REVIEW ARTICLE

A SYSTEMATIC OVERVIEW ON NOSE TO BRAIN DRUG DELIVERY SYSTEM IN TREATMENT OF NEURODEGENERATIVE DISORDERS

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ABSTRACT

Improving the treatment of neurodegenerative disorders such as Parkinson's (PD) and Alzheimer's disease (AD) has always been challenging. Compared with oral drug administration, nasal mucosa has emerged as a convenient target tissue for drug delivery because of its accessibility, high blood perfusion, greater surface area, permeability and ability to escape the first-pass metabolism. The BBB is the least reachable portion of the human body to active pharmacological molecules. While useful in the treatment of neurodegenerative disorders, conventional approaches fail to achieve maximum effectiveness. Hence, there is a need to invent therapeutic alternatives. This review comprises a brief explanation of the currently developed nose-to-brain drug delivery systems in treating neurodegenerative disorders. It further contrasts the strengths, disadvantages, and future viewpoints from which innovative drug research and therapy can be based.

Keywords: Nose, Brain, Blood-Brain Barrier (BBB), CNS, Neurodegenerative, Drug Delivery System

INTRODUCTION

Oral drug delivery is the furthermost anticipated route for drug delivery when systemic effects are intended. However, it fails to deliver countless therapeutic agents to the brain effectively due to several drawbacks such as the slow onset of action, poor bioavailability (40% to 45 %), the limited half-life of 1-2 h, experiencing hepatic first-pass metabolism, and rapid clearance by hepatic and the renal system[1]. Associated with oral drug administration, nasal mucosa has emerged as a versatile target tissue for drug distribution due to accessibility, strong blood perfusion, larger surface area, penetrable endothelial membrane and the potential to resist the first-pass metabolism[2,3]. Nose-to-brain delivery operates by the olfactory area at the top of the nasal cavity, and the neuroepithelium is the only exposed CNS segment to the external atmosphere[4].

Considering the numerous advantages intranasal drug delivery offers, it is developing as a satisfactory substitute for the oral and parental route for CNS disorders[5]. The evolution of novel nasal systems signifies substantial challenges in controlled drug targeting and delivery[6]. Olfactory sensory neurons are bipolar neurons that communicate with neural signals to the brain. The turbinate zone is employed for systematic drug absorption covered with a pseudostratified columnar epithelium comprising ciliated, non-ciliated, basal, and mucus-secreting cells. The olfactory epithelium includes nerve cells that comply with the olfactory bulb, creating a connection between the brain and the external environment, which is favorable for drug delivery[2].

Mechanism of nose to brain drug delivery

Drugs administered intranasally are conveyed along olfactory sensory neurons to yield noteworthy concentrations in the CSF and olfactory bulb. This nasal mucosa region directly links the nose and brain, which is used to target CNS-acting drug moieties used in

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conditions like Alzheimer's and Parkinson's diseases[7]. In the olfactory pathway, the drug enters the olfactory bulb and brain tissue or cerebrospinal fluid via the olfactory epithelium. In the trigeminal route, the drug is administered through the nervous system[8]. After a nasal cavity receives the drug (Fig.1), it permeates through the highly perfused mucous membrane to the systemic circulation and may or may not pass through the BBB and invade the brain. However, olfactory epithelium, olfactory neurons and trigeminal nerves all play a significant role in drug delivery to the brain[9]. These pathways are the combination of the cerebrospinal fluid, vasculature and lymphatic system. However, the therapeutics and delivery system's characteristics can be sensitive to one predominant pathway[10]. The pathways involved in drug delivery across the olfactory epithelium are classified

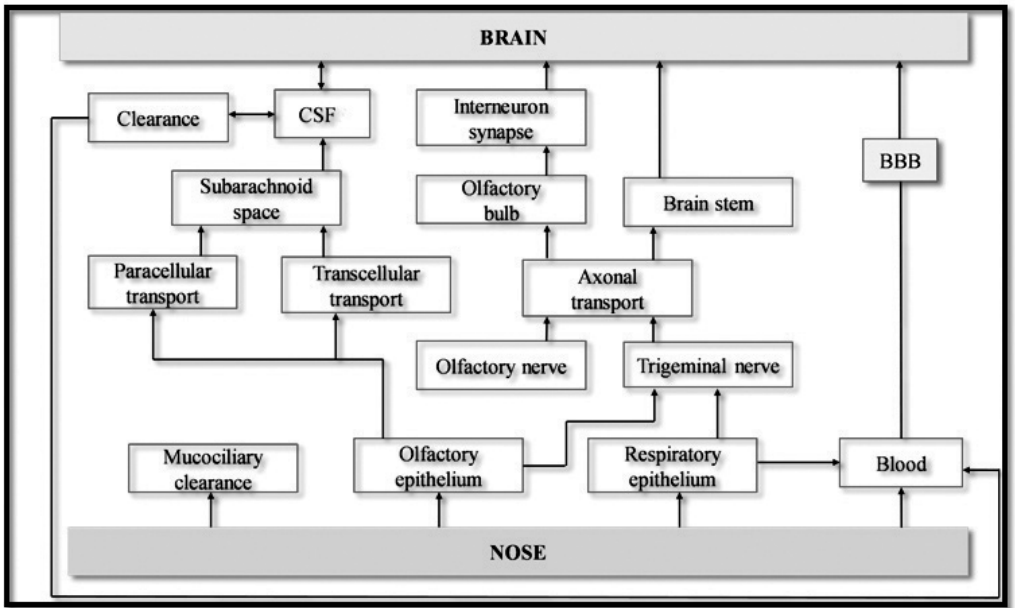

Fig. 1: An overview of the possible fate of drugs after nasal administration. BBB, Blood-brain barrier; CSF, cerebrospinal fluid[17]

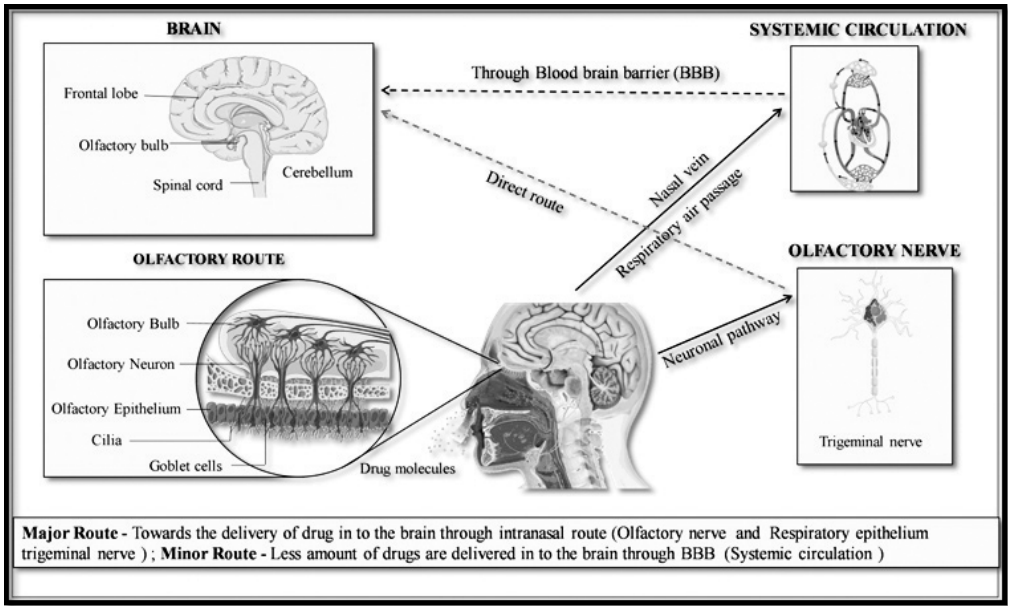

Fig. 2: The primary route of drug transport from the nasal cavity to the brain is via the neuronal pathway (olfactory and trigeminal nerve) and the minor route is via systemic circulation (via BBB). The figure also depicts the respiratory epithelium and olfactory nerves in the nasal cavity[30]

Table I: Nose to brain drug delivery systems

Type	Nanocarriers	Drug	Characteristics	References
Polymeric nano formulations	Polymeric nanoparticles	Borneol	Enhanced absorption of dopamine,and cellular uptake by modification with low toxicity	57
	Micelles	Curcumin	The microenvironment could be controlled to reduce the hyperactive microglia and protect damaged neurons	58
	Dendrimers	G4HisMal	Controlled structure, nanoscopic size, and greater tunable accessibility of numerous functional groups on the surface	59
Miscellaneous nanocarriers	Nano-emulsion	Memantine	Pharmacokinetic readings of radiolabelled formulation directed intranasal displayed greater uptake of drug	60
	Micro-emulsion	Rivastigmine	Chitosan used as co-surfactant showed mucoadhesive property,enhanced bioavailability by paracellular transport	61,62
	Nano gel	Insulin	Protection of insulin from protease degradation	47,48
	Gold nanoparticles	Resveratrol	Enhanced nasal permeation significantly enhanced spatial memory recovery: X-ray imaging, photothermal and photodynamic therapy	42,63
	Carbon nanotubes	Angiopep- 2	High brain uptake, thinner diameter, and faster clearance rate	64
	Liposome	Glial cell line-derived neutrophilic factor	Cationic liposomes interact at the olfactory epithelium, thereby increasing transport to the brain	65
Lipid nano formulation	Niosomes	Bromocriptine Mesylate	They are osmotically active and have an extended storage period	65
	Solid lipid nanoparticles	RVG-9R and BACE1 siRNA	Total encapsulation was obtained via chitosan coating, and penetration ability of the siRNA over the epithelial cell	66

in Table I. A trans-cellular pathway comprises various mechanisms such as receptor-mediated endocytosis, fluid-phase endocytosis, or passive diffusion; Small lipophilic molecules have been demonstrated to migrate across brain tissue using transcellular diffusion, a non-saturable mechanism (Fig. 2).

Furthermore, the diffusion might also be affected if the material is an efflux transporter substrate[11]. A paracellular pathway is restricted via tight junctions of the olfactory epithelium and olfactory neurons in their central sustentacular cells. Paracellular transportation through an aqueous channel is precisely designed for small hydrophilic molecules[12]. The olfactory nerve pathway functions by neuronal endocytotic or pinocytotic contrivances and also, the transportation of the drug to the olfactory bulb is via intracellular and extracellular neurons. The more enormous biological molecules, such as peptides and proteins, follow the endocytosis mechanism[13,14]. Extracellular transport mechanisms comprise the rapid movement of molecules in the nasal epithelium. It takes only several minutes to 30 min for a drug to reach the site of action[15]. Drugs can also be boosted inside these channels by the modified structural changes because of depolarization and axonal propagation of the action potential in neighboring axons[16].

The blood-brain barrier (BBB)

The BBB is the region of the human body that is least accessible to active pharmaceutical compounds. Traditional techniques, although effective in the treatment of neurodegenerative illnesses, fall short of achieving optimal effectiveness. Consequently, it is anticipated that around 98 percent of drugs dynamic towards brain disorders avoid crossing the BBB rendering therapy for these very complicated conditions unachievable[18]. Hence, there is a need to invent therapeutic alternatives[19]. Lipophilic membranes surround the BBB's endothelial cells. Thus, medications that can permeate the CNS must travel from the hydrophilic environment of the blood to the hydrophobic environment in endothelial cells.

Additionally, drugs can permit via small pores loaded with water or through the cellular channels[20]. This process is influenced by drug properties such as molecular size, drug lipophilicity, drug ionization, and plasma protein binding[21]. Studies have presented that lipid-soluble molecules with a low molecular weight of around 400–600 Da are mostly transported across the BBB. In contrast, large or hydrophilic molecules require special assistance like gated channels, proteins, ligand-specific receptors, and ATP-mediated energy[22, 23]. In contrast to drug molecule structural changes, such as increasing lipophilicity or reducing molecular size, blood-brain barrier permeability can be improved by decreasing efflux transport and boosting transcellular diffusion penetrability, or by transiently interrupting tight junction complexes[24].

Neurodegenerative Diseases

Alzheimer's disease

More than 25 million people live with dementia globally, most of whom suffer from Alzheimer's disease (AD)[25]. A clinical syndrome is described by a liberal decay in two or more cognitive domains, including memory, language, executive and visuospatial function[26], personality, and behavior, which causes loss of abilities to perform instrumental and necessarydaily living activities. Alzheimer's disease (AD) accounts for 80% of all dementia diagnoses[27]. The clinical manifestations will initiate with restricted forgetfulness and concern in memory imprinting, further progress to temporary memory impairment, and lastly, long-term memory problems. Plaques and tangles eventually spread throughout the brain[28]. Accumulation of amyloid-beta (Aβ) peptides, neurofibrillary tangle development of phosphoric tau proteins, and detrimental neuronal inflammation is the initial AD progression feature. The primary objective of enhanced therapeutic strategies is to eliminate A plaque/tau tangle development and neutralize their aggregations surrounding neurons[29]. The evolution of Alzheimer's disease treatment will revolve around avoiding beta-amyloid plaque accumulation or assisting with its removal[20].

Parkinson's disease

Parkinson's disease is presently the second most common cause of death after Alzheimer's disease, affecting over 6.3 million people. It is identified by the progressive weakening of motor activities due to damage to dopamine-releasing neurons in the brain's substantia nigra[31]. As serious motor injuries are the core reasons for this disease, this disease's diagnosis is mostly delayed, resulting in more difficulty in its management. Use of proteins like human glial cell line-derived neurotrophic factor (hGDNF) is a promising treatment for this disease[32]. Pathologically, the damage of dopaminergic neurons is detected in the substantia nigra[33]. The significant disease indications are caused by a dopaminergic deficiency in the striatum and include tremors, hypokinesia, diminished balance and body rigidity. Parkinson's disease's principal characteristic is the occurrence of intracellular eosinophilic inclusions called Lewy bodies, which are abnormal protein aggregates[34]. Several dopaminergic agonists are available and used for Parkinson's disease treatment[20].

Nose to brain drug delivery systems

Studies done by Rehman et al. showcased that intranasal administration of nanoparticles proved enhanced brain and plasma concentration of the drug and simultaneously enhanced brain and plasma area under the curve (AUC) compared with the oral administration[35]. Curcumin-loaded PLGA nanoparticles could expand the bioavailability by at least nine-fold, compared with curcumin alone[36]. Polymeric nanoparticles are perceived as capable transporters for intranasal drug administration[24] that follow receptor-mediated endocytosis across BBB[37]. Hagl et al., 2015, concluded that curcumin micelles improved the bioavailability of curcumin around 10-to 40-fold in murine plasma and brain tissue[38]. These micelles showed the prevention of mitochondrial dysfunction and neurodegeneration, responsible for age-associated disorders like Alzheimer's disease[38]. Micelles are excellent delivery vehicles for brain medications due to their capacity to solubilize lipophilic molecules in the hydrophobic core area via hydrophobic interaction and hydrogen bonding enabling facile administration, as well as their ability to conjugate with specific targeting ligands[39]. Dendrimers' three-dimensional structure is accountable

for their variety of distinctive properties, Such features include the existence of different functional groups at the border, a globular nanosized structure, and hydrophilic or hydrophobic voids in the interior, and a low polydispersity index, as well as a broad range of potential applications[40]. Nanoemulsions seem to be ternary systems comprising an oil, a surfactant, and water, with or without the inclusion of a co-surfactant. They are metastable, spontaneously synthesized dispersions with droplet diameters ranging from 2 to 100 nm[41,42]. The capability of surface targeting and the capacity to solubilize pharmaceuticals that are hydrophobic (O/W nanoemulsions) or hydrophilic (W/O nanoemulsions) potentially aid in the reception of nanoemulsions and their encapsulated drugs via receptor-mediated endocytosis of cells[39]. Micro-emulsions are thermodynamically stable colloidal dispersions synthesized spontaneously by incorporating water, oil, surfactants and co-surfactants [43]. Droplet diameters vary between 10 and 100 nm, yielding optically transparent dispersions.

A mucoadhesive microemulsion, consisting of polymers like carbomers or chitosan, offers a better duration of residence in the nasal cavity, demonstrating rapid and efficient absorption of drugs[44]. Misra et al. reported improved drug transport across the nasal cavity utilizing mucoadhesive micro-emulsions to control various brain or brain-associated disorders[45]. Nano-gels, a novel class of drug delivery carrier systems and bio macromolecules[46], have been recommended for incorporation in the BBB. Insulin administration to the brain has been developed using nanogels and delivers insulin's protective role in Alzheimer's disease[47]. Nanogels are hydrogel constituents with a nanoscale three-dimensional network. They are swellable, interconnected networks that can hold a considerable amount of water. Their swelling capacity is influenced by aspects such as the chemical structure of the matrix of polymers, the degree of polymerization, exogenous triggers, and charge density. Their ability to expand and collapse is significant for drug loading and release[48].

Inorganic nanoparticles are uniform in size and form monodisperse solutions; their surfaces can be modified to allow BBB permeability[49]. It was shown that PEGylated silica nanoparticles can cross the intact BBB via vascular endothelial cell transcytosis, with subsequent diffusion into the cerebral parenchyma and dispersion in neurons[50]. Insulin-targeted gold nanoparticles can be used as computed tomography contrast agents to highlight specific brain areas. Dual-functionalized gold nanoplasmonic particles recognize -amyloid peptides in the brain[51]. Recent research showed that SiO_2-NPs up-regulated α-synuclein expression, the hallmark of PD[52].

Liposomes are nanosized vesicles with an aqueous inner core surrounded by uni-lamellar or multi-lamellar phospholipid-based membranes[39]. Its surface can be improved by targeting agents achieving transport across BBB[53]. Liposomes can accommodate hydrophobic and hydrophilic drugs in their phospholipid bilayers and aqueous core, respectively[40]. Titze-de-Almeida et al. employed siRNA delivered in a cationic liposome formulation to reduce neuronal nitric oxide synthase in Parkinson's disease, which has been implicated in a dopaminergic loss in PD[54]. Nevertheless, liposomes have significant drawbacks enclosing rapid systemic removal, rapid metabolic destruction of phospholipids, stability issues after prolonged storage, inability to deliver sustained drug release[55], and moderately effective lipophilic compound entrapment[56]. Mono-, di-, and triglycerides, fatty acids, steroids, and waxes combine to synthesize lipid nanocarriers that are stabilized by diverse kinds of emulsifiers[53]. Galantamine hydrobromide acts as an acetylcholinesterase inhibitor for Alzheimer's disease treatment, showing cholinergic side effects. Compared to the native drug, *in vivo* evaluations of the created system revealed remarkable memory restoration potential in cognitive-deficit mice. The designed carriers provided double the bioavailability of the standard drug, emphasizing the system's potential for treating Alzheimer's disease[40] (Table I).

Limitations of the nose to brain drug delivery

The intranasal route of drug delivery possesses many advantages; however, the clinical use of intranasal formulations still has a long way to go. Partial drug permeability from the nasal mucosa, enzymatic degradation, mucociliary clearance, short drug retention time, and nasomucosal toxicity are certain characteristic limitations of intranasal drug delivery. Additionally, the nasal mucosa's protective barriers resist intranasal therapy's effectiveness, and only 1% or <1% of the drug reaches the brain after administration. In addition, the nature and effectiveness of the drug and excipients should be considered. Given its modest capacity, the nasal cavity can only hold a tiny amount of formulation (100-200 L) at a time when compared to the oral or IV routes (25 cm^3). Furthermore, the tonicity, viscosity, and pH (5.0–6.5) of the preparation also play essential roles in drug development. Thus, there is a requirement to focus on a suitable formulation's progress to overcome these barriers[38].

CONCLUSION

The intranasal route provides numerous benefits and can overcome some restrictions; thus, it favors substitute drug administration routes over the parental and oral routes. It is estimated that the intranasal route could be a future method for drug delivery to the brain. The focus of this review has been on the implementation of an appropriate intranasal drug delivery system for the treatment of brain diseases. A wide range of drugs, proteins, peptides, biological agents, and cells are currently under examination for intranasal delivery, expecting promising conclusions.

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