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Innovative Nose-To-Brain Drug Delivery Strategies for Neuroprotection in Diabetes-Associated Cerebral Ischemia: Advances, Challenges and Translational Perspectives

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ABSTRACT

Intranasal delivery has gained significant attention as a non-invasive and efficient route to target neuroprotective agents directly to the brain, especially in managing diabetes-associated cerebral ischemia. This delivery bypasses the blood-brain barrier, maximizing therapeutic concentrations in the central nervous system while minimizing systemic exposure and associated side effects. Studies on intranasal insulin and insulin-like growth factor-1 (IGF-1) have demonstrated neuroprotection via vasodilatory, anti-inflammatory, antithrombotic effects and improved neuronal metabolism, functional connectivity and neurotransmitter regulation. Intranasal administration of exendin-4, a glucagon-like peptide-1 receptor agonist used for diabetes, has also shown promising neuroprotective effects in animal models of ischemic stroke by reducing infarct volume and neurological deficits without significant peripheral effects. Moreover, evidence suggests that intranasal insulin ameliorates experimental diabetic neuropathy by directly targeting the nervous system, avoiding systemic insulin exposure that can lead to hypoglycaemia and restoring key signalling pathways in dorsal root ganglia. Overall, intranasal delivery represents a feasible, safe and effective approach for neuroprotective therapy in diabetic stroke and neuropathy, demonstrating compelling potential for clinical translation.

Keywords: Intranasal delivery, Nose-to-brain transport, Diabetic stroke, Neuroprotection, Blood-brain barrier, Nanocarriers, Cerebral ischemia

Abbreviations Section: BBB, CNS, MCAO, IGF-1, PLGA, NLC, NPs

1. Introduction

Diabetes mellitus is a chronic metabolic disorder characterized by persistent hyperglycemia resulting from defects in insulin secretion, insulin action or both[1]. Globally, the prevalence of diabetes is rapidly increasing, with significant implications for public health due to its association with cardiovascular and cerebrovascular complications[2]. One of the most severe neurological complications observed in diabetic patients is cerebral ischemia, commonly manifesting as ischemic stroke,

which leads to substantial morbidity and mortality[3]. Diabetic patients not only have a higher risk of stroke but also experience more severe neurological deficits and poorer recovery outcomes compared to non-diabetic individuals[4,5]. The pathophysiology underlying diabetes-associated cerebral ischemia involves complex mechanisms such as impaired cerebral blood flow autoregulation, increased oxidative stress, neuroinflammation and enhanced neuronal apoptosis[6,7].

Despite advances in acute ischemic stroke management, including thrombolytic therapies and mechanical thrombectomy, therapeutic options specifically targeting neuroprotection in diabetic stroke remain limited[8]. The development of effective neuroprotective agents is critical for limiting infarct size and improving neurological function post-stroke; however, systemic administration of these agents faces major obstacles, primarily the blood-brain barrier (BBB)[9]. The BBB is a highly selective semipermeable barrier that restricts the entry of most therapeutic molecules into the brain, thereby limiting drug bioavailability at the ischemic site[10]. Consequently, novel drug delivery strategies that can effectively circumvent the BBB and enhance targeted brain delivery are urgently needed.

Intranasal (IN) drug delivery has emerged as a promising non-invasive approach for delivering neuroprotective agents directly to the brain, bypassing the BBB through the olfactory and trigeminal neural pathways[11,12]. The nasal route offers multiple advantages such as rapid drug absorption, avoidance of first-pass metabolism and the potential for self-administration, thereby improving patient compliance[13]. Intranasal delivery exploits the unique anatomical connection between the nasal cavity and the central nervous system (CNS), enabling direct transport of therapeutics along neuronal pathways[14]. This route provides an efficient means to deliver a wide range of drugs, including peptides, proteins and small molecules, which are otherwise challenging to administer systemically[15,16].

Significant progress has been made in understanding the nasal anatomy, physiology and the underlying mechanisms governing nose-to-brain transport[17]. Key advancements include the development of innovative formulations such as nanoparticles, mucoadhesive gels and in situ forming systems, which enhance drug stability, mucosal retention and brain targeting efficacy[18,19]. Alongside these technological breakthroughs, various neuroprotective agents-both synthetic like insulin and natural compounds such as melatonin-have been investigated for intranasal delivery with encouraging preclinical and early clinical results[20,21]. These agents demonstrate the ability to modulate key pathological processes including oxidative stress, inflammation and apoptosis in diabetes-associated cerebral ischemia[22].

(Figure 1) explain schematic illustration of intranasal drug transport pathways to the central nervous system. Following administration, drugs interact with the nasal epithelium and underlying lamina propria and are transported via olfactory and trigeminal neural pathways, perivascular channels and systemic circulation. In the olfactory region, drugs access the cerebrospinal fluid and olfactory bulbs, while distribution within the brain occurs through bulk CSF flow and perivascular spaces. These routes also contribute to bidirectional solute clearance between the CNS and the periphery.

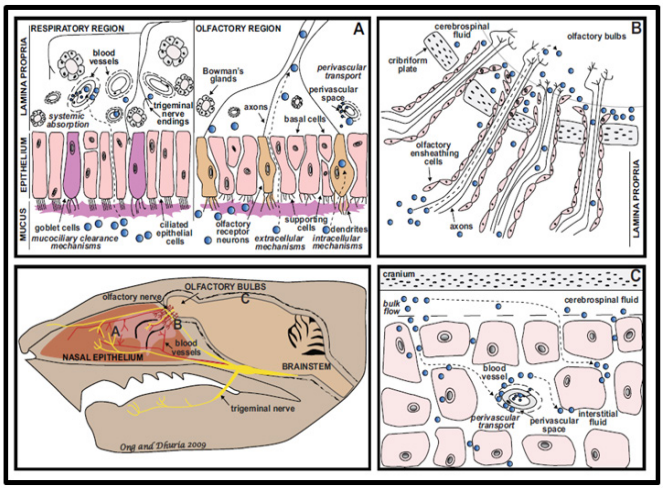

Figure 1: Mechanisms and Pathways of Intranasal Drug Delivery to the Central Nervous System[11].

(Figure 2) demonstrates a conceptual overview of Intranasal Delivery as a promising route for drug administration, particularly targeting the central nervous system. It shows that drugs administered through the nasal cavity can reach the brain via the olfactory and trigeminal nerve pathways, thereby bypassing the blood-brain barrier. The diagram highlights neuroprotective agents such as insulin and melatonin as therapeutic candidates delivered through this route. It also outlines key formulation strategies-including nanoparticles, mucoadhesive gels and enzyme inhibitors-designed to enhance drug absorption, stability and residence time in the nasal mucosa.

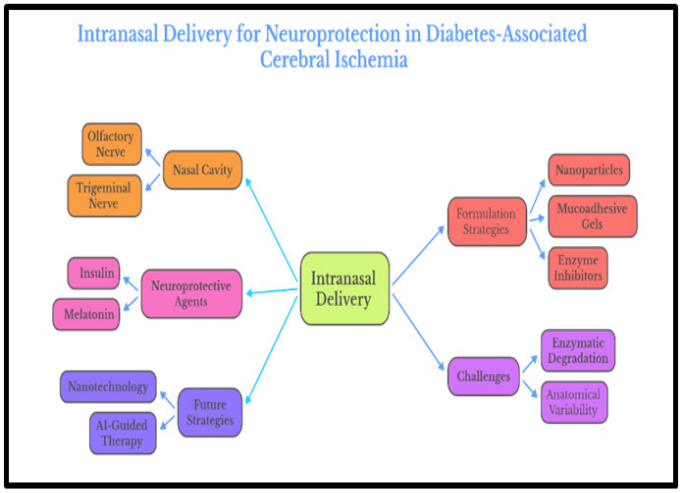

Figure 2: Intranasal Delivery Strategies for Neuroprotection in Diabetes-Associated Cerebral Ischemia.

However, despite promising data from animal models and pilot clinical studies, several translational challenges impede the widespread clinical adoption of IN neuroprotective therapies[23]. These include anatomical variability of the nasal cavity, mucociliary clearance, enzymatic degradation of peptides and regulatory hurdles concerning safety and efficacy evaluation[24]. Additionally, there is a need for comprehensive clinical trials to establish optimized dosing regimens and long-term safety profiles[25].

In this review, we provide an updated and comprehensive analysis of the physiology of nose-to-brain drug delivery, current formulation strategies and the spectrum of neuroprotective agents relevant to diabetes-associated cerebral ischemia and

evidence from preclinical and clinical studies. We also critically discuss challenges and future perspectives focused on enhancing the translational success of intranasal neuroprotective therapies. Collectively, this review aims to highlight the promising role of intranasal delivery as a novel paradigm to improve outcomes in patients suffering from diabetes-associated cerebral ischemia and stroke.

2. Anatomy and Physiology: Nose-to-Brain Transport

The nasal cavity serves as a direct anatomical interface between the external environment and the brain, allowing drug delivery strategies to bypass the restrictive blood-brain barrier (BBB) via the nose-to-brain route[26]. The olfactory region, located in the upper part of the nasal cavity, is characterized by olfactory sensory neurons whose axons project directly into the olfactory bulb of the brain[27]. This unique neuroanatomical arrangement permits intracellular axonal transport of molecules from the nasal mucosa to the central nervous system (CNS)[28].

Two major pathways mediate nose-to-brain transport: the olfactory nerve pathway and the trigeminal nerve pathway. The olfactory pathway transmits substances via neuronal uptake and axonal transport across the cribriform plate to the olfactory bulb[29]. The trigeminal nerve pathway innervates the respiratory region of the nasal cavity and provides an additional conduit for drug delivery toward the brainstem and spinal cord[30]. Both pathways support extracellular diffusion via perineural channels and endocytosis, facilitating rapid drug movement into the CNS while minimizing systemic exposure[31].

The nasal mucosa itself consists of pseudostratified ciliated columnar epithelial cells, basal cells, mucus-secreting goblet cells and an underlying lamina propria with a network of blood vessels and nerves[32]. The epithelium forms tight junctions that regulate permeability, while the mucus layer and mucociliary clearance mechanisms serve as physiological barriers, influencing drug residence time and bioavailability[33]. These barriers pose challenges for sustained drug absorption but are mitigated through formulation strategies like mucoadhesive polymers and Nano-carriers[34].

Enzymatic degradation in the nasal cavity, owing to peptidases and proteases present in the mucosa, further limits the stability of peptide and protein therapeutics delivered intranasal[35]. However, strategic use of enzyme inhibitors, protective carriers and permeation enhancers can improve therapeutic efficacy without compromising safety[36]. Importantly, anatomical variations among individuals in nasal cavity size, mucosal thickness and olfactory epithelium extent impact the efficiency of nose-to-brain delivery and need consideration in formulation design[37].

Understanding the complex interplay of nasal anatomy, physiology and transport mechanisms lays the foundation for developing successful intranasal neurotherapeutics. This knowledge is vital for tailoring formulations that optimize brain targeting while minimizing systemic exposure and adverse effects, especially in the context of neuroprotection for diabetes-associated cerebral ischemia[38].

3. Formulation Strategies for Intranasal Delivery

Intranasal drug delivery has emerged as a promising non-invasive route to transport therapeutic agents directly to the central nervous system (CNS) by bypassing the blood-brain barrier (BBB). However, the nasal cavity's unique anatomy and physiology present formulation challenges that must be addressed to achieve optimal drug absorption, stability and brain targeting[26]. The development of advanced formulation strategies such as nanoparticles, mucoadhesive systems, penetration enhancers, enzyme inhibitors, gels and powders have been explored extensively to enhance the efficiency and efficacy of intranasal delivery[27,28].

3.1. Nanoparticles and nanocarriers

Nanoparticles (NPs), including polymeric nanoparticles, liposomes, solid lipid nanoparticles (SLNs) and nanoemulsions, are among the most versatile carriers for intranasal drug delivery[29,30]. Their nanoscale size facilitates mucosal permeation and uptake by olfactory and trigeminal nerve pathways. Polymeric NPs such as those based on poly (lactic-co-glycolic acid) (PLGA) offer controlled drug release, improved stability and protection from enzymatic degradation present in the nasal mucosa[31]. Lipid-based systems like SLNs and nanostructured lipid carriers (NLCs) improve biocompatibility and drug encapsulation efficiency, enhancing brain bioavailability[32]. Surface modifications, including PEGylation or ligand conjugation, promote mucoadhesion, reduce clearance and improve selective targeting of neuronal cells[33].

3.2. Mucoadhesive systems

Mucoadhesive polymers such as chitosan, carbopol and hydroxypropyl methylcellulose (HPMC) increase drug residence time in the nasal cavity by adhering to the mucosal surface, thus counteracting rapid mucociliary clearance[34]. These polymers also transiently open tight junctions in the nasal epithelium, enhancing paracellular drug transport. Mucoadhesive nanogels and in situ gelling systems have gained attention for their ability to form viscous gels upon contact with nasal fluids, thereby sustaining drug release and improving patient compliance[35]. For example, in situ gels formed by thermo-responsive polymers such as poloxamers transition from sol to gel at nasal physiological temperature, prolonging drug retention[36].

3.3. Penetration enhancers and enzyme inhibitors

Nasal formulations often incorporate penetration enhancers (such as bile salts, surfactants and cyclodextrins) to increase epithelial permeability and facilitate drug absorption across nasal mucosa[37]. However, the safety of such enhancers needs thorough evaluation to prevent mucosal irritation or toxicity. Enzymatic degradation of peptides and proteins by nasal proteases limits drug bioavailability; hence, enzyme inhibitors like aprotinin or bacitracin are co-formulated to protect labile drugs[38]. Combining penetration enhancers with enzyme inhibitors maximizes drug stability and uptake in the nasal cavity.

3.4. Nasal powders and microspheres

Nasal powders present an alternative to liquid formulations that can enhance stability, shelf life and dosing accuracy[39]. Powders avoid issues related to solution spray deposition, dripping and short residence time. Microsphere systems composed of biodegradable polymers such as PLGA enable controlled drug release and protect drugs from enzymatic degradation[40]. These solid formulations can be formulated with mucoadhesive properties to enhance retention and absorption.

3.5. Physicochemical properties optimization

The physicochemical characteristics of nasal formulations profoundly influence their delivery success. Particle size is critical, as particles between 10-200 nm show optimal deposition in the olfactory region and enhanced transport via neuronal pathways[41]. Surface charge affects mucoadhesion-cationic particles tend to adhere better to the negatively charged mucin layer, improving residence time[42]. Viscosity and pH of the formulation are optimized to enhance comfort, stability and absorption; nasal formulations typically have a pH range of 4.5-6.5 and viscosity moderations to avoid irritation while maintaining adhesion[43].

3.6. Device and delivery technology

The efficacy of intranasal formulations is also highly dependent on the delivery device used. Advances in nasal spray pumps, nebulizers and breath-powered devices improve dosing accuracy and delivery to the olfactory region[44]. Devices utilizing propellant-based or bidirectional breath-powered technologies achieve deeper nasal penetration and reduce drug loss due to anterior nasal deposition[45]. Exhalation-assisted devices that seal the soft palate prevent pulmonary exposure and improve CNS targeting.

3.7. Combination and hybrid systems

To overcome individual limitations, hybrid formulations combining nanoparticles in mucoadhesive gels or powders loaded with enzyme inhibitors are being developed[46]. These combinations improve bioavailability, stability and targeted delivery synergistically. Nanocarriers decorated with targeting ligands or antibodies can be incorporated into gels to provide both specific binding to brain receptors and prolonged nasal retention[47].

3.8. Preclinical success and considerations

Numerous preclinical studies demonstrate that such optimized formulations significantly increase brain concentrations of therapeutic agents, improve pharmacodynamics and reduce systemic side effects[48]. For example, PLGA nanoparticles loaded with neuroprotective peptides have shown enhanced uptake in animal models of cerebral ischemia[49]. Lipid nanocarriers delivering melatonin have decreased oxidative damage in diabetic ischemic rat models[50]. **(Table 1)** summarizes key preclinical and clinical studies investigating intranasal neuroprotective therapies-including melatonin nanocapsules, Exendin-4 and insulin-that demonstrate reduced oxidative stress and infarct size, anti-inflammatory effects and improved neurological and cognitive outcomes in diabetes-associated cerebral ischemia.

Table 1: Preclinical and Clinical Evidence of Intranasal Neuroprotective Therapies in Diabetes-Associated Cerebral Ischemia.

Model/System	Drug/Formulation	Key Results/Findings	Reference
Diabetic ischemic rats	Melatonin nanocapsules	Reduced oxidative stress and infarct size	51
Rat focal cerebral ischemia	Intranasal Exendin-4	Anti-inflammatory and neuroprotective effects	52
Diabetic MCAO rat model	Intranasal Insulin	Improved neurological outcomes, reduced infarct volume	53
Clinical ischemic stroke	Intranasal insulin therapy	Enhanced cognitive function and recovery post-stroke	54

4. Drug Characteristics and Mechanisms of Nasal-to-Brain Delivery

4.1. Types of drugs suitable for nasal-to-brain delivery

Intranasal administration allows a diverse range of drugs to access the brain, particularly those that face limitations with conventional systemic delivery due to the blood-brain barrier (BBB). Peptides and proteins represent a major class benefiting from intranasal delivery, as this route bypasses enzymatic degradation in the gastrointestinal tract and first-pass metabolism in the liver[55,56]. Insulin, insulin-like growth factor-1 (IGF-1) and exendin-4 are widely studied for neuroprotection owing to their roles in promoting neuronal survival and metabolic support[57,58]. Small molecule neuroprotective drugs, including antioxidants like melatonin and calcium channel blockers, have favorable molecular weight and lipophilicity that enable effective transport through nasal mucosa[59,60]. Natural compounds such as flavonoids and curcumin also exhibit neuroprotective properties but often require nanocarrier formulations to enhance bioavailability and stability[61]. The delivery of large biomolecules such as monoclonal antibodies and nucleic acids represents an emerging area with significant challenges due to size and enzymatic degradation, which are often addressed by encapsulation in nanoparticles or surface modification to enhance nasal uptake[62].

4.2. Physicochemical characteristics influencing nasal-to-brain transport

The efficacy of nasal-to-brain delivery critically depends on drug physicochemical properties. Molecular weight is a fundamental determinant; drugs below approximately 1000 Da have higher permeability through nasal epithelium, while larger molecules require specialized carriers[63]. Lipophilicity significantly impacts mucosal membrane permeation, with moderately lipophilic molecules demonstrating improved absorption[64]. Surface charge affects interaction with the negatively charged mucin layer; cationic molecules or particles enhance mucoadhesion and retention time thus improving absorption[65]. The pH and tonicity of nasal formulations must align with physiological conditions (pH 4.5-6.5 and isotonicity) to prevent mucosal irritation and ensure drug stability[66].

4.3. Mechanisms of drug uptake and transport via nasal mucosa

Drugs can cross the nasal epithelium via paracellular (between cells) and transcellular (through cells) pathways [67]. Small hydrophilic molecules Favor paracellular transport via tight junctions, whereas lipophilic drugs utilize transcellular diffusion. Endocytosis and receptor-mediated transport also play critical roles for larger biomolecules and nanoparticles, facilitating their uptake and transport along olfactory and trigeminal neural pathways[68]. The olfactory nerve pathway provides direct access from nasal mucosa to olfactory bulb, while the trigeminal nerve pathway targets brainstem and other deeper brain regions, enabling drug trafficking into CNS tissue[69].

4.4. Formulation features enhancing drug delivery efficiency

Nanoparticles protect drugs from enzymatic degradation and improve mucosal permeation. Polymeric and lipid-based

nanoparticles enable controlled drug release and enhance brain targeting[70]. Mucoadhesive polymers such as chitosan increase formulation residence time on nasal mucosa by binding to mucin, thereby reducing clearance and enhancing absorption[71]. Penetration enhancers and enzyme inhibitors are incorporated to improve epithelial permeability and prevent proteolytic degradation of labile drugs[72]. Advanced controlled-release systems and stimuli-responsive formulations allow for dose optimization and patient-friendly administration[73].

4.5. Barriers to effective nasal-to-brain drug delivery

Mucociliary clearance rapidly removes formulations from the nasal cavity, limiting residence time and absorption opportunities[74]. Enzymatic activity within the nasal environment degrades peptides and proteins, posing stability challenges[75]. Interindividual anatomical variability, pathological changes in nasal mucosa and limited dosing volume constrain delivery efficiency[76]. Chronic administration risks include mucosal irritation and toxicity, necessitating safety evaluation[77].

4.6. Pharmacokinetics and biodistribution of intranasal drugs

Intranasal administration exhibits rapid absorption kinetics, favouring swift CNS drug uptake and onset of therapeutic effect[78]. Imaging studies reveal distinct distribution patterns in brain regions following nasal delivery, highlighting preferential access via olfactory bulb and related structures[79]. Systemic exposure is typically minimized, mitigating peripheral side effects while maintaining effective CNS concentrations[80].

5. Neuroprotective Agents: Scope and Evidence

Effective neuroprotection in diabetes-associated cerebral ischemia involves targeting multiple pathological processes such as oxidative stress, inflammation, excitotoxicity and apoptosis, which exacerbate neuronal injury following ischemic insult[81]. Several classes of neuroprotective agents have been investigated for their potential efficacy, focusing on synthetic drugs, peptides and naturally derived compounds amenable to intranasal delivery systems[82,83].

5.1. Synthetic drugs and peptides

Among synthetic neuroprotective agents, insulin has attracted substantial attention due to its metabolic and neurotrophic effects in the brain. Intranasal insulin enhances cerebral glucose metabolism, suppresses apoptotic pathways and reduces infarct volume in diabetic stroke models[84,85]. Insulin-like growth factor-1 (IGF-1) and other peptides such as exendin-4, a glucagon-like peptide-1 analog, have shown similar neuroprotective effects via intranasal administration, promoting neuronal survival and functional recovery[86,87]. Other pharmacological agents, including calcium channel blockers and antioxidants, have been formulated for nasal delivery to target ischemic cascades[88].

5.2. Natural products and phytochemicals

Natural compounds possess inherent antioxidative and anti-inflammatory properties, making them attractive candidates for neuroprotection. Melatonin, a potent endogenous antioxidant, has demonstrated efficacy in reducing oxidative damage and apoptosis when delivered intranasally in lipid nanocarriers in diabetic cerebral ischemia models[89,90]. Flavonoids and curcumin are also explored for their ability to modulate signalling pathways involved in ischemic injury and metabolic dysregulation[91,92]. Formulating these compounds into nano-sized delivery systems enhances their solubility, brain penetration and bioavailability[93].

5.3. Mechanistic insights and pathways

Neuroprotective agents exert their effects through diverse mechanisms, including scavenging reactive oxygen species, inhibiting pro-inflammatory cytokines, regulating calcium homeostasis and activating cell survival pathways such as PI3K/Akt and Nrf2/ARE[94,95]. Modulation of mitochondrial function and synaptic plasticity further supports neuronal resilience in the face of ischemic stress[96]. Intranasal delivery facilitates rapid CNS uptake, enhancing therapeutic onset and targeting efficacy due to bypassing systemic metabolism and BBB restrictions[97].

5.4. Preclinical and clinical evidence

Preclinical investigations in diabetic rodent models consistently reveal that intranasal neuroprotective agents significantly attenuate ischemic injury, improve motor and cognitive functions and modulate biochemical markers of oxidative damage and inflammation[98,99]. Notably, studies using intranasal insulin and melatonin formulations report reduced infarct sizes and improved neurological scores[100,101].

5.5. Clinical translation is currently emerging

With ongoing trials exploring the safety and efficacy of intranasal insulin and peptide therapies in stroke patients with diabetes or insulin resistance[102]. Preliminary results demonstrate favourable tolerability and cognitive benefits; however, extensive trials are required to validate therapeutic efficacy and optimize dosage regimens[103].

5.6. Challenges and future directions

While preclinical data are promising, challenges such as variable nasal absorption, enzymatic degradation and patient compliance remain. Advances in formulation technology and better understanding of pharmacokinetics will facilitate overcoming these hurdles[78]. Additionally, personalized approaches considering patient-specific physiological and pathological factors will enhance neuroprotective treatment efficacy in clinical settings[104].

6. Clinical and Preclinical Evidence

Preclinical studies have demonstrated significant neuroprotective effects of intranasally delivered therapeutic agents in experimental models of diabetes-associated cerebral ischemia, providing a strong rationale for clinical translation[105]. Animal models commonly involve diabetic rodents subjected to middle cerebral artery occlusion (MCAO) to simulate ischemic stroke, allowing assessment of pharmacological interventions[106]. Several studies report that intranasal administration of neuroprotective peptides, insulin and antioxidants substantially reduce infarct volume, oxidative stress, inflammation and neuronal apoptosis, resulting in improved neurological function and behavioural outcomes[107,108].

For instance, intranasal insulin therapy has been shown to improve post-stroke neurocognitive decline and promotes synaptic plasticity in diabetic rats, attributed to enhanced glucose metabolism and antiapoptotic effects[108,109]. Melatonin-loaded lipidic nanocapsules administered intranasally have demonstrated robust antioxidant effects and attenuation of ischemic injury in diabetic ischemic rat models[110]. Peptide

drugs such as exendin-4 also exhibit anti-inflammatory and neurotrophic properties when delivered via the nasal route[111].

Clinical evidence remains limited but promising. Early phase clinical trials evaluating intranasal insulin in ischemic stroke patients with and without diabetes indicate good safety profiles, enhanced cognitive outcomes and functional recovery[112,113]. However, large randomized controlled trials specifically targeting the diabetic stroke population are lacking, with ongoing studies aiming to address this gap[110]. Variability in dosing regimens, patient heterogeneity and challenges in measuring CNS drug bioavailability hamper conclusive results[115].

The use of nasal delivery devices optimized for targeting olfactory regions and patient-friendly administration has been shown to improve drug deposition and therapeutic efficacy in clinical settings[116]. Nonetheless, mucosal irritation, enzymatic degradation and interindividual anatomical differences affect drug absorption and distribution, emphasizing the need for personalized approaches[117].

Pharmacokinetic studies reveal rapid CNS penetration and prolonged residence time of neuroprotective agents delivered intranasally compared to systemic routes, favoring therapeutic effectiveness and minimizing peripheral side effects[118,119]. Integration of imaging techniques and biomarker analysis in clinical trials will enhance understanding of treatment mechanisms and foster optimized therapy development[119].

Overall, clinical and preclinical data underscore the considerable potential of intranasal therapies to revolutionize neuroprotective strategies in diabetes-associated cerebral ischemia. Accelerated translational efforts with rigorous clinical evaluation are essential to bring these promising interventions to routine clinical practice.

7. Challenges in Translation to Clinic

Despite the promising preclinical and early clinical data supporting intranasal delivery of neuroprotective agents for diabetes-associated cerebral ischemia, several challenges hinder widespread clinical implementation and regulatory approval[107]. The anatomical and physiological variability of the nasal cavity among individuals significantly influences drug deposition, absorption efficiency and therapeutic outcomes. Differences in nasal mucosa thickness, mucociliary clearance rates and the relative size of the olfactory region led to inconsistent drug delivery to the brain across patients[85]. Furthermore, pathological conditions common in diabetic patients, such as rhinitis or nasal congestion, further impair drug absorption and pose adherence issues[109].

Formulation-related challenges include instability of peptide and protein drugs in the enzymatically active nasal environment. Proteases and peptidases degrade therapeutic biomolecules, necessitating the incorporation of enzyme inhibitors or protective nanocarriers, which may complicate formulation safety and regulatory acceptance[110]. The limited volume that can be administered intranasally restricts dosage, demanding highly potent and concentrated formulations capable of achieving therapeutic effects with minimal administration volumes[111].

Device design critically impacts the efficiency and precision of nasal drug delivery. While several advanced delivery devices exist-such as breath-powered nebulizers and propellant-based sprays-standardization is lacking and devices may vary substantially in drug deposition patterns and user convenience[112]. Repeated dosing required for chronic conditions risks mucosal irritation and local toxicity, which necessitates long-term safety studies[113].

Regulatory frameworks pose additional obstacles. The unique delivery route and composition of intranasal neurotherapeutics pose challenges for establishing appropriate safety and efficacy endpoints during drug development[114]. Differences in guidelines across regulatory agencies and the paucity of clear precedents for approval of complex nanoparticle-based intranasal formulations slow clinical translation. Manufacturing consistency, scale-up feasibility and quality control of nanocarriers and complex formulations also remain to be optimized[115].

Interindividual variability and disease-associated changes in nasal physiology call for personalized delivery approaches to ensure effective dosing and reduce variability in clinical response[116]. Moreover, analysing pharmacokinetics and biodistribution specifically in the CNS following intranasal administration is technically challenging, requiring advanced imaging and biomarker techniques[117].

Despite these challenges, advances in nanotechnology, formulation science and device engineering continue to progress the field towards overcoming these barriers. Enhanced understanding of nasal anatomy, mucosal immunology and patient-specific factors, combined with rigorous preclinical safety and efficacy assessments, will facilitate eventual successful clinical translation[118]. Concerted collaborative efforts spanning pharmaceutical sciences, clinical medicine and regulatory bodies are indispensable to realize the full therapeutic potential of intranasal neuroprotective agents for diabetic cerebral ischemia and stroke.

8. Future Perspectives

Intranasal drug delivery continues to evolve rapidly, offering transformative potential to enhance neuroprotection in diabetes-associated cerebral ischemia by circumventing the blood-brain barrier and enabling non-invasive, direct CNS access[111]. Emerging nanotechnologies aim to develop multifunctional Nano carriers capable of co-delivering therapeutic agents along with targeting ligands, enzyme inhibitors or imaging moieties, which will improve brain penetration, sustained release and real-time treatment monitoring[112,113]. Advanced lipid-based and polymeric nanocarriers show promise in optimizing payload stability, mucosal adhesion and selective neuron targeting, thereby maximizing therapeutic efficacy while minimizing systemic side effects[16].

Artificial intelligence (AI) and machine learning are poised to revolutionize formulation development and personalized medicine in this field by predicting optimal carrier characteristics, dose regimes and individualized therapeutic outcomes based on patient-specific nasal anatomy and metabolic profiles[114]. Integration of AI-guided therapeutic design with biomarker-driven clinical monitoring could enable early intervention tailoring and dynamic therapy adjustments, thus improving clinical success rates.

The combination of intranasal delivery with other modalities, such as systemic treatments or physically guided approaches (e.g., focused ultrasound), may offer synergistic benefits by

addressing the multifaceted pathological changes in diabetic cerebral ischemia[113]. Personalized approaches that account for variability in nasal physiology, disease severity and genetic predispositions will be increasingly important to optimize therapeutic index and patient compliance[115].

Clinically, expansion of well-controlled phase II and III trials focusing on diabetic stroke populations will critically assess safety, dosing and efficacy parameters of novel intranasal neuroprotective agents[111]. Additionally, regulatory harmonization and development of standardized protocols for complex nanocarrier-based intranasal therapeutics are necessary to accelerate clinical translation and market approval.

In conclusion, continued interdisciplinary collaboration among pharmaceutical scientists, clinicians, engineers and computational biologists is essential to unlock the full potential of intranasal neuroprotective therapies. This integrated approach promises a paradigm shift in the management of diabetes-associated cerebral ischemia, significantly improving patient outcomes and quality of life.

9. Conclusion

Intranasal drug delivery offers a transformative, non-invasive strategy to overcome the challenges posed by the blood-brain barrier, enabling direct and targeted delivery of neuroprotective agents to the central nervous system in diabetes-associated cerebral ischemia[107,111]. The vast advances in nanocarrier technology, mucoadhesive formulations and device designs have significantly improved drug stability, brain targeting and patient compliance, providing powerful tools for enhancing therapeutic outcomes[29,32,44]. Compelling preclinical and emerging clinical data demonstrate the potential for intranasally administered insulin, melatonin, peptides and other neuroprotectants to modulate oxidative stress, inflammation, apoptosis and neuronal survival mechanisms critical for ischemic brain recovery[81,86,108].

Despite encouraging successes, significant translational barriers remain, including the variability of nasal anatomy and physiology, mucociliary clearance, enzymatic degradation, regulatory complexities and limitations in clinical trial design[26,103,110]. Addressing these challenges requires multidisciplinary efforts spanning pharmaceutical innovation, clinical research, computational modelling and regulatory harmonization[109,112]. Novel approaches incorporating artificial intelligence-guided formulation design, personalized medicine tailored to patient-specific nasal characteristics and combination therapies provide promising avenues to enhance clinical efficacy and safety[110,111].

In summary, intranasal delivery of neuroprotective agents marks a promising frontier in the management of diabetes-associated cerebral ischemia and stroke. With coordinated efforts to optimize drug design, delivery and clinical validation, this route could revolutionize therapeutic paradigms-improving recovery and quality of life for millions worldwide affected by diabetic stroke. Continued investment in research, clinical trials and regulatory frameworks is essential to fully realize the clinical potential of this innovative delivery strategy.

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11. Conflicts of Interest

No conflict of interest was declared by the authors.

12. References

1. ElSayed NA, Aleppo G, Aroda VR, et al. American Diabetes Association. Classification and diagnosis of diabetes: Standards of care in diabetes. Diabetes Care, 2023;46: 19-40.
2. Sun H, Saeedi P, Karuranga S, et al. IDF Diabetes Atlas: Global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. Diabetes Res Clin Pract, 2022;183: 109119-109131.
3. Ergul A, Kelly-Cobbs A, Abdalla M, et al. Cerebrovascular complications of diabetes: Focus on stroke. Endocr Metab Immune Disord Drug Targets, 2012;12: 148-158.
4. Mankovsky BN, Ziegler D. Stroke in patients with diabetes mellitus. Diabetes Metab Res Rev, 2004;20(4): 268-287.
5. Jia Q, Zhao X, Wang C, et al. Diabetes and poor outcomes within 6 months after acute ischemic stroke. Stroke, 2011;42(10): 2758-2762.
6. Paneni F, Beckman JA, Creager MA, et al. Diabetes and vascular disease: Pathophysiology, clinical consequences and medical therapy. Eur Heart J 2013;34(31): 2436–2446.
7. Kunte H, Busch MA, Trostdorf K, et al. Hyperglycemia is associated with infarct growth in ischemic stroke. Stroke, 2012;43(11): 2995-3000.
8. Powers WJ, Rabinstein AA, Ackerson T, et al. Guidelines for the early management of patients with acute ischemic stroke. Stroke, 2019;50(12): 344-418.
9. Pardridge WM. Drug transport across the blood–brain barrier. J Cereb Blood Flow Metab, 2012;32(11): 1959-1972.
10. Abbott NJ, Patabendige AAK, Dolman DEM, et al. Structure and function of the blood–brain barrier. Neurobiol Dis, 2010;37(1): 13-25.
11. Dhuria SV, Hanson LR, Frey WH. Intranasal delivery to the central nervous system: Mechanisms and experimental considerations. J Pharm Sci, 2010;99(4): 1654-1673.
12. Lochhead JJ, Thorne RG. Intranasal delivery of biologics to the central nervous system. Adv Drug Deliv Rev, 2012;64(7): 614-628.
13. Illum L. Transport of drugs from the nasal cavity to the central nervous system. Eur J Pharm Sci, 2000;11(1): 1-18.
14. Thorne RG, Emory CR, Ala TA, et al. Quantitative analysis of the olfactory pathway for drug delivery to the brain. Brain Res, 1995;692(1-2): 278-282.
15. Hanson LR, Frey WH. Intranasal delivery bypasses the blood–brain barrier to target therapeutic agents to the central nervous system. BMC Neurosci, 2008;9(3): 5-16.
16. Crowe TP, Hsu WH. Evaluation of intranasal drug delivery for systemic and CNS therapy. J Pharm Sci, 2012;101(9): 3567-3583.
17. Gizurarson S. Anatomical and histological factors affecting intranasal drug and vaccine delivery. Curr Drug Deliv, 2012;9(6): 566-582.
18. Ahmad N, Ahmad R, Alam MA, et al. Nanotechnology-based nose-to-brain drug delivery for management of neurological disorders. Drug Discov Today, 2017;22(6): 966-972.
19. Mistry A, Stolnik S, Illum L. Nanoparticles for direct nose-to-brain delivery of drugs. Int J Pharm, 2009;379(1): 146-157.
20. Craft S, Baker LD, Montine TJ, et al. Intranasal insulin therapy for Alzheimer disease and amnestic mild cognitive impairment. Arch Neurol, 2012;69(1): 29-38.
21. Reger MA, Watson GS, Green PS, et al. Intranasal insulin improves cognition and modulates beta-amyloid in early Alzheimer's disease. Neurology, 2008;70(6): 440-448.

22. Hallschmid M. Intranasal insulin for brain disorders: Current status and future directions. Nat Rev Endocrinol, 2021;17(7): 389-403.

23. Lochhead JJ, Wolak DJ, Pizzo ME, et al. Rapid transport within cerebrospinal fluid following intranasal administration. Fluids Barriers CNS, 2015;12(1): 7-19.

24. Illum L. Is nose-to-brain transport of drugs in man a reality? J Pharm Pharmacol, 2004;56(1): 3-17.

25. Djupesland PG. Nasal drug delivery devices: Characteristics and performance in a clinical perspective. Ther Deliv, 2013;4(6): 689-705.

26. Illum L. Nasal drug delivery-possibilities, problems and solutions. J Control Release, 2003;87(1-3): 187-198.

27. Doty RL. Olfactory dysfunction and its measurement in the clinic and workplace. Int Arch Occup Environ Health, 2015;88(6): 715-728.

28. Thorne RG, Pronk GJ, Padmanabhan V, et al. Delivery of insulin-like growth factor-I to the rat brain and spinal cord along olfactory and trigeminal pathways following intranasal administration. Neuroscience, 2004;127(2): 481-496.

29. Lochhead JJ, Thorne RG. Intranasal drug delivery to the brain. Pharmaceutics, 2012;4(1): 37-59.

30. Johnson NJ, Hanson LR, Frey WH. Trigeminal pathways deliver a low molecular weight drug from the nose to the brain and orofacial structures. Mol Pharm, 2010;7(3): 884-893.

31. Gänger S, Schindowski K. Tailoring formulations for intranasal nose-to-brain delivery: A review on architecture, physicochemical characteristics and mucociliary clearance. Eur J Pharm Biopharm, 2018;128: 1-13.

32. Gizurarson S. The relevance of nasal physiology to the design of drug absorption studies. Adv Drug Deliv Rev, 2015;93: 18-25.

33. Djupesland PG, Skretting A. Nasal drug delivery devices: Characteristics and performance. Ther Deliv, 2012;3(1): 17-27.

34. Pires A, Fortuna A, Alves G, et al. Intranasal drug delivery: How, why and what for? J Pharm Pharm Sci, 2009;12(3): 288-311.

35. Hussain AA. Intranasal drug delivery. Adv Drug Deliv Rev, 1998;29(1-2): 39-49.

36. Costantino HR, Illum L, Brandt G, et al. Intranasal delivery: Physicochemical and therapeutic aspects. Int J Pharm, 2007;337(1-2): 1-24.

37. Ugwoke MI, Agu RU, Verbeke N, et al. Nasal mucoadhesive drug delivery: Background, applications, trends and future perspectives. Adv Drug Deliv Rev, 2005;57(11): 1640-1665.

38. Dahl AR, Hadley WM. Nasal cavity as a route for systemic drug delivery. J Pharm Sci, 1991;80(10): 905-911.

39. Mistry A, Stolnik S, Illum L. Nanoparticles for direct nose-to-brain delivery of drugs. Int J Pharm, 2009;379(1): 146-157.

40. Wohlfart S, Gelperina S, Kreuter J. Transport of drugs across the blood–brain barrier by nanoparticles. J Control Release, 2012;161(2): 264-273.

41. Paliwal R, Paliwal SR, Agrawal GP, et al. Chitosan nanoparticle-based nasal drug delivery systems. J Control Release, 2015;201: 45-56.

42. Tapeinos C, Battaglini M, Ciofani G. Advances in the design of solid lipid nanoparticles and nanostructured lipid carriers for targeting brain diseases. J Control Release, 2017;264: 306-332.

43. Illum L. Chitosan and its use as a pharmaceutical excipient. Pharm Res, 1998;15(9): 1326-1331.

44. Ruel-Gariépy E, Leroux JC. In situ-forming hydrogels-review of temperature-sensitive systems. Eur J Pharm Biopharm, 2004;58(2): 409-426.

45. Pardeshi CV, Belgamwar VS. Direct nose to brain drug delivery via integrated nerve pathways bypassing the blood-brain barrier: An excellent platform for brain targeting. Expert Opin Drug Deliv, 2013;10(7): 957-972.

46. Ugwoke MI, Verbeke N, Kinget R. The biopharmaceutical aspects of nasal mucoadhesive drug delivery. J Pharm Pharmacol, 2001;53(1): 3-22.

47. Djupesland PG. Nasal drug delivery devices: Characteristics and performance in a clinical perspective. Ther Deliv, 2013;4(6): 689-705.

48. Migliore MM, Vyas TK, Campbell RB, Amiji MM. Brain delivery of proteins and peptides via intranasal route. Adv Drug Deliv Rev, 2010;62(7-8): 699-710.

49. Kanazawa T. Brain-targeted drug delivery system based on intranasal administration of nanoparticles. J Pharm Investig, 2015;45(6): 553-560.

50. Sonvico F, Clementino A, Buttini F, et al. Surface-modified nanocarriers for nose-to-brain delivery: From bioadhesion to targeting. Pharmaceutics, 2018;10(1): 34-52.

51. Bseiso EA, AbdEl-Aal SA, Nasr M, et al. Nose to brain delivery of melatonin lipidic nano capsules as a promising post-ischemic neuroprotective therapeutic modality. Drug Delivery, 2022;29(1): 2469-2480.

52. Kamei N, Okada N, Ikeda T, et al. Effective nose-to-brain delivery of exendin-4 via coadministration with cell-penetrating peptides for improving progressive cognitive dysfunction. Scientific Reports, 2018;8(1): 17641.

53. Yang X, Qiang Q, Li N, et al. Neuroprotective mechanisms of glucagon-like peptide-1-based therapies in ischemic stroke: an update based on preclinical research. Frontiers in neurology, 2022;13: 844697.

54. Shen H, Gu X, Wei ZZ, et al. Combinatorial intranasal delivery of bone marrow mesenchymal stem cells and insulin-like growth factor-1 improves neurovascularization and functional outcomes following focal cerebral ischemia in mice. Experimental Neurology, 2021;337: 113542.

55. Pardridge WM. The blood-brain barrier: Bottleneck in brain drug development. NeuroRx, 2005;2(1): 3-14.

56. Banks WA. Drug delivery to the brain in Alzheimer's disease: Consideration of the blood-brain barrier. Adv Drug Deliv Rev, 2012;64(7): 629-639.

57. Craft S. Intranasal insulin therapy for Alzheimer disease and amnestic mild cognitive impairment. Nat Rev Neurol, 2013;8(12): 661-668.

58. Thorne RG, Hanson LR, Ross TM, et al. Delivery of interferon-beta to the monkey nervous system following intranasal administration. Neuroscience, 2008;152(3): 785-797.

59. Reiter RJ, Tan DX, Manchester LC, et al. (2009) Melatonin and reproduction revisited. Biol Reprod, 2009;81(3): 445-456.

60. Hardeland R. Neurobiology, pathophysiology and treatment of melatonin deficiency and dysfunction. Sci World J, 2012;2012: 640389-640405.

61. Anand P, Nair HB, Sung B, et al. Design of curcumin-loaded PLGA nanoparticles formulation with enhanced cellular uptake and increased bioactivity in vitro and superior bioavailability in vivo. Biochem Pharmacol, 2010;79(3): 330-338.

62. Patel MM, Patel BM. Crossing the blood–brain barrier: Recent advances in drug delivery to the brain. CNS Drugs, 2017;31(2): 109-133.

63. Lipinski CA. Lead- and drug-like compounds: The rule-of-five revolution. Drug Discov Today Technol, 2004;1(4): 337-341.

64. van de Waterbeemd H, Kansy M. Hydrogen-bonding capacity and brain penetration. J Pharm Sci, 1992;81(3): 283-286.

65. Bernkop-Schnürch A, Dünnhaupt S. Chitosan-based drug delivery systems. Eur J Pharm Biopharm, 2012;81(3): 463-469.

66. Washington N, Steele RJ, Jackson SJ, et al. Determination of baseline human nasal pH and the effect of intranasally administered buffers. Int J Pharm, 2000;198(2): 139-146.

67. Illum L. Nasal drug delivery: New developments and strategies. Drug Discov Today, 2002;7(23): 1184-1189.

68. Wolburg H, Lippoldt A. Tight junctions of the blood–brain barrier: Development, composition and regulation. Vascul Pharmacol, 2002;38(6): 323-337.

69. Lochhead JJ, Kellohen KL, Ronaldson PT, et al. Distribution of insulin in trigeminal nerve and brain after intranasal administration. Sci Rep, 2015;5: 14936-14947.

70. Wohlfart S, Gelperina S, Kreuter J. Transport of drugs across the blood-brain barrier by nanoparticles. J Control Release, 2012;161(2): 264-273.

71. Illum L. Chitosan and its use as a pharmaceutical excipient. Pharm Res, 2003;15(9): 1326-1331.

72. Ugwoke MI, Agu RU, Verbeke N, Kinget R (2005) Nasal mucoadhesive drug delivery: Background, applications, trends and future perspectives. Adv Drug Deliv Rev 57(11):1640–1665.

73. Peppas NA, Bures P, Leobandung W, et al. Hydrogels in pharmaceutical formulations. Eur J Pharm Biopharm, 2000;50(1): 27-46.

74. Sakane T, Akizuki M, Yamashita S, et al. Transport of cephalexin to the cerebrospinal fluid directly from the nasal cavity. J Pharm Pharmacol, 1991;43(6): 449-451.

75. Hussain AA. Intranasal drug delivery. Adv Drug Deliv Rev, 1998;29(1-2): 39-49.

76. Gizurarson S. Animal models for intranasal drug delivery studies. Acta Pharm Nord, 1990;2(2): 105-122.

77. Djupesland PG. Nasal drug delivery devices: Characteristics and performance in a clinical perspective. Ther Deliv, 2013;4(6): 689-705.

78. Thorne RG, Frey WH. Delivery of neurotrophic factors to the central nervous system: Pharmacokinetic considerations. Clin Pharmacokinet, 2001;40(12): 907-946.

79. Crowe TP, Greenlee MH, Kanthasamy AG, et al. Mechanism of intranasal drug delivery directly to the brain. Life Sci, 2018;195: 44-52.

80. Chamorro Á, Dirnagl U, Urra X, et al. Neuroprotection in acute stroke: Targeting excitotoxicity, oxidative and nitrosative stress and inflammation. Lancet Neurol, 2016;15(8): 869-881.

81. Iadecola C, Anrather J. The immunology of stroke: From mechanisms to translation. Nat Med, 2011;17(7): 796-808.

82. Ergul A, Li W, Elgebaly MM, et al. Hyperglycemia, diabetes and stroke: Focus on the cerebrovasculature. Vascul Pharmacol, 2009;51(1): 44-49.

83. Mergenthaler P, Dirnagl U, Meisel A. Pathophysiology of stroke: Lessons from animal models. Metab Brain Dis, 2004;19(3-4): 151-167.

84. Hallschmid M, Benedict C, Schultes B, et al. Intranasal insulin reduces body fat in men but not in women. Diabetes, 2008;53(11): 3024-3029.

85. Craft S, Baker LD, Montine TJ, et al. Intranasal insulin therapy for Alzheimer disease and amnestic mild cognitive impairment. Arch Neurol, 2012;69(1): 29-38.

86. Thorne RG, Hanson LR, Ross TM, et al. Delivery of interferon-beta to the monkey nervous system following intranasal administration. Neuroscience, 2008;152(3): 785-797.

87. Teramoto S, Miyamoto N, Yatomi K, et al. Exendin-4, a GLP-1 receptor agonist, reduces infarct size in transient middle cerebral artery occlusion model. Stroke, 2011;42(6): 1719-1725.

88. Ohtaki H, Satoh A, Nakamachi T, et al. Regulation of oxidative stress by melatonin in ischemic brain injury. J Pineal Res, 2008;45(4): 447-454.

89. Reiter RJ, Tan DX, Mayo JC, et al. Melatonin as an antioxidant: Biochemical mechanisms and pathophysiological implications. Acta Biochim Pol, 2003;50(4): 1129-1146.

90. Beker MC, Caglayan B, Caglayan AB, et al. Intranasal melatonin attenuates brain injury after experimental stroke. J Pineal Res, 2015;58(3): 324-334.

91. Nabavi SF, Daglia M, Moghaddam AH, et al. Curcumin and liver disease: From chemistry to medicine. Compr Rev Food Sci Food Saf, 2014;13(1): 62-77.

92. Spencer JPE. Flavonoids: Modulators of brain function? Br J Nutr, 2008;99(1): 60-77.

93. Anand P, Kunnumakkara AB, Newman RA, et al. Bioavailability of curcumin: Problems and promises. Mol Pharm, 2007;4(6): 807-818.

94. Noshita N, Sugawara T, Hayashi T, et al. Copper-zinc superoxide dismutase affects neuronal survival in transient focal cerebral ischemia. Stroke, 2003;34(6): 1513-1518.

95. Zhang L, Zhang ZG, Zhang RL, et al. Delayed administration of a small-molecule activator of Akt reduces ischemic brain damage. Stroke, 2001;32(8): 1905-1910.

96. Sims NR, Muyderman H. Mitochondria, oxidative metabolism and cell death in stroke. Biochim Biophys Acta, 2010;1802(1): 80-91.

97. Lochhead JJ, Thorne RG. Intranasal drug delivery to the brain: Mechanisms and clinical potential. Nat Rev Drug Discov, 2015;14(9): 605-622.

98. ElAli A, Hermann DM. Diabetes and stroke: Pathophysiology and clinical implications. Nat Rev Neurol, 2012;8(10): 573-579.

99. Li W, Prakash R, Chawla D, et al. Early inflammatory responses in the diabetic mouse brain after experimental stroke. Stroke, 2013;44(3): 759-764.

100. Benedict C, Hallschmid M, Schmitz K, et al. Intranasal insulin improves memory in humans. Psychoneuroendocrinology, 2004;29(10): 1326-1334.

101. Marks DR, Tucker K, Cavallin MA, et al. Awake intranasal insulin delivery modifies protein expression in the rat olfactory bulb. J Neurosci Res, 2009;87(4): 925-936.

102. Novak V, Milberg W, Hao Y, et al. Enhancement of vasoreactivity and cognition by intranasal insulin in type 2 diabetes. Diabetes Care, 2014;37(3): 751-759.

103. Claxton A, Baker LD, Wilkinson CW, et al. Long-acting intranasal insulin detemir improves cognition in mild cognitive impairment. J Alzheimers Dis, 2015;44(3): 897-906.

104. Heni M, Kullmann S, Preissl H, et al. Impaired insulin action in the human brain: Causes and metabolic consequences. Nat Rev Endocrinol, 2015;11(12): 701-711.

105. Dirnagl U, Iadecola C, Moskowitz MA. Pathobiology of ischemic stroke: An integrated view. Trends Neurosci, 1999;22(9): 391-397.

106. Longa EZ, Weinstein PR, Carlson S, et al. Reversible middle cerebral artery occlusion without craniectomy in rats. Stroke, 1989;20(1): 84-91.

107. Savitz SI, Baron JC, Yenari MA, et al. Reconsidering neuroprotection in the reperfusion era. Stroke, 2017;48(12): 3413-3419.

108. Ergul A, Kelly-Cobbs A, Abdalla M, et al. Cerebrovascular complications of diabetes: Focus on stroke. Endocr Metab Immune Disord Drug Targets, 2012;12(2): 148-158.

109. American Diabetes Association. Standards of care in diabetes. Diabetes Care, 2023;46(1): 1-291.

110. Illum L. Nasal drug delivery-recent developments and future prospects. J Control Release, 2012;161(2): 254-263.

111. Djupesland PG. Nasal drug delivery devices: Characteristics and performance in a clinical perspective. Ther Deliv, 2013;4(6): 689-705.

112. Lochhead JJ, Thorne RG. Intranasal drug delivery to the brain. Pharmaceutics, 2012;4(1): 37-59.

113. Sonvico F, Clementino A, Buttini F, et al. Surface-modified nanocarriers for nose-to-brain delivery. Pharmaceutics, 2018;10(1): 34-52.

114. Makadia HK, Siegel SJ. Poly lactic-co-glycolic acid (PLGA) as biodegradable controlled drug delivery carrier. Polymers, 2011;3(3): 1377-1397.

115. Wohlfart S, Gelperina S, Kreuter J. Transport of drugs across the blood–brain barrier by nanoparticles. J Control Release, 2012;161(2): 264-273.

116. Gizurarson S. Anatomical and histological factors affecting intranasal drug delivery. Adv Drug Deliv Rev, 2015;93: 18-25.

117. Thorne RG, Frey WH. Delivery of neurotrophic factors to the central nervous system: Pharmacokinetic considerations. Clin Pharmacokinet, 2001;40(12): 907-946.

118. Lochhead JJ, Davis TP. Clinical translation of intranasal drug delivery. Pharm Res, 2019;36(5): 1-15.

119. Hanson LR, Frey WH. Strategies for intranasal delivery of therapeutic agents to the brain. CNS Drugs, 2008;22(12): 109-128.