation on CNS disorders, can offer valuable insights into the complex interplay between the peripheral and central systems. Continued exploration of these mechanisms will improve the ability to diagnose, monitor, and treat disorders that bridge the nasal cavity and CNS.

Trigeminal Nerve: Indirect Transmission

The trigeminal nerve (cranial nerve V) is a critical component of the NBA, which connects the nasal cavity to diverse regions of the CNS. Unlike the olfactory nerve, which provides rapid and direct access to the brain, the trigeminal nerve facilitates sustained and targeted transport to deeper CNS structures, including the brainstem, midbrain, and spinal cord. By bypassing the BBB, this pathway offers substantial advantages for drug delivery and therapeutic interventions, particularly in conditions that require prolonged regional targeting of the CNS.[26] Intranasal delivery of substances employs both intracellular and extracellular transport mechanisms along the trigeminal nerve. However, extracellular diffusion through the perineural spaces is typically dominant, albeit slower than that through the olfactory nerve pathways. This mechanism has been validated extensively in preclinical studies. For instance, curcumin-loaded polycaprolactone (PCL) nanoparticles effectively permeate the trigeminal nerve mucosa and accumulate in the brainstem regions within hours of nasal administration.[27] Similarly, PLGA nanoparticles have demonstrated efficient transport and bioavailability of neuroprotective agents targeting the brainstem, further validating the therapeutic potential of this route.[28]

Nanoparticle optimization plays a pivotal role in the development of this drug-delivery pathway. For example, PEGylated PLGA nanoparticles enhance nasal cavity retention and allow sustained drug release, although excessive PEGylation can reduce trigeminal nerve permeability. To address this, functionalized nanoparticles modified with targeting ligands such as rabies virus glycoprotein (RVG) have been developed to improve payload delivery specifically to brainstem regions. This targeting strategy is particularly promising for conditions such as migraines and neurodegenerative diseases.[22,29] Other emerging clinical applications have also highlighted the therapeutic potential of the trigeminal pathway. In comparison with intravenous administration, intranasal delivery of eletriptan hydrobromide nanoparticles has been shown to increase the activation of trigeminal neurons, resulting in improved CNS drug levels and substantial therapeutic efficacy for migraine treatment.[30] Similarly, solid lipid nanoparticles and lipid-based carriers have shown high bioavailability for neuroprotective agents in preclinical models of PD and AD, further validating the importance of the trigeminal route for long-term therapeutic strategies.[28,31]

Overall, the trigeminal nerve pathway complements the olfactory route by providing sustained and targeted delivery of larger molecules to critical CNS regions. This dual contribution enhances the potential of NBA as a platform for developing advanced therapeutic interventions, offering a robust solution for conditions requiring precision, prolonged effectiveness, and regional CNS targeting.[32,33]

Immune and Inflammatory Pathways

The immune and inflammatory pathways of the NBA play central roles in mediating the effects of nasal inflammation on CNS health, while also reflecting the bidirectional relationship between peripheral and central immune responses. Nasal inflammation, driven by allergens, pathogens, or environmental toxins, triggers the release of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1β, and IL-6, which disrupt the nasal epithelial barrier and increase its permeability.[34,35] This allows immune cells and inflammatory mediators to access the CNS through pathways

such as the olfactory and trigeminal nerves. For instance, chronic rhinosinusitis (CRS) is characterized by type 2 inflammation involving cytokines such as IL-4, IL-13, and IL-5, which can impair OSNs but also compromise mucosal integrity, creating an entry point for inflammation to propagate to the CNS.[36,37] Conversely, neuroinflammatory conditions such as AD and PD can lead to anosmia and further weaken mucosal defenses, demonstrating the bidirectional impact of nasal and CNS pathologies.[38,39]

Microglial activation is a hallmark of the CNS inflammation associated with the NBA. Chronic nasal inflammation primes microglia, making them hyperresponsive to subsequent immune challenges. Activated microglia amplify neuroinflammatory responses by releasing pro-inflammatory cytokines, reactive oxygen species (ROS), and neurotoxic mediators, thereby perpetuating a cycle of neuronal damage.[40,41] This mechanism is particularly relevant in neurodegenerative diseases such as AD and PD, where sustained microglial activation contributes to the progression of the disease. Additionally, inflammatory mediators, such as matrix metalloproteinases (MMPs), degrade tight junction proteins in both the nasal epithelium and BBB, facilitating the entry of peripheral immune signals into the CNS. For example, type 1 inflammation mediated by interferon-gamma (IFN-γ) induces epithelial-to-mesenchymal transition in the nasal epithelium, exacerbating tissue remodeling and barrier dysfunction.[42,43] The bidirectional nature of inflammation complicates the interplay between the periphery and the CNS. Peripheral inflammation, such as CRS or AR, can activate central pathways such as the hypothalamic-pituitary-adrenal (HPA) axis, driving systemic immune responses and neuroinflammatory cascades.[44,45] Conversely, CNS inflammation resulting from neurodegenerative conditions can exacerbate nasal inflammation through neuroimmune feedback loops, impairing mucosal barrier function and OSNs.[46,47] This cyclical interaction underscores the importance of the NBA in linking nasal health to systemic and CNS pathologies.

While the physiological roles of immune responses and barrier integrity within the NBA have been well emphasized, the specific triggering mechanisms for inflammatory factor release, the precise neural circuits involved in signal transmission, and the molecular pathways and corresponding receptors through which these effects are targeted remain insufficiently explored. Furthermore, the cascade of responses within the CNS triggered by the disruption of nasal mucosal and BBB integrity—such as the activation of specific brain regions and alterations in electrophysiological signals—has yet to be fully elucidated. Further investigation utilizing techniques such as electroencephalographic (EEG) monitoring and optogenetic-based neural tracing is warranted. Validation in animal models would provide more compelling evidence in this regard. Targeting the immune and inflammatory pathways within this axis represents a promising therapeutic avenue for mitigating neuroinflammatory conditions and restoring barrier integrity in both the nasal cavity and CNS.

Microbial Pathways: Interactions Between the Nasal Microbiota and CNS Health

The nasal microbiota, a complex ecosystem of commensal and potentially pathogenic microorganisms, plays a pivotal role in mediating the relationship between the nasal cavity and the CNS through the NBA. Emerging evidence indicates that microbial dysbiosis in the nasal cavity, characterized by imbalances in microbial communities, can disrupt mucosal immunity, trigger inflammatory cascades, and directly or indirectly propagate neuroinflammation. These processes underscore the fact that the nasal microbiota is a crucial mediator in the mechanisms linking the nasal environment to CNS health and pathology.

Microbial dysbiosis facilitates the transfer of inflammatory and immune signals from the nasal cavity to the CNS via multiple mechanisms. Pathogens such as *Staphylococcus aureus* and *S. pneumoniae* have been shown to invade the nasal epithelium, releasing toxins and pro-inflammatory molecules that disrupt epithelial integrity and allow immune signaling molecules to access the CNS.[48,49] These inflammatory mediators travel through neural routes such as the olfactory and trigeminal nerves, creating direct communication pathways between the nasal cavity and other brain regions. For instance, bacterial endotoxins such as lipopolysaccharides (LPS) can activate Toll-like receptors (TLRs) on neural and epithelial cells, amplifying inflammatory responses that extend to the CNS.[17,50] Experimental studies have demonstrated that such neuroinflammatory cascades contribute to neurodegenerative diseases such as AD and PD, further highlighting the role of microbial-mediated pathways in linking nasal health to CNS dysfunction.[51] Additionally, recent findings have suggested that nasal *Mycoplasma pneumoniae* infections can increase systemic and neuroinflammatory responses, contributing to mood disorders such as depression.[52] By disrupting immune homeostasis and stimulating the release of

pro-inflammatory cytokines, *M. pneumoniae* may indirectly influence CNS function and exacerbate depressive symptoms, linking nasal infections to neuropsychiatric outcomes.[53]

In addition to immune modulation, microbial metabolites play an important role in connecting the nasal microbiota to the CNS. Beneficial metabolites such as short-chain fatty acids (SCFAs), which are produced by commensal bacteria, can promote anti-inflammatory effects and enhance BBB integrity, facilitating neuroprotection. Conversely, in states of dysbiosis, the production of neurotoxic byproducts such as hydrogen sulfide and nitric oxide increases, exacerbating oxidative stress and mitochondrial dysfunction in neurons.[54,55] Furthermore, certain pathogens, including *Chlamydia pneumoniae* and *Haemophilus influenzae*, utilize neural pathways for direct CNS invasion, bypassing the BBB and inducing localized neuroinflammation.[56–58] These direct microbial invasions establish clear anatomical and functional connections between the nasal cavity and brain, positioning the microbiota as a key regulator of nose-brain interactions. Systemic interactions between the nasal microbiota and other microbial ecosystems, such as the gut microbiota, further emphasize the holistic nature of NBA. Dysbiosis in the nasal cavity can propagate inflammatory signals through the systemic circulation, amplifying neuroinflammatory responses via shared immune pathways. For example, microbial imbalances in both the gut and nasal cavities have been implicated in the exacerbation of PD, illustrating the interconnectedness of these ecosystems and their collective impact on CNS health.[59–61] Together, these findings establish that the nasal microbiota is a critical component of the mechanisms linking the nasal cavity to CNS health through immune, metabolic, and direct microbial pathways.

Insights from the Braak/Dual-Hit Hypothesis

The Braak/dual-hit hypothesis offers a coherent neurodegenerative framework for understanding how peripheral nasal exposures—operating through the nose–brain axis—may initiate or accelerate central proteinopathy.[62] It was originally developed to explain how α-synuclein pathology spreads, both in space and over time, in diseases like Parkinson's. It proposes that an environmental agent, such as a pathogen or toxin, enters the brain through one of two distinct portals: the olfactory epithelium or the gut. Once inside, it moves along neural circuits, propagating from cell to cell in a prion-like fashion.[63] Within the NBA, this model reframes the olfactory nerve not merely as a conduit for sensory transduction, but as a vulnerable entry route through which exogenous agents—including ambient micro/nanoparticles, viral pathogens, or inflammatory mediators—can gain access to the central nervous system and trigger pathological protein aggregation.

Experimental and post-mortem evidence lends credence to this naso-central axis of pathogenesis.[64] Following intranasal instillation, α-synuclein fibrils have been shown to undergo anterograde and retrograde transport along olfactory sensory neurons, reaching the olfactory bulb within hours and progressively involving limbic structures, the amygdala, and brainstem nuclei over weeks to months. This trajectory closely parallels Braak's proposed staging scheme for sporadic PD, in which olfactory bulb pathology precedes nigrostriatal involvement. Clinically, the near-ubiquitous presence of olfactory dysfunction in early PD—often manifesting years before motor symptoms—further underscores the nose as a plausible point of entry.[65] More recent work using traceable nanoparticles has demonstrated that size, surface charge, and persistence in the nasal mucosa govern not only the efficiency of axonal translocation, but also the subsequent microglial response and induction of α-synuclein misfolding in second-order neurons.

Crucially, the relationship between nasal insult and central neurodegeneration is not unidirectional. The dual-hit hypothesis also accommodates a feedback loop in which established CNS pathology exacerbates peripheral vulnerability. In PD and AD, central α-synuclein or tau deposition has been shown to modulate autonomic and sensory efferents that innervate the nasal mucosa, impairing epithelial barrier integrity and reducing odorant receptor expression.[66] This reciprocal crosstalk creates a self-perpetuating cycle: nasal inflammation facilitates CNS entry of pathogenic particles, while ongoing neurodegeneration weakens nasal defenses, rendering the host increasingly susceptible to subsequent environmental hits.

Beyond the olfactory route, the dual-hit framework draws attention to the possibility of synergistic peripheral portals. Micro/nanoparticles deposited in the nasopharynx may be cleared into the gastrointestinal tract, where they can engage the gut–brain axis in parallel. Emerging evidence suggests that nasal and intestinal exposures may act in concert, each capable of seeding pathology and accelerating progression through distinct but converging neural circuits.[67] This has implications for experimental design: studies focusing solely on one portal may underestimate the cumulative burden of peripheral proteinopathy induction.

Despite its heuristic value, the Braak/dual-hit hypothesis remains incompletely validated with respect to the NBA, particularly in the context of anthropogenic particulate exposure. Most supporting data derive from rodent models using supraphysiological doses of preformed fibrils or labelled particles; whether chronic, low-dose exposure to real-world environmental particulates is sufficient to initiate authentic α-synuclein pathology in humans remains unresolved. Moreover, the precise biophysical determinants governing axonal uptake, retrograde transport kinetics, and trans-synaptic transfer are only beginning to be delineated.

Micro/Nanoparticles in NBA

According to our literature review, micro/nanoparticles can play a dual role of being pathogenic and therapeutic and the mechanisms can be seen in Figure 2.

As Pathogenic Agents: harmful micro/nanoparticles from environmental, industrial, microbial, and natural sources can exploit the NBA. Due to their small size and properties, they bypass protective barriers like the nasal epithelium and BBB, entering the CNS. Once inside, they trigger neurotoxicity, neuroinflammation, and oxidative stress, contributing to neurological damage and posing significant public health risks.

As Therapeutic Carriers: in contrast, engineered therapeutic micro/nanoparticles can utilize the same NBA pathway for beneficial purposes. Designed for precise delivery, they transport drugs or genetic material (eg, siRNAs) directly to the brain. This approach effectively treats neuroinflammatory and neurodegenerative conditions while minimizing systemic side effects, turning the NBA into a targeted route for intervention.

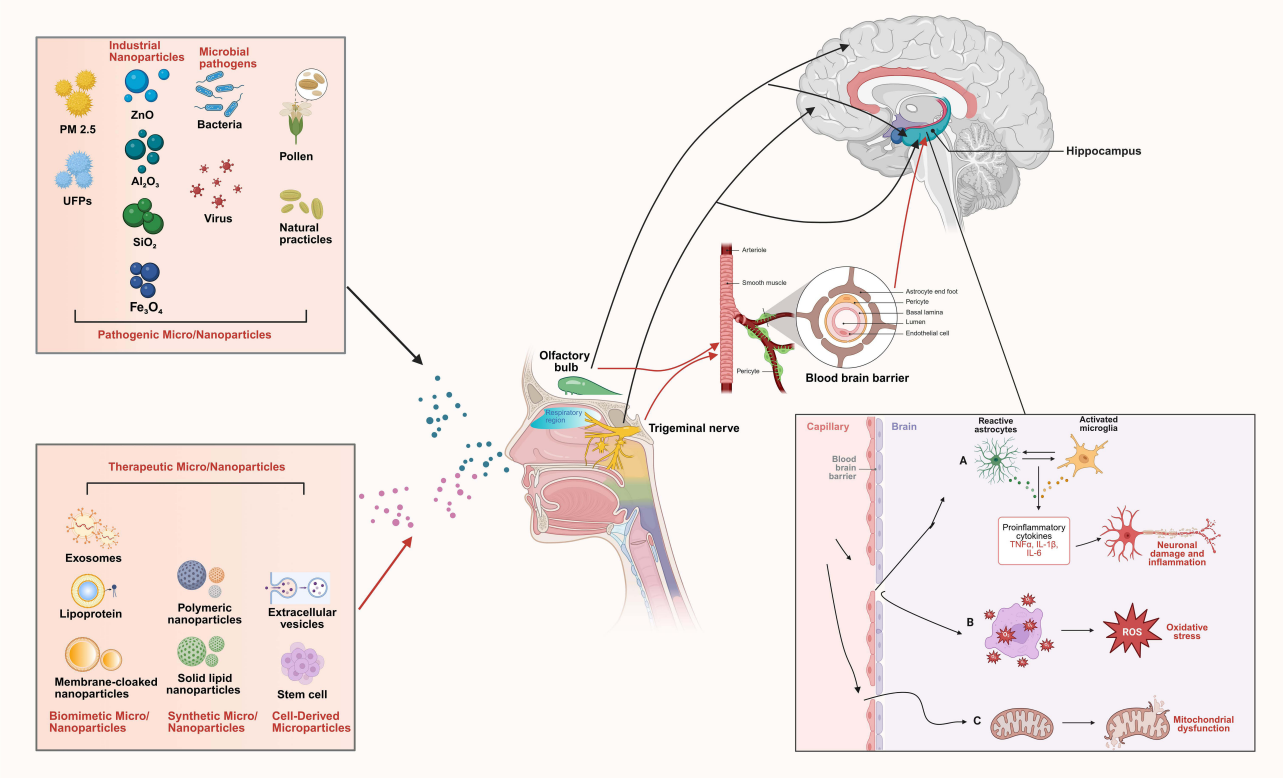


Figure 2 Mechanisms related to the pathogenic and therapeutic effects of micro/nanoparticles through NBA. Once the pathogenic and therapeutic micro/nanoparticles enter the nasal cavity, their smaller size allows penetration into the CNS through the nasal mucosa, mainly through the olfactory or trigeminal nerves. Within CNS, **(A)** these particles activate microglia and astrocytes, triggering the release of pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α, resulting in chronic inflammation, neuronal damage, and the disruption of normal synaptic function. In addition, they can exacerbate neurotoxicity by **(B)** inducing oxidative stress and **(C)** disrupting mitochondrial function. (outside the box, the black arrows represent the pathway of pathogenic micro/nanoparticles, while the red arrows represent the pathway of therapeutic micro/nano-particles).

Abbreviations: NBA, nose-brain axis; CNS, central nervous system; IL-1β, Interleukin-1β; IL-6, Interleukin-6; TNF-α, tumor necrosis factor-α; UFPs, ultrafine particles; ROS, reactive oxygen species.

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The NBA serves as a critical double-edged pathway: it can be infiltrated by pathogenic particles causing neurological disorders, yet it also offers a promising delivery route for precisely engineered therapeutic nanoparticles designed to treat those very disorders. This duality underscores the importance of understanding particle-biomaterial interactions for both toxicology and advanced drug development.

Pathogenic Micro/Nanoparticles

Environmental Pollutants: PM2.5, Ultrafine Particles and Micro-Nanoplastics

Particulate matter (PM), particularly PM2.5 (particulate matter with diameter ≤ 2.5 μm) and ultrafine particles (UFPs; particles with diameter ≤ 100 nm), is one of the most studied contributors to NBA dysfunction. PM2.5 is derived from combustion processes, vehicular emissions, and industrial activities. Its small size enables penetration through the nasal mucosa into the CNS, predominantly via the olfactory and trigeminal nerves.[68] Within the CNS, PM2.5 activates microglia and astrocytes, triggering the release of pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α.[69,70] This cascade results in chronic inflammation, neuronal damage, and the disruption of normal synaptic functions. In addition, PM2.5-associated heavy metals such as manganese exacerbate neurotoxicity by inducing oxidative stress and disrupting mitochondrial function. These metals promote amyloid-beta deposition and tau hyperphosphorylation, which are hallmarks of AD.[71,72] Animal studies have demonstrated a direct relationship between long-term exposure to PM2.5 and cognitive decline, with affected animals exhibiting impairments in spatial memory and learning tasks. UFPs represent an even greater threat because of their nanoscale size and increased surface area, which increase their reactivity and ability to cross biological barriers. Studies have shown that UFPs accumulate in the olfactory bulb and hippocampus, where they induce substantial neuroinflammation and synaptic dysfunction.[73,74] Unlike larger PM particles, UFPs directly interact with neuronal structures, thereby amplifying oxidative stress and inflammatory responses.

Micro- and nanoplastics (MNPs, <5 mm and <100 nm) are environmental contaminants found in human tissues including the brain.[75] Brain MNP levels are ~12-fold higher than in liver and kidneys (up to 30-fold), with potential effects on neurodevelopment and cognition.[76] From 2016 to 2024, brain MNP concentrations rose by ~50%. Compositionally, ~75% are polyethylene (PE), with polypropylene (PP) and others making up the rest.[76] Morphologically, brain MNPs are predominantly nanoscale fragments (<200 nm long, <40 nm wide).

Inhaled or systemically circulating MNPs may enter the central nervous system via nasal deposition and olfactory pathways, where they interact with vascular endothelial cells and immune cells.[77] Mechanistically, MNPs are proposed to induce oxidative stress, thereby activating the neuroimmune microenvironment.[77] This is primarily characterized by the activation of microglia and astrocytes, accompanied by increased release of pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α. Such neuroinflammatory responses may synergistically contribute to microvascular obstruction, impaired local cerebral perfusion, synaptic plasticity deficits, and disruptions in neuronal signaling, ultimately exerting detrimental effects on neural network function.[78] Elevated brain MNP burdens have been observed in individuals with neurocognitive disorders, including dementia.

The aforementioned evidence not only elucidates the specific mechanisms by which environmental pollutants contribute to the pathogenesis of CNS diseases at the molecular experimental level, but has also been further validated in transgenic animal models. In addition, multi-omics technologies have been employed to identify potential genes involved, supported by large-scale clinical studies. However, human-based experimental evidence has primarily focused on the health effects of PM2.5 derived from traffic and fuel combustion, while PM2.5, micro-nanoplastics from other sources has not been sufficiently examined. Moreover, other air pollutants such as nitrogen oxides and ozone may also act synergistically in disease progression, potentially influencing or confounding the experimental outcomes. Although the present study suggests that PM2.5 and micro-nanoplastics can influence the development of neurodegenerative diseases through neuroinflammatory pathways mediated by the NBA, it did not directly assess the specific pathways involving pro-inflammatory factors or related genes. Therefore, these findings may not fully capture the overall impact of PM2.5 and micro-nanoplastics on neuropathological health outcomes.

Industrial Nanoparticles

Engineered nanoparticles, which are widely used in consumer products, medical devices, and industrial processes, pose emerging risks to the NBA and CNS. These nanoparticles can penetrate the CNS via the olfactory and trigeminal pathways, bypassing the BBB and subsequently inducing oxidative stress, neuroinflammation, and cellular toxicity. Zinc oxide (ZnO), aluminum oxide (Al_2O_3), and silica (SiO_2) nanoparticles are among the most studied for their neurotoxic effects. For example, ZnO nanoparticles have been shown to accumulate in the olfactory bulb and hippocampus after intranasal exposure, where they trigger mitochondrial dysfunction, generate ROS, and impair dopaminergic neurons. These effects have been linked to motor deficits and an increased risk of PD, highlighting the vulnerability of the NBA to industrial nanoparticles.[79,80] Similarly, Al_2O_3 nanoparticles disrupt hippocampal signaling pathways, induce neuroinflammation, and promote neuronal apoptosis.[81] These processes result in synaptic loss, impaired memory formation, and cognitive deficits, underscoring the role of Al_2O_3 in exacerbating neurodegenerative conditions such as AD. Another nanoparticle of particular concern is airborne magnetite (Fe_3O_4), a byproduct of urban pollution and industrial activities. Magnetite nanoparticles have been identified in human brain tissue, where they act as catalytic agents for ROS production and exacerbate amyloid-beta aggregation, a hallmark of AD. Their strong association with neurodegenerative pathology emphasizes the systemic implications of chronic nanoparticle exposure.[81,82] A particularly concerning nanoparticle is airborne magnetite (Fe_3O_4), which is associated with urban pollution. Magnetite nanoparticles have been detected in human brain tissue, where they catalyze ROS production and promote amyloid-beta aggregation. Their presence in AD plaques underscores their role in accelerating neurodegenerative processes.[83,84] In addition, titanium dioxide (TiO_2) nanoparticles, which are commonly used in cosmetics and food products, can enter the CNS following intranasal exposure, where they induce neurobehavioral abnormalities such as anxiety-like behaviors and learning impairments. Studies have highlighted the role of TiO_2 nanoparticles in disrupting BBB integrity, increasing neuroinflammation, and altering neurotransmitter levels, particularly in regions critical for cognitive function.[85] Furthermore, industrial nanoparticles such as SiO_2 and carbon-based particles exacerbate CNS injury by amplifying glial activation and neuroinflammatory responses, which can propagate neuronal damage over time.[86]

The aforementioned evidence, through integrated analysis combining molecular, cellular, and animal experiments with multi-omics technologies, have comprehensively examined the impact of industrial nanoparticles on CNS diseases and its underlying mechanisms. These findings highlight the bidirectional vulnerability of the NBA to environmental pollutants and industrial nanoparticles, which not only disrupt neuronal homeostasis, but also exacerbate neurodegenerative processes. Given the widespread presence of these nanoparticles in the environment and consumer goods, stringent monitoring, regulation, and further research are essential to mitigate nanoparticle-induced CNS toxicity.[87,88] However, the lack of large-scale epidemiological evidence or direct experimental studies conducted in human somewhat diminishes the persuasiveness of these results, warranting further investigation in future research.

Microbial Agents and Pathogens

Microbial pathogens, including bacteria and viruses, exploit the NBA as a critical route for CNS invasion, bypassing the BBB via neural pathways such as the olfactory and trigeminal nerves.[89] Bacterial pathogens, such as *S. pneumoniae* and *H. influenzae*, adhere to nasal epithelial cells, disrupt mucosal barrier integrity, and gain enhanced access to the CNS through the perineural spaces. These infections often result in severe neurological complications, including meningitis and encephalitis.[53,90,91] *S. pneumoniae* produces pneumolysin, a toxin that induces epithelial cell death, exacerbates neuroinflammation, and triggers neuronal apoptosis, ultimately accelerating brain damage and cognitive deficits.[92] Additionally, emerging evidence suggests that nasal infections caused by *M. pneumoniae* can increase systemic inflammatory responses and contribute to mood disorders, such as depression. And nasal staphylococcus aureus can produce a sex hormone-degrading enzyme that breaks down testosterone and estradiol, thereby reducing the concentrations of dopamine and serotonin in the brains of mouse models and inducing depressive-like behaviors,[92] demonstrating the bidirectional impact of microbial dysbiosis on the brain and peripheral immune signaling.

The gut microbiota has been confirmed in numerous significant studies to be associated with the pathogenesis of CNS diseases such as cerebral ischemia and AD, and it can promote the biotransformation of certain drugs.[93–95] The gut-brain axis theory provides a new research perspective for revealing the synergistic pathological changes between the brain and

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gut. According to this theory, there exists a bidirectional regulatory mechanism between the CNS and the gut microbiota. Drug intervention strategies based on the gut-brain axis can advance the treatment of CNS diseases by reducing neuroinflammation and oxidative stress.[96] Research by Mishima et al demonstrated that mice with chronic nasal inflammation exhibited significant alterations in the composition of their gut microbiota, with notable sexual dimorphism.[97] The gut microbiota regulates the state of nasal inflammation through specific mechanisms, which is then transmitted to higher brain regions via olfactory neural circuits, triggering neuroinflammation in areas such as the piriform cortex, hypothalamus, and amygdala. The gut microbiota may also be involved in the regulation of NBA, warranting further exploration.

Viral pathogens, particularly severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), have garnered substantial attention owing to their capacity to exploit the NBA for entry into the CNS. SARS-CoV-2 binds to angiotensin-converting enzyme 2 (ACE2) receptors expressed on the nasal epithelial cells, facilitating viral replication and subsequent migration to the brain via the olfactory nerve. This form of neuroinvasion has been implicated in anosmia (loss of smell), cognitive impairment, and persistent neurological sequelae such as brain fog and neuroinflammation.[98,99] Recent findings have indicated that SARS-CoV-2 induces glial activation and alters neuroimmune homeostasis, linking acute viral infections to long-term neurodegenerative risk factors. Other neurotropic viruses, including herpes simplex virus (HSV) and influenza A virus, similarly utilize the olfactory and trigeminal pathways to invade the CNS, underscoring the susceptibility of the NBA to virus-mediated neuropathology. This growing body of evidence highlights the role of the NBA as a conduit for microbial entry, contributing not only to acute CNS infections, but also to chronic neuroinflammatory conditions and neuropsychiatric sequelae. Understanding the molecular mechanisms underlying microbial neuroinvasion is critical for developing preventive strategies and therapeutics to mitigate CNS pathologies.

Pollen and Other Natural Particles

Natural particles such as pollen are allergens that also contribute to NBA dysfunction. Upon hydration, pollen grains release submicron particles and bioactive molecules such as proteases and lipids. These molecules disrupt the nasal epithelial barrier and activate TLRs, initiating inflammatory responses that can propagate to the CNS. Studies have shown that pollen exposure exacerbates AR and asthma, conditions that are often accompanied by neuroinflammatory responses.[100,101] In urban environments, pollen interacts synergistically with air pollutants such as PM2.5, which amplifies immune activation and oxidative stress. These interactions worsen both the respiratory and neurological conditions, linking pollen exposure to a heightened risk of CNS inflammation.[102,103] Emerging evidence suggests that pollen-induced neuroinflammation may have long-term effects on cognitive health, although further research is required to confirm these links.

Therapeutic Potential of Micro/Nanoparticles

Biomimetic Micro/Nanoparticles

Biomimetic micro/nanoparticles represent a groundbreaking advancement in the field of drug delivery, particularly for applications targeting the brain via the NBA. These particles are engineered to emulate the structure and function of natural biological systems such as exosomes, cell membranes, and lipoproteins. Their unique ability to mimic the physicochemical and biological properties of natural entities provides several advantages, including enhanced drug compatibility, increased targeting specificity, prolonged circulation time, and minimal immune system recognition. These characteristics make biomimetic nanoparticles highly effective at crossing the BBB and delivering therapeutic agents directly to the CNS.[104,105]

Recent advances in biomimetic nanoparticle technology have shown significant promise for treating neurodegenerative diseases. A key approach involves using exosome-inspired nanoparticles that mimic the structure and function of natural exosomes—cell-derived vesicles important for intercellular communication. By coating nanoparticles with exosome membranes, researchers have created targeted systems able to deliver therapeutic small interfering RNAs (siRNAs) directly to damaged brain areas.[106] For instance, in AD models, such nanoparticles were designed to carry siRNAs against caspase-3 and β-site amyloid precursor protein cleaving enzyme 1 (BACE1).[107,108] This approach effectively reduced neuronal death and cleared amyloid plaques, hallmark features of AD' s pathology. The treatment

also improved synaptic integrity and enhanced memory in animal studies, offering a potential non-invasive therapy for AD's disease. Owing to the success of exosome-based systems, researchers have explored the use of exosome-mimicking nanoparticles modified with specific targeting ligands such as RVG peptides.[109] These ligands are known for their high affinity for neuronal cells, making them ideal for enhancing the precision of drug delivery. In Huntington's disease models, RVG-modified nanoparticles successfully delivered therapeutic RNA molecules to neuronal tissues, resulting in improved motor function and reduced neurodegeneration.[110,111]

In addition to RNA delivery, the use of bioinspired lipid-coated nanoparticles has emerged as a promising strategy for the treatment of PD. By integrating neural cell membrane components into nanoparticle designs, researchers have developed systems that exhibit superior biocompatibility and retention in the nasal cavity. In addition to facilitating efficient transport to the brainstem, these lipid-coated nanoparticles can also provide neuroprotection by reducing oxidative stress and enhancing mitochondrial function. Preclinical studies have demonstrated that these particles can effectively mitigate the loss of dopaminergic neurons, a critical pathological feature of PD, thereby improving motor coordination and the overall quality of life in animal models.[112]

Subsequent innovations in biomimetic nanoparticle technology have focused on leveraging hybrid systems that combine natural and synthetic components. For example, cell-membrane-cloaked nanoparticles have been developed to enhance drug delivery and immune evasion. These hybrid systems employ cell membranes from platelets or red blood cells to provide a biologically derived surface coating, which prolongs systemic circulation while enabling active targeting of inflammatory or diseased brain regions.[113] These systems have shown promise in preclinical models of multiple sclerosis and traumatic brain injury, in which they have demonstrated the ability to deliver anti-inflammatory and neuroprotective drugs with high precision.[114]

Another emerging avenue of biomimetic nanoparticle research involves the use of targeted biomimetic vesicles in combination therapies. These vesicles are engineered to co-deliver multiple therapeutic agents such as chemotherapeutics, gene-editing tools, and neuroprotective drugs. For example, biomimetic nanoparticles functionalized with tumor-targeting peptides have been used to deliver a combination of paclitaxel and clustered regularly interspaced short palindromic repeats (CRISPR)-Cas9 constructs in glioblastoma models.[115] This approach has been shown to enhance tumor suppression and reduce systemic toxicity, underscoring the potential of biomimetic systems to revolutionize the treatment of aggressive CNS cancers.[116]

In addition to extensive preclinical studies, significant progress has been made in the clinical translation of exosome-based therapies. Currently, several clinical trials are underway or planned: An exploratory Phase I study of induced pluripotent stem cell-derived exosomes (GD-iEXo-002), administered as nasal drops for refractory focal epilepsy, is ongoing at Peking Union Medical College Hospital in China, sponsored by Guidon Pharmaceutics Ltd; A blinded randomized controlled trial is planned in Moscow, Russia, to investigate intranasal administration of MSC-derived exosomes in extremely low birth weight infants.[117]

Despite these promising advancements, several challenges regarding clinical translation of biomimetic nanoparticles remain unresolved. Issues such as large-scale manufacturing, stability during storage, and potential immunogenicity must be addressed to ensure their safety and efficacy for human applications.[118] Additionally, further studies are required to optimize the pharmacokinetics and biodistribution of these systems, and to evaluate their long-term effects in chronic disease models.[119]

In conclusion, biomimetic micro/nanoparticles have shown immense potential for transforming the landscape of CNS drug delivery. By emulating the properties of natural biological systems, these nanoparticles offer unprecedented opportunities for targeted, efficient, and non-invasive therapeutic interventions. Future research should focus on refining these technologies and overcoming translational barriers to unlock their full potential in clinical settings.

Synthetic Micro/Nanoparticles

Synthetic micro/nanoparticles have garnered substantial attention as versatile drug-delivery platforms owing to their exceptional ability to be tailored for specific therapeutic applications. Within the context of the NBA, these nanoparticles offer a unique advantage in overcoming the BBB by enabling direct delivery through the olfactory and trigeminal

pathways. This targeted approach can improve therapeutic efficacy and minimize systemic side effects, making synthetic nanoparticles highly promising options for treating CNS disorders such as glioblastoma, AD, and PD.

One of the most advanced classes of synthetic nanoparticles is polymeric nanoparticles, which are fabricated from biodegradable materials such as chitosan and PLGA. These polymers are well-known for their biocompatibility, stability, and ability to encapsulate hydrophilic and hydrophobic drugs. Recent studies have explored their application via the nose and brain by designing PLGA-chitosan nanoparticles optimized for nasal retention and mucosal penetration. For instance, these nanoparticles were engineered to co-deliver cetuximab (an epidermal growth factor receptor [EGFR] inhibitor) and metabolic modulators directly to glioblastoma multiforme (GBM) tumor sites via the nasal cavity.[114,120] This approach bypassed the systemic circulation and BBB, ensuring precise drug delivery and significantly enhancing anti-tumor efficacy in preclinical models.[121] Furthermore, a randomized double-blind trial demonstrated that patients with olfactory dysfunction lasting more than 6 months showed significantly improved olfactory function and a marked reduction in calcium levels in their nasal mucus after receiving chitosan nasal gel.[122]

Another important class is solid lipid nanoparticles (SLNs), which provide a lipid-based matrix capable of encapsulating lipophilic drugs, protecting them from degradation, and increasing their solubility.[123] SLNs have demonstrated remarkable potential for delivering PD therapies through the nose-brain pathway. A notable example is pramipexole-dihydrochloride-loaded SLNs, which were optimized for nasal administration. These nanoparticles showed enhanced uptake through the nasal epithelium and targeted delivery to the substantia nigra of the brain.[112] This approach increased dopamine bioavailability, reduced oxidative stress, and mitigated dopaminergic neuronal degeneration in animal models, leading to improved motor function and overall neurological health.[124]

An emerging innovation in this field is the development of stimuli-responsive nanoparticles designed to release their therapeutic payloads in response to specific conditions, such as ROS, pH changes, or enzymatic activity commonly found in diseased brain regions.[125,126] For nose-to-brain applications, ROS-responsive nanoparticles have been engineered to deliver siRNAs targeting the amyloid-beta pathways in AD. When administered intranasally, these nanoparticles utilize the elevated ROS levels in the brain to trigger the release of siRNAs and achieve precise spatiotemporal control.[106,127] This strategy significantly reduced amyloid plaque burden and improved cognitive performance in preclinical AD models, underscoring the value of such targeted approaches.[105,128]

Hybrid nanoparticles combine polymers and lipids to achieve structural stability, improved biocompatibility, and better targeting. They have become promising platforms for nose-to-brain drug delivery by addressing issues like poor mucosal adhesion, short nasal retention, and low BBB permeability.

Sukumar et al developed hybrid nanoparticles with a gelatin methacryloyl (GelMA)-based hydrogel core and a phosphatidylcholine lipid coating for glioblastoma therapy.[114] These nanoparticles co-delivered the chemotherapeutic drug temozolomide and the imaging agent indocyanine green via intranasal administration. The GelMA core offered stable, controlled drug release, while the lipid coating enhanced nasal adhesion and retention. This system effectively delivered drugs to brain tumors, improving treatment and enabling real-time imaging.

Raj et al designed lipid–polymer hybrid nanoparticles using a chitosan-grafted polyethylene glycol (PEG) hydrogel and phospholipids to deliver dopamine precursors and antioxidants for Parkinson's disease.[129] Chitosan improved mucoadhesion and sustained release, while PEG increased biocompatibility and reduced immune reactions. Given intranasally, the particles used olfactory and trigeminal pathways to bypass the BBB and reach affected brain regions.[112]

Bonaccorso et al formulated agarose–lipid hybrid nanoparticles to encapsulate amphotericin B for treating fungal meningitis. The polysaccharide agarose improved drug stability and nasal adhesion, and the lipid layer promoted penetration across the nasal epithelium. Through nose-to-brain pathways, high drug levels were achieved in the meninges, effectively clearing infection while lowering systemic toxicity.[130]

Ali et al created spanlastic nanoparticles with a deformable lipid bilayer (Span 60 and Tween 80) to deliver piperine for epilepsy management. This flexible system enhanced nasal mucosal penetration, provided prolonged and controlled drug release, and successfully transported piperine to the brain via olfactory and trigeminal routes. As a result, seizure frequency was reduced, neuroprotection was strengthened, and cognitive function was restored in preclinical models.[131]

Cell-Derived Microparticles

By leveraging the NBA to bypass the BBB and deliver therapeutic molecules directly to the brain, cell-derived microparticles, particularly extracellular vesicles (EVs) such as exosomes, offer promising platforms for CNS therapies. EVs derived from mesenchymal stem cells (MSCs) have shown potential in modulating neuroinflammation and clearing amyloid plaques in AD.[132] In addition, neuron-derived EVs (NDEVs) have demonstrated superior neuronal targeting, facilitating synaptic recovery in traumatic brain injury.[133,134] In PD, dopaminergic neuron-derived exosomes effectively restored motor function by delivering dopamine and antioxidants to the substantia nigra,[134,135] and macrophage-derived EVs, which target tumors with integrin-functionalized vesicles to reduce growth and invasiveness, have been explored for glioblastoma treatment.[136] Astrocyte-derived exosomes have also shown promise in the treatment of fungal meningitis, achieving high CNS drug concentrations and reducing inflammation.[137,138] Although EVs display remarkable versatility and adaptability in CNS applications, challenges such as scalability, standardized production, and disease-specific targeting optimization must be addressed to ensure successful clinical translation.

In addition to EVs, the intranasal delivery of stem cells represents a transformative and non-invasive approach for CNS therapies, effectively bypassing the BBB via the olfactory and trigeminal pathways. This method capitalizes on the inherent ability of stem cells to home onto injury sites, modulate inflammation, and promote neuroregeneration, indicating their promising therapeutic potential across diverse CNS disorders. For instance, the intranasal delivery of stem cells has shown efficacy in conditions ranging from neurodegenerative diseases such as PD[139] and AD[140] to glioblastoma[141] and ischemic stroke.[142] Studies have consistently demonstrated that targeted migration of stem cells to affected brain regions, facilitated by nasal transport mechanisms, results in reduced neuroinflammation, enhanced neuronal repair, and improved functional recovery.[143,144] Clinical and preclinical studies have also highlighted the versatility of this approach. Jiang et al demonstrated the preliminary clinical benefits of intranasal neural stem cell transplantation in patients with PD, with significant improvements in motor function observed at six months post-treatment. Jeon et al demonstrated efficient glioblastoma targeting via paracrine signaling and immune modulation. Furthermore, Wei et al demonstrated that intranasally delivered hypoxia-preconditioned MSCs enhanced repair in ischemic stroke models by localizing to ischemic regions and reducing the infarct volume. An open-label, single-center Phase I/II trial evaluating the safety and efficacy of allogenic adipose MSC-derived exosomes in Alzheimer's disease patients is being conducted at Ruijin Hospital, Shanghai Jiao Tong University, sponsored by Cellular Biomedicine Group Ltd.[145] Despite these promising advancements, challenges persist in optimizing the delivery efficiency, scalability, and therapeutic consistency of cell-derived microparticles such as exosomes and stem cells. Key hurdles include standardizing production, increasing targeting precision, and addressing the variability in efficacy across CNS pathologies. Future efforts should focus on refining the engineering strategies and exploring the synergies between exosomes and stem cell technologies to increase their therapeutic potential and clinical applicability.

Inspirations from the NBA for Peripheral-Central Communications

Insights from the NBA to Body-Brain Communication

Body-brain communication has emerged as a transformative framework for understanding the dynamic interactions between peripheral organs and the CNS. Since the discovery of the gut-brain axis, which highlights the role of microbial metabolites in influencing brain function and behavior, studies have revealed several other communication axes, including the heart-brain, lung-brain, liver-brain, kidney-brain, spleen-brain, and muscle-brain axes.[146] Each of these pathways provides unique insights into the impact of peripheral organ systems on CNS homeostasis, disease progression, and neuroimmune modulation. For instance, the gut-brain axis, one of the most well-studied body-brain communication systems, highlights the role of gut microbiota-derived metabolites such as SCFAs in regulating neuroinflammation and cognitive function.[147] Similarly, the lung-brain axis emphasizes the effect of respiratory pathogens and environmental pollutants on neuroinflammation and neurodegeneration, particularly through systemic immune activation.[148] Moreover, the heart-brain axis highlights the intricate relationships among cardiovascular health, cerebral blood flow, and cognitive decline, with increasing evidence linking heart dysfunction to neurodegenerative diseases.[149]

In addition to the visceral organ axes, sensory organs are gaining recognition for their role in body-brain communication. For example, the eye-brain axis can mediate neurodegenerative and inflammatory processes, and retinal changes are associated with CNS diseases such as AD and multiple sclerosis.[150] Similarly, studies on the throat-brain and larynx-brain axes have demonstrated how inflammatory or microbial disruptions in the upper respiratory tract can influence brain function via shared neural pathways.[151] As discussed in this review, the NBA represents a distinct and critical communication route because of its direct anatomical connection to the CNS. While other body-brain axes predominantly rely on systemic circulation to transmit signals, the NBA bypasses the BBB through the olfactory and trigeminal pathways. This direct link enables the rapid transport of pathogens, cytokines, and therapeutic agents, establishing the NBA as both a pathogenic and therapeutic pathway. Importantly, the NBA also shares some characteristics with other axes, particularly in its reliance on microbial communities and immune signaling mechanisms to mediate peripheral-central communication. Exploration of body-brain axes, including the gut-brain, heart-brain, and lung-brain systems, has opened new avenues for understanding systemic diseases and their impact on brain health. However, the role of the nasal microbiota, as well as the environmental and inflammatory factors within the NBA, deserves further investigation to determine the full potential of the NBA in modulating neuroimmune pathways and influencing CNS pathology. Future studies focusing on the shared mechanisms across the body-brain axes, such as immune activation, microbial dysbiosis, and neuroinflammation, may provide integrated therapeutic strategies for systemic and CNS disorders.

Advantages of the NBA Over Other Body-Brain Axes

Owing to its anatomical and physiological properties, the NBA is a uniquely efficient pathway for CNS interventions. Unlike the gut-brain and lung-brain axes, which rely on systemic circulation and intermediary processes for signal transduction, the NBA bypasses the BBB via the olfactory and trigeminal nerves. This direct access enables rapid and localized delivery of therapeutic agents such as nanoparticles and stem cells to specific brain regions, minimizing systemic dilution and delays.[152] For example, nanoparticles loaded with anti-inflammatory drugs can effectively target inflamed hippocampal regions through the NBA and reduce neuroinflammation without causing systemic toxicity. Furthermore, the NBA can enhance therapeutic precision by minimizing off-target effects that are common in systemic delivery. For instance, dopamine-loaded nanoparticles and siRNA therapies for neurodegenerative diseases such as PD and AD have demonstrated significant improvements in targeting the substantia nigra and amyloid plaques, respectively, while reducing peripheral toxicity.[153] Additionally, the non-invasive nature of nasal delivery avoids the risks associated with invasive methods, making it more accessible for patients with chronic conditions and vulnerable populations.

In addition to CNS-targeted therapies, the NBA holds substantial potential for systemic modulation. In comparison with the gut-brain axis, the NBA enables faster signal transmission, where microbial metabolites such as SCFAs rely on slower systemic pathways.[154] The NBA can also regulate other body-brain communication systems, such as gut-brain signaling, by modulating vagal nerve activity.[155] Olfactory stimulation has been shown to improve autonomic balance and reduce inflammation linked to lung-brain interactions during respiratory infections. Recent advancements in nanotechnology and stem cell-derived exosomes have further enhanced the bioavailability and targeting capabilities of the NBA. These strategies have demonstrated potential as neuroregenerative therapies for ischemic stroke and AD, highlighting the versatility of this axis in addressing a broad range of CNS and systemic disorders.[156] This integration of cutting-edge therapeutic strategies positions the NBA as a cornerstone for future systemic and CNS-targeted therapeutic advancements.

Therapeutic Opportunities and Safety Imperatives: "Treating Nasal Diseases Through the Brain" and "Treating Brain Diseases Through the Nose"

The bidirectional delivery facilitated by the NBA offers a foundation for innovative therapeutic strategies, allowing for the integrated treatment of both CNS and nasal disorders. This dual potential opens up transformative opportunities to address diseases through targeted and cross-acting interventions. For "treating brain diseases through the nose", the intranasal delivery of therapeutic agents has demonstrated significant success in bypassing the BBB to directly target the affected CNS regions. For example, dopamine-loaded nanoparticles can improve motor deficits in PD models by

efficiently delivering therapeutic cargo to dopaminergic neurons in the substantia nigra.[157] Similarly, exosome-based carriers loaded with siRNAs and neuroprotective agents can reduce amyloid plaque deposition, mitigate neuroinflammation, and promote neuronal repair in AD.[158] In addition to neurodegeneration, the intranasal delivery of anti-inflammatory agents and growth factors has shown promise for ischemic stroke recovery by facilitating neuroregeneration and reducing brain tissue damage.[159]

Conversely, for "treating nasal diseases through the brain", neuromodulation of CNS circuits offers novel approaches for managing nasal pathologies. For instance, CRS and AR are strongly influenced by neurogenic inflammation mediated through the central neural pathways. Targeting brain areas associated with sensory processing and autonomic control can alleviate nasal inflammation and improve symptom management.[160] Studies have also highlighted the potential of brain-derived signaling to influence nasal mucosal immunity, restore epithelial barrier function, and reduce susceptibility to recurrent infections. For example, central interventions that modulate the HPA axis are effective in reducing nasal inflammation triggered by systemic stress responses.[161] Furthermore, interventions targeting the nasal microbiome provide exciting avenues for bidirectional therapy. The nasal cavity harbors diverse microbial communities that influence local and CNS health. Dysbiosis of the nasal microbiota has been linked to neurodegenerative and inflammatory conditions such as CRS, cognitive decline, and depression. Regulation of the nasal microbiota through probiotics, antimicrobial agents, or immune-modulating therapies has shown potential for improving nasal mucosal immunity, while indirectly modulating CNS inflammation and cognitive function.[146,162]

The therapeutic promise of the nose–brain axis is inseparable from a clear-eyed commitment to safety—and to the principles of Safe-and-Sustainable-by-Design.[163] The very features that enable non-invasive access to the CNS also open the door to distinct risks. Approaches that aim to treat nasal disease by modulating central circuits need to be assessed not just for efficacy, but for neural selectivity: imprecise targeting could just as easily disrupt olfactory signaling or spill into circuits involved in mood and cognition. On the other side of the equation, intranasal nanoparticles designed to reach the brain bring their own set of concerns—mucosal barrier disruption, accumulation in the olfactory bulb, chronic microglial activation driven by prolonged particle persistence, and unclear clearance trajectories.[10] Delivery efficiency alone is no longer sufficient as a benchmark. Translational development must now contend with biodistribution, degradability, residence time, and the distinction between local and remote toxicity. An SSbD-oriented mindset—one that favors biodegradable materials, surface chemistries that evolve after barrier crossing, and dosing regimens that respect the regenerative capacity of the nasal epithelium—needs to move from aspirational to foundational.[164] The real question going forward is not whether NBA-based therapeutics can work, but whether they can do so without introducing new, long-term neurobiological liabilities.

Summary and Prospects

The NBA is not only a transformative pathway for drug delivery but also a bidirectional communication system between the nasal cavity and the CNS, facilitating intricate organ–organ interactions. Unlike traditional therapeutic strategies that focus solely on the delivery to the BBB, strategies focused on the NBA are based on the direct influence of peripheral signals, ranging from cytokines to environmental particulates, on CNS health and function. For example, inflammatory cytokines and microRNAs triggered by environmental pollutants, such as PM2.5, propagate neuroinflammation and cognitive impairment through the olfactory and trigeminal pathways. Conversely, therapeutic interventions targeting brain disorders, such as neurodegenerative diseases or neuroinflammation, can utilize the NBA to modulate nasal or peripheral immune responses, exemplifying the potential for "treating brain diseases through the nose" and "treating nasal diseases through the brain". This reciprocal influence underscores the broader importance of the NBA as an interactive system rather than merely a unidirectional drug-delivery pathway. We have made a summary of potential micro/nanoparticles that play a role in disease pathogenesis and therapy through the NBA which can be seen in Table 1.[72,109,110,165–193]

The implications of the NBA extend beyond CNS-targeted therapies, serving as a model for understanding and leveraging other body-brain communication systems. While axes such as the gut-brain or lung-brain pathways depend on systemic intermediaries, the NBA offers a direct, localized mechanism to study peripheral-to-central signaling and vice versa. By exploring the interplay between nasal inflammation and CNS disorders or brain-directed interventions that

Table 1 Potential Micro/Nanoparticles Acting Through the Nose-Brain Axis in Disease Pathogenesis and Treatment

Micro/Nanoparticles Type	Size	Zeta	Disease	Reference
Pathogenic Micro/Nanoparticles				
Environmental Pollutants	–	–		
$PM_{2.5}$			Alzheimer's disease	Hüls et al[72]
$PM_{2.5}$(50 μg/mL)	–	–	Parkinson's disease	Du et al[165]
Sulfur dioxide (SO_2)	–	–	Parkinson's disease	Chung et al[166]
$PM_{2.5}$ (> 15 $\mu g/m^3$)	–	–	Multiple sclerosis	Gallo et al[167]
Nitrogen Dioxide (NO_2)	–	–	Multiple sclerosis	Marco et al[168]
$PM_{2.5}$	2.5–10 μm	–	Vascular dementias	Lin et al[169]
$PM_{2.5}$	≤ 2.5 μm	–	Allergic rhinitis	Chai et al[170]
NO_2	–	–	Allergic rhinitis	Mao et al[171]
Industrial Nanoparticles				
Nanoscale-alumina (Al_2O_3-NPs)	30–60 nm	−20 mV	Alzheimer's disease	Myeong et al[172]
Al_2O_3	22.63 ± 5.64nm	−39.3mV	Neurodegenerative disease	Xi et al[173]
ZnO nanoparticles	19.61 ± 5.83 nm	+27 mV	Alzheimer's and Parkinson's disease	Lynch et al[174]
Silica nanoparticles (SiO_2-NPs)	156±26.2nm	−11.1±1.3mV	Parkinson's and Alzheimer's diseases	Xue et al[175]
Microbial Agents and Pathogens				
SARS-CoV-2	-	-	Neurodegenerative disease	Smith et al[176]
Neisseria meningitidis	-	-	Meningitis	Wijdicks et al[177]
Helicobacter pylori			Alzheimer's diseases	Xie et al[178]
Herpes simplex virus	-	-	Encephalitis	Boivin et al[179]
Pollen and Natural Particles				
Pollen	-	-	Allergic rhinitis	Giorgio et al[180]
Mold spore	-	-	Alzheimer's diseases	Priya et al[181]
Dust mite	-	-	Alzheimer's diseases	Sahu et al[182]
Dust mite	-	-	Allergic rhinitis	Hellings et al[183]
Therapeutic Micro/Nanoparticles				
Biomimetic Micro/Nanoparticles				
Rabies virus glycoprotein peptides	189.7± 12.3 nm	−22.8 ± 0.8 mV	Multiple sclerosis	Shi et al[109]
Liposomes	53-70 nm	−12.3 mV	Alzheimer's Disease	Wang et al[184]
Polydopamine	64 ± 9 nm	+25 mV	Parkinson's Disease	Javier et al[185]
Selenium/Human Serum Albumin	~60 nm	−29.1 mV	Parkinson's Disease	Xu et al[186]

(*Continued*)

Table 1 (Continued).

Micro/Nanoparticles Type	Size	Zeta	Disease	Reference
Synthetic Micro/Nanoparticles				
Polymeric nanofibers	347 ± 2 nm	1.87 ± 0.04 mV	Alzheimer's disease	Ece et al[187]
Cyclodextrin-based nanoparticles	169 ± 6.20nm	15–16 mV	Huntington's disease	Monique et al[110]
Chitosan nanoparticles	188.9 ± 0.2 nm	36.2 ± 0.2 mV	Allergic rhinitis	Lee et al[188]
PLGA nanoparticles	198.1 ± 3.4 nm	−29.1±1.7mV	Parkinson's Disease	Karin et al[189]
Cell-Derived Microparticles				
RAW264.7 cell membrane	47.6 ± 7.5 nm	−23 mV	Parkinson's Disease	Qing et al[190]
Exosomes	10-30nm	− 30 mV	Memory disfunction	Mikel et al[191]
Mesenchymal stem cell	-	-	Traumatic brain injury	Li et al[192]
Red Blood Cell Microparticles	-	-	Intracerebral hemorrhage	Ashish et al[193]

mitigate nasal diseases, studies on the NBA can inspire new approaches to address systemic inflammation, neuroimmune crosstalk, and organ-specific pathologies. Moreover, these findings can provide a platform for the integration of environmental toxicology, neuroscience, and precision medicine, thereby driving innovations in diagnostic biomarkers, neuroprotective strategies, and systemic disease management.

Current research on the NBA remains largely at the preclinical stage. Future efforts should prioritize multicenter clinical studies to further evaluate its specific therapeutic efficacy. Building on this, machine learning techniques—such as causal inference models and graph neural networks—can be employed to integrate multimodal data (eg, proteomic, metabolomic, and microbiome profiles). This approach aims to reverse-engineer the core pathway networks connecting peripheral biomarkers with central imaging features, thereby uncovering novel therapeutic targets. Additionally, predictive models based on baseline clinical, biochemical, and imaging characteristics can be constructed to simulate treatment outcomes and optimize patient selection prior to therapy, thus maximizing the efficiency of medical resources. By systematically decoding the language of the nasal-brain axis and leveraging intelligent technologies to translate this knowledge into personalized and preventive diagnostic and therapeutic strategies, our ultimate goal extends beyond restoring a single sensory function. This integrated perspective will position the NBA not only as a gateway for CNS therapies, but also as a foundational framework for advancing the understanding of peripheral-to-central communications and inter-organ interactions across the body.

Data Sharing Statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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.

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Disclosure

The authors declare no conflicts of interest in this work.

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