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Review Article

An Elucidation of Contemporary Brain Targeting Tactics Employed in the Treatment of Neurodegenerative Diseases

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ABSTRACT

Neurodegenerative diseases (NDDs), a global growing concern, are posing significant social and economic challenges, making the efficient delivery of medications to the brain a pressing demand. Over the past decade, several strategies have been developed to facilitate brain targeting, to circumvent the formidable obstacle presented by the blood-brain barrier (BBB). These tactics encompass both non-invasive and invasive approaches, with the utilization of nanocarriers being increasingly prevalent due to the various advantages they offer. Likewise, the intranasal (IN) delivery of drugs is considered one of the most practical non-invasive techniques that can bypass the BBB, mitigating systemic adverse effects and reducing administered doses, in addition to, the added pros of greater bioavailability, and enhanced cerebral exposure at comparable oral doses. This review aims to elucidate recent approaches employed in the delivery of therapeutics to the brain, with a thorough emphasis on the IN route for targeted drug delivery.

Keywords: *Neurodegenerative diseases; Blood-brain barrier; Intranasal; Lipid-based Nanoparticles.*

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1. Introduction

Neurodegenerative diseases (NDDs) encompass a pathological state characterized by the progressive death of the neurons in the central nervous system (CNS), leading to the manifestation of either motor impairment (ataxia) or memory loss (dementia). Mitochondrial dysfunctions, excitotoxicity, and apoptosis are recognized as the main pathological factors contributing to the aging and development of NDDs, including Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), and Multiple Sclerosis (MS) **[1]**. The etiology of neurodegeneration is believed to include a complex interaction of several elements, involving both environmental influences and genetic predisposition. However, it has been postulated that redox metal misuse plays a pivotal part in this process, since a significant proportion of the observed symptoms may be attributed to aberrant metal metabolism **[2]**. Annually, more than 10 million people worldwide suffer from NDDs, with an onset that can occur at any age, but is more likely in the elderly. This figure is expected to grow by 20% over the next decade as the aging population increases and lives longer. NDDs impose a vital

health risk since they are the fourth leading cause of death in the developed world, right after heart diseases, cancer, and strokes **[3].**

Despite the therapeutic potential of several medicines for the treatment of CNS diseases, only a tiny fraction of these compounds (< 5%) have been utilized clinically, all due to the blood-brain barrier (BBB) obstacle **[4]**. Brain bioavailability is impeded by two primary barriers: the blood-cerebrospinal fluid barrier (BCSFB) and BBB, with the latter causing substantial hindrance to accessing the brain parenchyma **[5]**. Anatomically, the BBB is composed of three distinct layers, as illustrated in **Fig. 1**. The innermost layer consists of endothelial cells forming the capillary wall, and is characterized by the presence of tight junctions (TJs). Adjacent to the endothelial cell layer is the basement membrane, followed by a layer composed of pericytes and astrocytic feet processes, situated on the basement membrane **[6].**

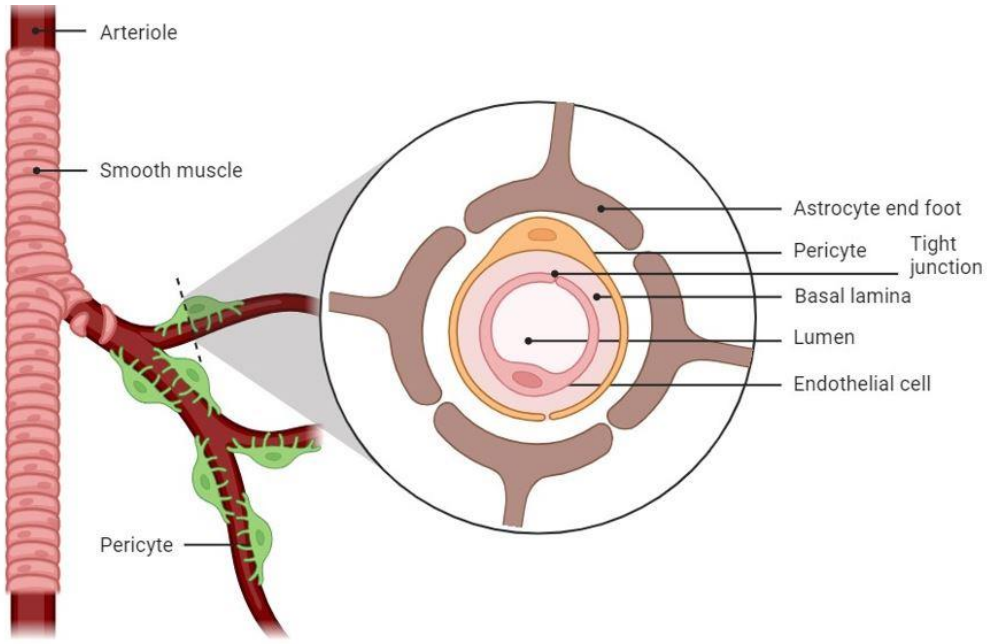

Fig. 1. A schematic illustration of the blood-brain barrier as a section of the neurovascular unit **(created by Biorender®)**

The BBB serves as a multifaceted barrier, including physical, metabolic, and immunological functions. One aspect to consider is the presence of TJs, which act as a physical barrier that hinders the paracellular movement of tiny hydrophilic molecules. On the contrary, the establishment of metabolic and immunological barriers is expedited by the presence of various receptors and transporter proteins, such as efflux pumps, which selectively facilitate the entry of essential chemicals while impeding the passage of others **[7]**. **Fig. 2.** depicts all the transport pathways that particles exploit to traverse the BBB.

Accordingly, the limited ability of only a few medications to traverse the BBB is a major challenge, especially in light of the expected increase in the prevalence of NDDs. Hence, it can be argued that the neuro-pharmaceutical market is poised to become the dominant sector within the industry, with an anticipated

advancement in BBB drug delivery technologies **[8].**

Typically, traditional methods of treating NDDs comprise the uptake of these medicines into the CNS via systemic circulation, and to achieve therapeutic concentrations, high doses or prolonged treatment regimens are required, with a likelihood of systemic toxicity. As a result, researchers are actively seeking other methods to facilitate the delivery of active ingredients directly into the CNS without necessitating an increase in their systemic levels **[9].**

This review aims to elucidate contemporary approaches employed in the delivery of therapeutics to the brain. It will highlight the potential of the IN pathway as a viable approach for brain targeting.

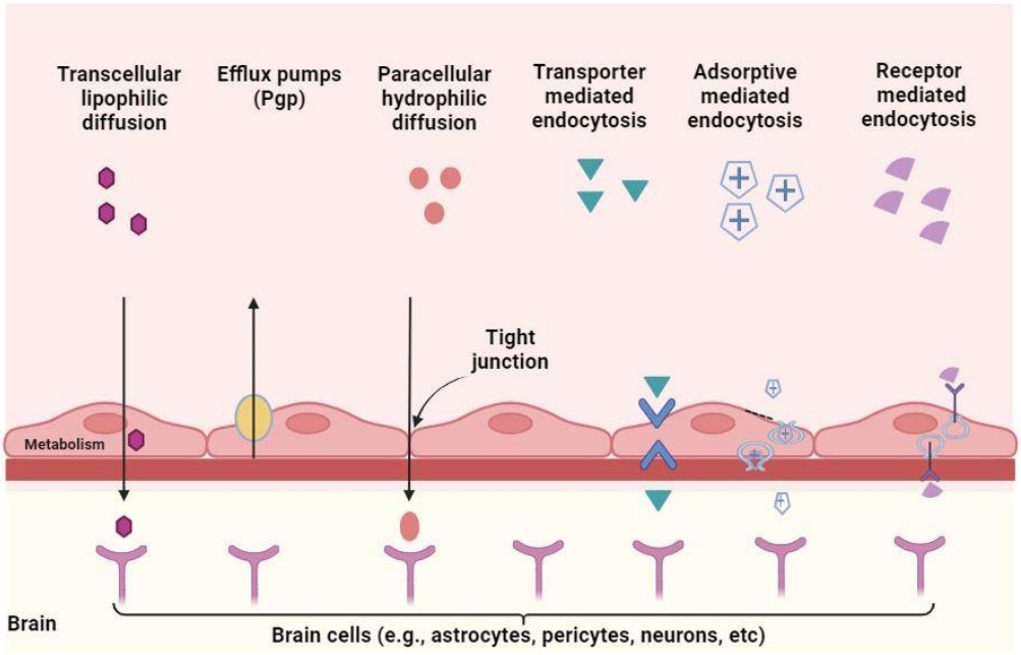

Fig. 2. The various transport pathways across the blood-brain barrier **(created by Biorender®)**

2. Strategies for Enhanced Central Nervous System Drug Delivery

In the last few decades, there has been a growing emergence of multidisciplinary techniques aimed at enhancing medication concentrations in the brain. As illustrated in **Fig. 3.** These advances are mainly based on the following primary strategies: the method of drug administration, manipulation of the drug composition, disruption of the BBB physiology, and the utilization of nanocarriers. Here, we will provide a quick overview of these paths of access.

2.1. Invasive Techniques

In general, few nutrients and peptides can pass through the BBB to reach an effective concentration in the brain tissue after intravenous or oral administration**.** Therefore, to systemically deliver sufficient amounts of potent drugs (e.g., neurotrophic factors and anticancer drugs) to the CNS, these drugs will inevitably spread to other tissues and cause severe adverse effects. Hence, sometimes, it is necessary to break the BBB or to deliver these drugs directly into the brain tissue **[10].** Nevertheless, it is essential to note that all direct procedures encounter challenges related to; infection dangers, elevated neurosurgery expenses, the requirement for specialized

expertise, and limited effectiveness in cases with diffuse tumors, metastasis, Alzheimer's disease, Parkinson's disease, epilepsy, etc. These invasive techniques include intracerebral, intraventricular, and intrathecal injections

Intracerebral injection involves the direct administration of drugs into the parenchymal space of the brain through openings in the skull. The intracerebral implantation of therapeutics containing a biodegradable polymeric matrix is a highly traumatic drug delivery strategy that has been used in several clinical studies **[11]**. The Food and Drug Administration (FDA) 1996, approved carmustine (Gliadel®) containing poly anhydride polymer wafer for recurrent high-grade gliomas. By using diffusion and hydrolytic polymer breakdown mechanisms, this matrix effectively achieves a prolonged and controlled release of active components over a period of about two months **[12]**. Nevertheless, the heightened susceptibility to trauma and inadequate medication penetration beyond the resection cavity has posed limitations on the application of this local administration approach **[13]**.

The intraventricular approach involves the direct injection of drugs into the cerebral ventricle, resulting in the fast distribution of medicines in concentrated amounts inside the ventricles and subarachnoid regions of the brain **[14]**. This method is particularly suitable for treating meningioma and metastatic cells present in the cerebrospinal fluid (CSF). Despite the clear advantage of this approach, this provides efficient and expedited transportation of medications to the intended location. This pathway possesses the capacity to elicit trauma, cerebral edema, catheter malfunction, infections, and maybe fatal outcomes **[15-16].**

While the intrathecal injection is considered less intrusive compared to the intracerebral route, it does not enable significant drug accumulation inside the brain parenchyma, which is crucial for sustained drug delivery. This type of treatment was found to be effective for spinal and disseminated meningeal disorders, whereas, glioblastoma does not exhibit the same level of convenience in response to this approach **[17].**

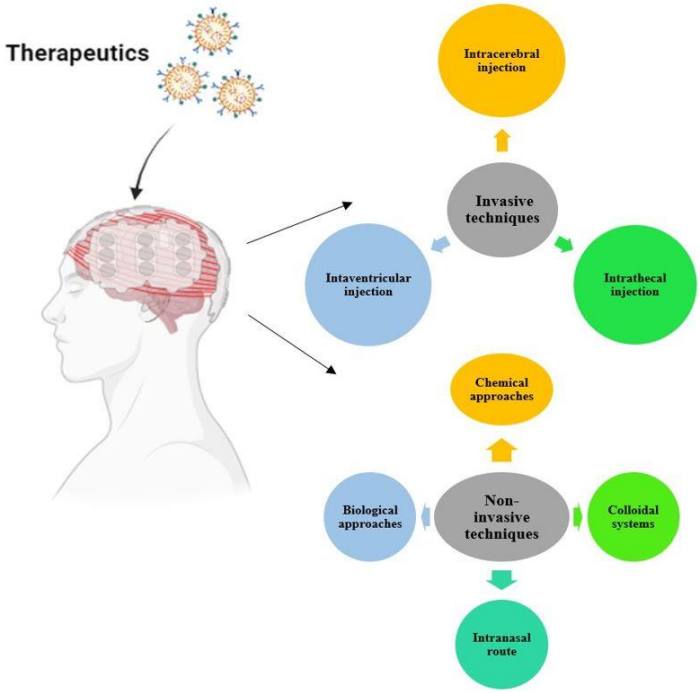

Fig. 3. The contemporary techniques for brain disease drug delivery **(created by Biorender®)**

2.2. Non-invasive Techniques

Non-invasive techniques for targeting drugs across the BBB primarily include mechanisms like intranasal delivery, the use of nanoparticles, chemical drug modification, biological approaches, and BBB disruption **[18]**. Although this approach is typically associated with enhanced safety by minimizing the likelihood of consequences such as infection or bleeding, may exhibit reduced efficacy in some medication or disease scenarios. This limitation might be attributed to the constrained drug dosage that can be administered or the precision required for targeting a particular site. **[19]**.

2.2.1. Chemical Approaches

Chemical approaches are based on modifying the chemistry of drugs to enhance their unfavorable physical and chemical characteristics, such as solubility or permeability through membranes.

2.2.1.1. Prodrugs

The term "prodrug" was proposed by Adrien Albert in 1958. Prodrugs can be defined as chemical compounds that possess minimal or negligible pharmacological action, but undergo biotransformation processes to generate therapeutically active metabolites. It is imperative to exercise caution before employing this approach since certain prodrug molecules possess the potential to modify the initial tissue distribution, as well as, the effectiveness and toxicity of the parent drug **[20]**.

Chemically, a prodrug is classified into four major classes **[21]**, namely; carrier-linked, precursors, macromoleculars, and drug-antibody conjugates. In carrier-linked prodrugs, the pharmaceutical ingredient is chemically connected to a carrier, known as the pro-moiety, and activation of this drug-carrier complex takes place by hydrolysis (in the case of esters, amides, and imines), oxidation, or reduction. *Bioprecursors* are compounds that lack a pro-moiety but can still be activated by oxidation, reduction, or hydrolysis. As for macromolecular prodrugs, the carrier is a macromolecule such as polyethylene glycol (PEG). And finally, in drug-antibody conjugates, the utilized carrier is an antibody specifically formulated to target and bind to cancer cells**.**

Currently, a plethora of investigations are being conducted in the field of prodrug research for NDDs. For example, the metabolism of dopamine (DA), a neurotransmitter that plays a crucial role in the development of PD, occurs quickly after it is taken orally, this prevents it from crossing the BBB by passive diffusion. Therefore, the creation of a prodrug strategy is required to overcome this challenge. Amino acid prodrugs of dopamine facilitate the transportation of this cationic model into the brain through the L-type amino acid transporter 1 (LAT1, SLC7A5). The latter is a potential avenue for delivering drugs with limited brain penetration, exploiting a phenylalanine moiety that is connected to the parent drug, DA, by an amide linkage **[22]**. An additional illustration of a prodrug that was designed to ameliorate subsisting PD drugs is Levodopa (*L*-Dopa) (SINEMET®). *L*-Dopa is the gold standard therapy for PD patients. Researchers have created several prodrugs to address the challenges related to *L*-Dopa, such as issues with bioavailability and peripheral metabolism. Amongst these prodrugs, XP21279, a prodrug of *L*-Dopa that is actively transported, has been investigated in individuals with PD who suffer from motor fluctuations. In the context of clinical trials, it was reported that XP21279 exhibited a reduction in motor fluctuations and a boost in average plasma *L*-Dopa concentrations in individuals with PD when contrasted to the levels recorded with Carbidopa-Levodopa (CD-LD). The relative bioavailability of XP21279 is estimated to be roughly 90% compared to immediate-release CD-LD,

however, the progress of prodrug research was ultimately halted as a result of performance challenges in achieving substantial primary results throughout clinical experiments **[23]**.

2.2.1.2. Molecular packaging

The transportation of peptides such as enkephalin, TRH (thyrotropin-releasing hormone), and Kyotorphin analogs across the BBB poses an intricate challenge due to their susceptibility to rapid inactivation by ubiquitin-specific peptidase 17; hence, it is imperative to address three interconnected challenges. First, as a way to augment passive transport, lipophilicity must be increased. Second, enzymatic stability must be ensured to mitigate premature degradation, and ultimately, the lock-in procedure may be utilized to facilitate precise targeting. This complex technique is known as molecular packaging, where the peptide unit is incorporated with a bulky molecule, dominated by groups responsible for directing it towards BBB traverse and inhibiting identification by peptidases **[24]**.

2.2.2. Biological Approaches

The primary focus of this approach revolves around comprehending the physiological and anatomical factors that influence the transport of substances across the BBB **[25]**. This approach embraces the preparation of chimeric peptides and cationic peptides.

2.2.2.1. Receptor-mediated delivery of chimeric proteins

This technique capitalizes on many specific transcytosis mechanisms designed to facilitate the passage of vital nutrients and signaling molecules that are unable to diffuse across the Cerebro-microvasculature, such as the delivery of insulin, transferrin, lactoferrin, and insulin-like growth factor **[26]**. Chimeric peptide delivery involves the conjugation of a non-transportable peptide with a transportable protein/peptide. This conjugate undergoes transcytosis across the BBB via receptor-mediated or absorptive-mediated mechanisms, followed by enzymatic cleavage by thiol reductase inside the parenchyma. A well-known example is the protein β-endorphin, a non-transportable protein, which forms a disulfide bond with the transportable protein-cationized albumin **[27]**.

2.2.2.2.Cell-penetrating peptides (CPPs)-mediated drug delivery

CPPs typically consist of amino acid sequences ranging from 5 to 30 residues that form peptides exhibiting amphipathic or cationic properties, thus, enabling their traverse across the cellular membrane. The field of CPPs originated with the discovery of a protein-transduction domain inside the trans-activator of transcription protein, as documented by a research team investigating the human immunodeficiency virus during the 1980s **[28]**. CPPs have been the subject of substantial research owing to their capacity to facilitate the intracellular transportation of cargo molecules **(Fig. 4.).** A diverse range of cargo, encompassing nucleic acids, nanoparticles, peptides, proteins, and small medicinal molecules, has been transported using CPPs **[29]**. CPP-based delivery systems have demonstrated the ability to effectively transport macromolecules across cellular membranes, especially the BBB, exhibiting a favorable balance between minimal cellular toxicity and high efficiency. This characteristic renders CPPs as potentially valuable therapeutic agents for treating NDDs **[30]**.

2.2.3. Colloidal Drug Carriers

Over the last few decades, many classes of nanocarriers, including liposomes, polymeric micelles, nanoparticles (NPs), and nanoemulsions, have been utilized to deliver drugs to the brain following

administration via various routes **[31-32].** Nanotechnology has exciting possibilities in the realm of brain drug targeting since it addresses many constraints associated with conventional drug delivery methods.

Nanocarriers, colloidal systems with dimensions ranging from 1 to 300 nm, constitute a variety of components, including lipid-based, polymeric, and metallic NPs. They serve as carriers for a therapeutic agent that could be encapsulated, adsorbed, covalently linked, or electrostatically bonded to the NP **[33]**. A variety of medications have been successfully delivered to the brain by adapting this concept, such as anticancer medications, antiparkinson drugs, cardiovascular drugs, analgesics, protease inhibitors, and various macromolecules **[34]**. In the subsequent section, we will explore examples of the three primary types of nanocarriers along with their respective uses for brain delivery.

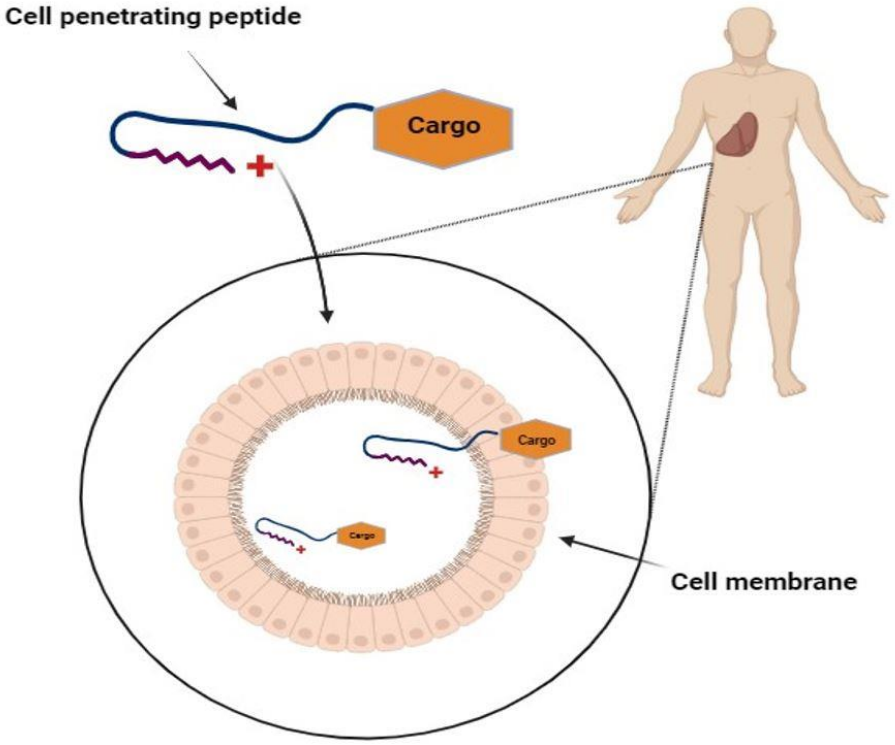

Fig. 4. The exploitation of cell-penetrating proteins in the context of drug delivery **(created by Biorender®)**

2.2.3.1. Liposomes

Liposomes are the most commonly used type of lipidic nanocarriers. They possess a lipid bilayer structure, which can exist in either unilamellar or multilamellar entities, characterized by their spherical appearance. These lipophilic phospholipid bilayers enclose an inner aqueous compartment and exhibit relatively low permeability **[35]** with a high tendency for surface modification. Liposomes have garnered significant interest as potential carriers for drug administration due to their biocompatibility, lack of toxicity, and ability to transport both lipophilic and hydrophilic drug molecules, thus safeguarding the cargo from destruction by plasma enzymes. Additionally, liposomes facilitate the transfer of their cargo across biological membranes, including the BBB, due to their structural imitation [**36]**.

Three main types of liposomes have been extensively discussed in the literature, based on their surface characteristics, *viz*, conventional

liposomes with no surface modification, PEGylated liposomes, also known as "stealth liposomes" due to their prolonged circulation time, and ligand-targeted liposomes (functionalized liposomes) **[37]**, as revealed in **Fig. 5**.

To overcome some limitations associated with conventional liposomes, such as rigidity and stability concerns, a modified class of liposomes characterized by their high flexibility and deformability, known as transfersomes, was developed. Cevc and Blume introduced transfersomes that consist of phospholipids and edge activators **[38]**, where edge activators were incorporated in the lipid bilayer to impart deformability to the vesicles **[39]**, resulting in enhanced drug loading capacity, increased stability, improved skin permeability, and sustained drug release **[40]**. Another kind of modified liposome is emulsomes, which constitute a solid fat core encapsulated inside multiple layers of phospholipids, thus, incorporating the attributes of both liposomes and emulsions. Due to the presence of a robust lipid core, emulsomes can encapsulate larger quantities of lipophilic medicinal molecules and provide a more extended-release duration compared to other lipid-based nanocarriers, such as liposomes or transfersomes **[41]**.

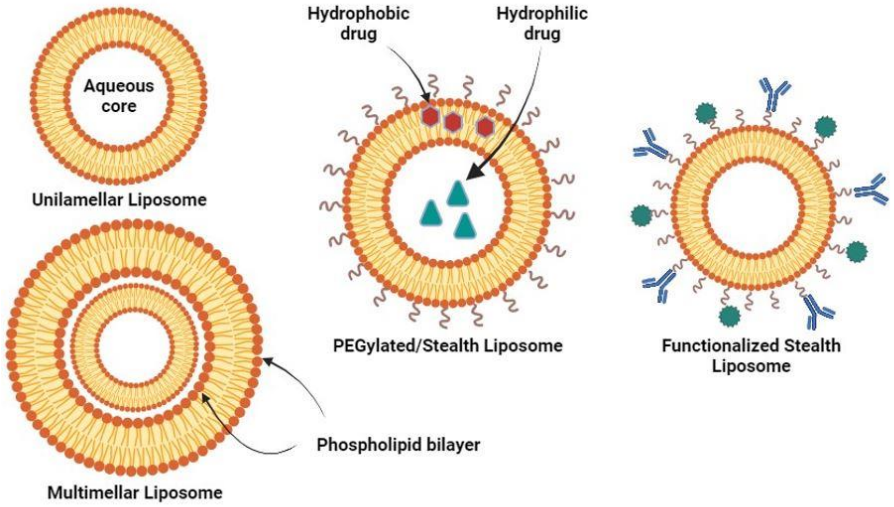

Fig. 5. Illustration of different types of liposomes **(created by Biorender®)**

2.2.3.2. Polymeric micelles

Polymeric micelles are nanosized colloidal polymeric particles constituting a hydrophobic core surrounded by a hydrophilic shell **[42].** The hydrophilic shell stabilizes the micelles in biological fluids, rendering them "invisible" to the immune system and enabling them to bypass the BBB. Meanwhile, the hydrophobic core provides an environment for poorly soluble drugs. The advantages of this nanosized system include increased drug solubility, enhanced drug delivery efficiency, and a reduced likelihood of systemic side effects. However, challenges exist, such as the potential for premature drug release before reaching the targeted site, possible toxicity from the carrier material, and variability in micelle stability. Furthermore, reproducibility with large-scale production of PMs remains a technical hurdle that should be overcome **[43].**

2.2.3.3. Metallic nanoparticles

Metallic nanoparticles are tiny particles with nanoscale dimensions (1-100 nm), and due to their size, they exhibit interesting physical and

chemical properties, rendering them highly useful in biomedical and pharmaceutical applications **[44].** For instance, their high surface area to volume ratio makes them highly interactive with biological entities, enabling controlled drug delivery and release **[45].** In various pharmacological contexts, extensive research has been conducted on metallic nanoparticles, including silver, gold, and iron oxide. These studies have explored a diverse array of uses, ranging from the targeted delivery of anticancer medications to the development of antibacterial agents. Their ease of surface functionalization also recommends their use in targeted delivery, thus, enhancing therapeutic efficacy while reducing side effects **[46]. Fig. 6.** summarizes the pros and cons of colloidal drug carriers.

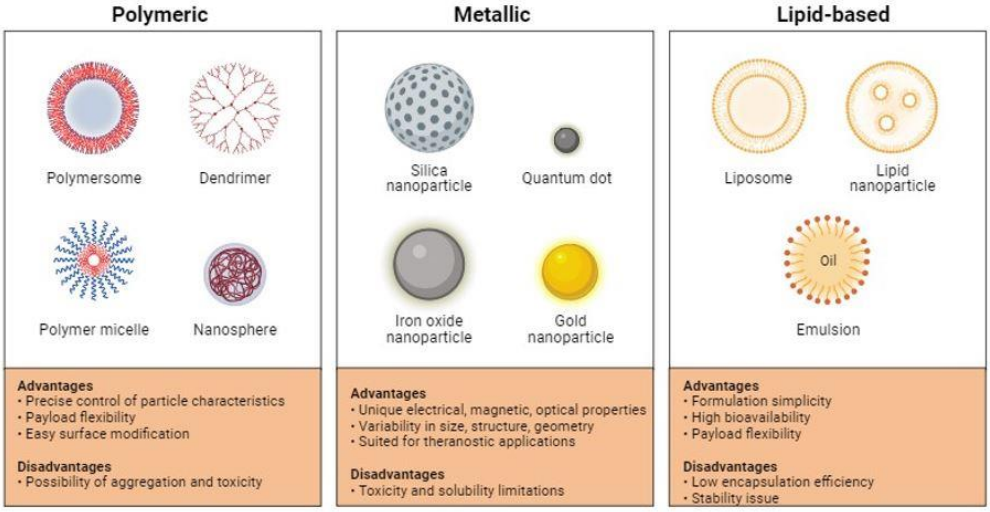

Fig. 6. Pros and cons of the different types of colloidal drug carriers **(created by Biorender®)**

2.2.4. BBB Disruption

In this strategy, direct targeting of drugs to the CNS is achieved by utilizing a particular chemical component or by employing external energy applications, such as ultrasonic waves or electromagnetic radiation, which open up TJs, hence, enabling successful penetration into the brain. The temporary disruption of the BBB may be induced using one of two distinct stimuli, either chemical or physical. In the chemical stimuli approach, a hyperosmolar chemical compound, such as mannitol, is used, which, due to its high hypertonicity/osmotic pressure, reduces endothelial cells' size, resulting in the opening of TJs. As for the physical stimuli, in this route, the disruption of BBB is accomplished by using ultrasound and electromagnetic radiation **[47-48].** The precise mechanism underlying these physical methods still needs to be explained, however, it is postulated that these waves induce the expansion and contraction of bubbles within the capillaries. The enlargement of giant bubbles leads to the complete filling of the capillary lumen, thereby, exerting a mechanical stretching force on the wall of the vessel, consequently, leading to a reversible disruption in TJs **[49].**

Nevertheless**,** the approach of BBB disruption may potentially damage healthy brain tissue and result in side effects such as bleeding and inflammation. Additionally, the procedure is typically only effective for a short time and may not be suitable for all patients or conditions **[50].** Therefore, it is essential to consider this procedure's risks and benefits carefully and discuss its pros and cons with the healthcare

provider before deciding.

2.2.5. Intranasal (IN) Delivery

Since the 1980s, there has been an increasing interest in IN drug delivery, since it serves as a non-invasive route, whether targeting drugs to the brain or for a systemic action. Despite the apparent integrity of the nasal epithelium, the intercellular junctional complex of its mucosa exhibits poor tightness, mostly attributed to the presence of leaky epithelial tissue. Also, the mucosa, lamina propria, and permeable epithelium exhibit extensive vascularization, offering an ideal surface for systemic drug absorption **[51].**

The primary physiological roles of the nasal cavity encompass the regulation of olfaction (sense of smell), facilitating air intake into the respiratory system, and eliminating large particles, especially pathogens, from inhaled air. For effective administration of the therapeutic molecules through the nasal route, their anatomical and physiological features must be considered when designing delivery systems for the CNS. Therefore, understanding the physiology and anatomy of nasal mucosa is imperative **[52].** The nasal cavity of the human body possesses a combined capacity ranging from 15 to 20 mL and an aggregate surface area spanning from 150 to 160 cm^2 **[53].** The nasal cavity is padded by a mucosal layer covering its epithelium. In conjunction with the cilia on the outermost layer of ciliated cells, the mucus serves as the principal mechanism of defense within the nasal cavity. This defense mechanism, called mucociliary clearance, involves the initial entrapment of inhaled pathogens and particles in the mucus. Subsequently, the coordinated movement of the cilia propels the entrapped substances towards the nasopharynx, thereby, facilitating the removal of harmful agents at regular intervals of 15 to 20 min **[54].** The nasal cavity can be divided into three regions, as shown in **Fig. 7.**, the nasal vestibule, the olfactory, and the respiratory regions **[55].**

The vestibular area is situated close to the apertures of the nostrils, where drug absorption is quite low compared to the other two regions mostly due to its limited surface area, which is roughly 0.6 cm2, as well as, the absence of cilia on the epithelial cell surface. The respiratory region, which encompasses a significant portion of the nasal cavity, comprises the respiratory epithelium, with a substantial surface area of around 130 cm^2, mostly attributed to the abundance of cells that feature many microvilli. Since the respiratory region is characterized by its extensive surface area and vascularity, it serves as the primary location for systemic drug absorption, provided that pharmaceuticals are capable of traversing the mucus layer. The trigeminal nerves, arising from the brain stem, innervate the respiratory area and have been identified as a possible nerve pathway for medication delivery to the CNS **[56].** On the other hand, the olfactory area is situated in the superior aspect of the nasal cavity, spanning a limited distance along both the septal area and the lateral wall. The olfactory epithelium, like the respiratory epithelium, has a pseudostratified structure. However, it distinguishes itself by harboring specialized olfactory receptor cells that play an essential role in the sense of smell **[57].** This particular region assumes a significant function in facilitating the direct delivery of drugs to the brain and its CSF chamber via the olfactory nerve **[58].** Therefore, the olfactory and trigeminal nerves can access the brain directly by circumventing the BBB **[59].** This direct short route, facilitated by the submucosal space of the nose, is the most expeditious pathway for drug brain targeting. Advanced drug delivery technologies have also been employed to enhance mucoadhesion, augment nasal permeability, facilitate regulated drug release, enhance drug

deposition at the olfactory epithelium, and promote intranasal medication transport to the brain **[60].** Intracellular and paracellular drug transport pathways from the nasal cavity to the CNS through olfactory neurons and supporting cells are shown in **Fig. 7**.

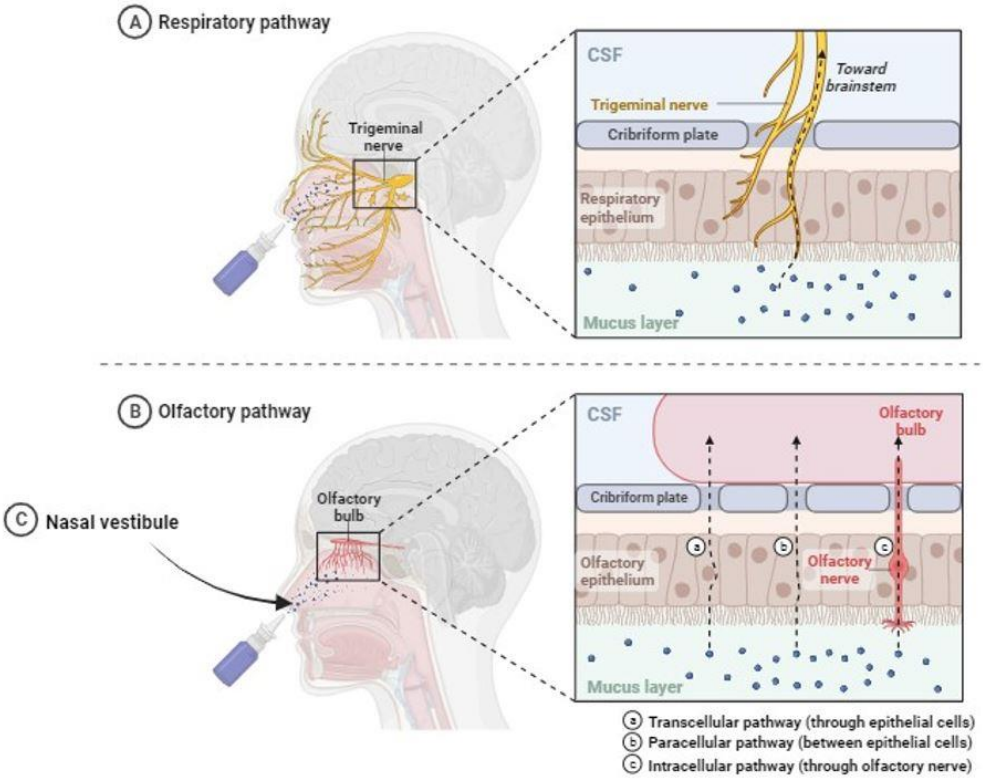

Fig. 7. Drug transport pathways to the Central Nervous System via the intranasal route **(created by Biorender®)**

The primary benefits of IN delivery include its convenient use, which enables self-administration, the rapid onset of action, and its ability to bypass the gastrointestinal and hepatic first-pass effects, thus, minimizing systemic exposure, and reducing potential peripheral side effects. Consequently, the nasal route is advantageous for delivering active substances with low oral bioavailability **[61].** However, noteworthy obstacles exist, including the anatomical, physiological, and biochemical properties of the target location. One of the primary obstacles pertains to mucus in the nasal mucosa and the associated ciliary movement, which can potentially restrict the duration of drug retention in the nasal cavity and hinder its movement toward the CNS. Also, the limited drug delivery volume inside each nostril and the anatomical positioning of the olfactory nerve may impede it **[62].** The inclusion of metabolic enzymes in the olfactory region should also be taken into account throughout the formulation design for the nose-to-brain pathway.

Therefore, IN formulations must consist of biocompatible ingredients to prevent rapid elimination by mucociliary clearance and/or degradation by the enzymes **[63].** Several approaches have been investigated to address these issues, the majority of which were designed to improve the absorption and permeability of molecules, by prolonging their residence time in the nasal mucosa and concentrating the medication in the brain. Various tactics can be employed to boost drug delivery, such as the

utilization of permeation enhancers (e.g. Tween 80, span 60, and bile salts), mucoadhesive polymers (e.g. chitosan; a glycoprotein that constitutes the principal component of the nasal mucus layer), enzyme inhibitors, cell-penetrating peptides, and nanosized drug delivery systems, either individually or in combination **[64-65].**

As for more recent advances in drug delivery via the IN route, Impel Neuropharma has successfully designed a novel device known as the Precision Olfactory Delivery (POD™) technology, which enables the administration of drugs into the deep nasal cavity for enhanced absorption and consistency **[66].** There is also Optinose, a bi-directional delivery device that utilizes the patient's inherent exhalation force to expel the prescribed dosage from the device. The act of closing the soft palate serves to prevent any potential deposition of the powder substance into the respiratory system. Also, SipNose has successfully engineered a nasal device that operates through the act of drinking, facilitating the administration of tiny particle aerosols while minimizing their accumulation in the lower airways **[67].**

From all the strategies mentioned above to bypass the BBB for efficient treatment of NDDs, it can be concluded that the ideal approach is the dual combination of delivering drugs encapsulated in nanocarriers via the IN route. Therefore, **Table 1** summarizes different types of nanocarriers used to target therapeutic agents to the brain via the IN route while highlighting the associated challenges.

Table 1. A summary of nanocarriers used for brain targeting of drugs via the intranasal route.

Nanocarrier type	Drug	Disease	Therapeutic Outcomes	References
Emulsomes	Eletriptan Hydrobromide	Migraine	The results of the optimized Eletriptan mucoadhesive emulsomes formula after IN administration depicted significantly higher C_{max} and AUC $_{(0-8)}$ than IV and IN drug solutions.	**[68]**
Gold nanoparticles	Temozolomide	Glioblastoma multiforme	*In vitro*, studies of Temozolomide-conjugated gold nanoparticles on glioma cells showed an increase in cellular absorption and toxicity, with a higher incidence of cell death in comparison to the Temozolomide solution.	**[69]**
Graphene Oxide Nanosheets	NR	NR	The findings revealed that nose-to-brain delivery was size-dependent, with the smallest graphene oxide sheets deposited in the microglia.	**[70]**
Gold nano prisms and nanospheres	NR	Alzheimer's disease	IN delivery deposited higher gold concentrations in the brain, about 55 times the IV route.	**[71]**
Polymeric nanoparticles	Frovatriptan	Migraine	The results showed that the drug distribution in the brain following IN administration was significantly higher than the IV route.	**[72]**
Transfersomes	Resveratrol	Alzheimer's disease	The C_{max} of Resveratrol in the tailored transferosomal *in situ* gel was 2.15 folds that of the oral suspension, and the AUC was 22.5 folds.	**[73]**
Emulsomal-thermogels	Oxcarbazepine	Epilepsy	IN Oxcarbazepine-exosomal-thermals	**[74]**

			showed higher drug targeting efficiency to the brain compared to the drug solution and marketed oral suspension.	
Nano-emulsion	Selegiline	Parkinson's disease	IN nanoemulsion showed improved selegiline brain delivery compared to IN and IV drug solutions.	**[75]**
Liposomes	Quetiapine	Schizophrenia	The findings confirmed that the liposomal dispersion exhibited higher efficacy in delivering the drug to the brain compared to the simple colloidal dispersion when administered intranasally.	**[76]**
Mesoporous silica nanoparticles	Chrysin and Curcumin	Oxidative CNS disorders	The study provided evidence indicating that nanoparticles with a size less than 500 nm could be internalized by olfactory cells.	**[77]**
Emulsomes	Oxcarbazepine	Epilepsy	Following IN administration of Emulsomal oxcarbazepine, pharmacokinetic results revealed higher brain concentrations to the IV solution and oral marketed product.	**[78]**
Polymeric nanoparticles	Tramadol	Depression	The study revealed that the delivery of Tramadol-loaded chitosan NPs *in situ* gel enhanced the nose-to-brain delivery compared to equivalent drug formulations.	**[79]**
Polymeric nanoparticles	Ropinirole	Parkinson's disease	Following IN administration of Ropinirole hydrochloride-loaded chitosan nanoparticles, the brain bioavailability was found to be significantly higher compared with the drug solution.	**[80]**
Quantum dots	NR	NR	The dots exhibited rapid delivery from the nasal cavity to the brain by olfactory absorption, directed by axonal transport after nasal administration.	**[81]**
Liposomes	rivastigmine	Alzheimer's disease	The results indicated that the IN administration of rivastigmine solution and rivastigmine liposomes exhibited a superior distribution of rivastigmine and satisfactory retention in the CNS regions compared to IV administration.	**[82]**
Transfersomes	Olanzapine	Schizophrenia	The drug delivery efficacy to the brain after IN administration of olanzapine-loaded transfersomes, and nanocubic vesicles was higher compared to less deformable vesicles.	**[83]**
Polymeric nanoparticles	Olanzapine	Schizophrenia	The results showed greater uptake of IN Olanzapine nanoparticles compared to IV and IN Olanzapine solutions, with respective uptake levels of 6.35 and 10.86 times higher.	**[84]**
Polymeric nanoparticles	Buspirone	Anxiety disorder	The study revealed that the brain's AUC was 2.5 times higher in the IN mucoadhesive formulation compared to the IV drug solution.	**[85]**
Lipid nanocapsules	18β-Glycyrrhetinic acid	Alzheimer's disease	IN administration of lipid nanocapsules containing 18β-Glycyrrhetinic acid improved memory loss induced by scopolamine at a dose 50 folds lower than when taken orally.	**[86]**

***** AUC: Area under the curve, IN: Intranasal, IV: Intravenous, NPs, nanoparticles NR: Not reported, CNS: Central nervous system

Conclusions

A variety of techniques have been implemented to address the issue of restricted brain delivery caused by the impeding BBB. However, the field of nanotechnology continues to have immense importance in the context of CNS delivery, since the extensive use of diverse nanocarriers has resulted in a broad spectrum of methodologies aimed at enhancing brain targeting. The IN route presents a promising option for delivering medications to the brain that have a restricted ability to pass across the BBB, especially when these drugs are combined with appropriate mucoadhesive agents, which can selectively bind to specific ligands on the surfaces of drug carriers. Furthermore, the transition from conventional delivery methods to customized multifunctional nanocarriers holds the potential to significantly enhance the efficacy of treatments for NDDs, which collectively contribute to approximately 11% of the global disease burden. However, the sole utilization of formulation techniques is insufficient to exploit this avenue fully. There is ongoing research and development of novel devices aimed at addressing the challenges posed by the anatomical structure of the nasal cavity. These devices are designed to target the deposition of formulations in the olfactory region of the nasal cavity. Therefore, it may be anticipated that in the forthcoming years, the administration of medicinal substances through the nasal route will necessitate the development of advanced automated delivery apparatuses to guarantee a precise, consistent dosage.

Declarations

Ethics approval and consent to participate

Not applicable

Availability of data and material

All data generated or analyzed during this study are included in this published article in the main manuscript.

Conflict of Interest

The authors assert that there are no conflicts of interest.

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