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Intranasal Drug Delivery: Novel Delivery Route for Effective Management of Neurological Disorder

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ABSTRACT

Neurological disorders, such as Alzheimer's disease, Parkinson's disease, and epilepsy, pose significant challenges in treatment due to the blood-brainbarrier (BBB), which restricts drug delivery to the brain. The BBB's selective permeability hinders the efficacy of systemically administered drugs, leading to inadequate treatment outcomes and significant side effects. This paper provides a comprehensive review of innovative delivery routes that bypass or cross the BBB, enabling direct delivery of therapeutics to the brain.

Keywords: Nose, Intranasal, nasal drug formulations, Alzheimer's disease, Parkinson's disease

I. INTRODUCTION

The autonomic, peripheral, and central nervous systems of the body are all impacted by neurological disorders (NDs), which are diverse medical conditions [1][2]. Parkinson's disease, epilepsy, multiple sclerosis, Alzheimer's disease and other dementias, migraines, non-migraine headaches, and other neurological disorders are among the non-communicable neurological disorders [2].

With roughly one in three persons affected, neurological diseases are currently the largest cause of illness and disability worldwide. According to a 2021 study published in The Lancet Neurology, over 3 billion people globally suffer from a neurologicaldisorder[3].

Because of the protective structure of the brain, traditional drug delivery methods have difficulty delivering medications to the brain and central nervous system (CNS) in an effective and efficient manner. The ability of a therapeutic agent to cross the blood brain barrier (BBB) and cerebrospinal fluid (CSF), the two biggest barriers preventing hydrophilic and large lipophilic molecules from entering the brain, determines its clinical potency rather than its bioavailability.Therefore, when creating or constructing any drug delivery system, the physiochemical characteristics of the active therapeutic agents and the formulation for brain administration are taken into account[4].

Researchers are becoming more interested in intranasal drug administration as a possible delivery channel for brain targeting due to the connection between the brain and nose through the olfactory route and peripheral circulation. [5]

Therapeutic medicines that target the central nervous system (CNS) can potentially have a greater absorption rate and a lower metabolic environment by breaching the blood-brain barrier (BBB), since the nose is the sole organ or place where direct brain contact occurs. The drug molecule in the intranasal drug delivery system enters the nose through the mucosa and reaches the olfactory/trigeminal epithelium, which allows for non-invasive entry into the brain to produce the desired therapeutic effect[6,7]. Avoiding hepatic circulation, not only improves therapeutic efficacy but also lowers the systemic toxicity of centrally-acting drugs.

With a highly vascularized epithelium and a porous endothelium membrane, the nasal route is a dependable, easy, and easily accessible method of absorbing substances into the systemic circulation. This prevents the need for hepatic first-pass elimination. Furthermore, dose reduction, a speedier initiation of pharmacological activity, a quicker attainment of therapeutic blood levels, and fewer side effects are all made possible by

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intranasal drug administration[8,9]. The nasal cavity's low metabolic environment may be able to replicate the advantages of intravenous delivery while overcoming the drawbacks of the oral route[10].

1. Anatomy and physiology of the nose

I.Anatomy of the nose

The main orifice through which air enters the respiratory system to be used for breathing is the nose[11]. The nasal cavity is 120–140 mm deep, split in half by the nasal septum, a cartilaginous wall that connects the nasal vestibule to the nasopharynx. The nose has a capacity of approximately 16–19 ml and a surface area of about 160 cm2 [12]. The vestibular, turbinate, and olfactory areas are the three primary regions of the nose (Figure 1). The nasal cavity's smallest section is located in the vestibular region, which is located in the front of the nose. Since the majority of this region is covered by vibrissae, it can filter out aerodynamically larger than 10 µm particles that could be inhaled with air [11]. One of the nose's main vascular sections, the turbinate region is separated into superior, middle, and inferior parts (Figure 1). It is made up of basal, ciliated, non-ciliated, and mucus-secreting cells. Here is where medication absorption is most effective because the ciliated and non-ciliated cells are covered in non-motile microvilli, which increase the surface area [13].

Approximately 8% of the nasal epithelium's total surface area is made up of the olfactory region. It is crucial for the delivery of medications to the brain and CSF (cerebrospinal fluid). The epithelial cells are covered in a 5 µm-thick coating of mucus that collects foreign particles. Mucin, water, salts, proteins such as albumin, immunoglobulin, lysozyme, lactoferrin, and lipids make up mucous secretion [14]. The nasal secretions have a pH between 5.0 and 6.5 [12]. The olfactory nerve, which avoids the BBB, enters the central nervous system (CNS) directly through the olfactory area.

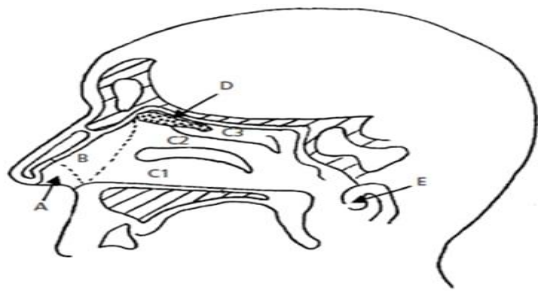

Figure 1: The Sagittal section of the nasal cavity shows the nasal vestibule (A), atrium (B), respiratory area: inferior turbinate (C1), middle turbinate (C2), and the superior turbinate (C3), the olfactory region (D) and nasopharynx (E).[15]

1.1 Surface epithelium

At the beginning of the passage, the surface lining of the vestibular area transforms from skin to a stratified squamous epithelium. The pseudostratified columnar epithelium lines the turbinate area. The non-ciliated, pseudostratified columnar epithelium that makes up the olfactory area. It is made up of four main cell types: basement membrane, goblet cells, columnar cells, and basal cells [13].

a) **Basal cells:**They do not reach the airway lumen and instead reside on the basement membrane as the progenitors of the other cell types. They have bundles of tonofilaments and cytoplasm that are electron-dense. Desmosomes and hemidesmosomes are two of their morphological specializations; the former facilitates adhesion between neighboring cells. It is thought that basal cells aid in columnar cells' adherence to the basement membrane[16]. This is corroborated by the observation that columnar cells only cling to the basement membrane via cell-adhesion molecules and lack hemidesmosomes [17].

b) **Columnar cells:**These cells are connected to neighboring cells by tight junctions apically and, in the uppermost part, by interdigitations of the cell membrane. The cytoplasm has multiple mitochondria in the apical part, indicating an active metabolism. All columnar cells, ciliated and non-ciliated, are covered in approximately 300 microvilli, uniformly distributed over the entire apical surface. These short, slender finger-like cytoplasmic expansions increase the surface area of the epithelial cells, promoting exchange processes across the epithelium. Additionally, by retaining the moisture necessary for ciliary function, the microvilli prevent the surface from drying out. The cilia have a typical ultrastructure, with each ciliated cell containing approximately 100 cilia, measuring 0.3 mm wide and 5 mm long[18].The distribution pattern of ciliated cells is in good agreement with a nasal airflow map, suggesting an inverse relationship between ciliated cell density and the nasal cavity's

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inspiratory air's linear velocity [19]. In comparison to the floor, the upper portion of the nasal cavity has less cilia. Low humidity and temperature are also thought to have a role in the decrease of ciliated cells. It makes sense that the anterior nasal cavity has a lower density of ciliated cells due to strong currents of cold, dry, and dirty air that bombard it [20].

c) **Goblet cells**: The goblet cell is another type of cell that is typical of the epithelium of the airway. There are a few small topographical variations, more in the posterior than in the front region of the nasal cavity. Goblet cell concentrations (4,000–7,000 cells per mm2) are comparable to those found in the trachea and major bronchi[21]. Comparing the goblet cell contribution to the nasal secretion volume, it is likely less than the submucosal glands' contribution. Goblet cells, which are not governed by the parasympathetic nervous system like glands are, and their release mechanisms are poorly understood. Goblet cells most likely react to external stimuli in their microenvironments, both chemical and physical.It is currently unknown which biochemical mediators and cytokines could cause goblet cells to secrete. As previously indicated, tight junctions on the apical end of the intercellular connection are what hold the surface epithelial cells together. It's interesting to note that tight connections surrounding full goblet cells have been observed to fragment and discontinue in ultrastructural studies[22].

d) **Basement membrane**:Under a light microscope, this layer of collagen fibrils—known as the "basement membrane"—supports the epithelium. According to statements based on biopsies from the anterior portion of the inferior turbinate, this membrane thickens in the bronchi in cases of chronic asthma, while it thickens in the nose in cases of rhinitis and in people without symptoms[23]. The explanation is most likely because there is no such thing as "a normal nose," because dry, unconditioned, and polluted air constantly impacts the nasal mucosa[20].

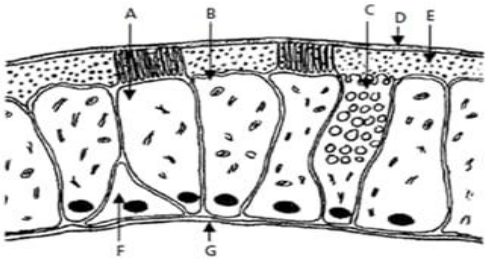

Figure2: Cell types of the nasal epithelium with covering mucous layer showing ciliated cell (A), non-ciliated cell (B), goblet cells (C), mucous gel-layer (D), sol layer (E), basal cells (F), and basement membrane (G).[13]

1.2 Inflammatory cells

There are a few lymphocytes, mostly T cells, but not many mast cells or eosinophils on the surface epithelium of a normal nose. Mast cells are commonly seen in the lamina propria, or "submucosa," along with a large number of lymphocytes that exhibit a 3:1 T to B cell ratio and a 2-3:1 T helper cell 1 1 (CD4 +) to T effector cell (CD8+) ratio [24]. Significantly, antigen-presenting Langerhans cells have been found in the lamina propria and normal surfactant epithelium by Fokkens et al. Therefore, when foreign or non-self macromolecules are inhaled or insufflated into the nose, the nasal mucosa appears to have a high potential for antigen identification and the start of immune responses[25].

1.3 Blood vessels

There are many blood vessels in the nasal mucosa's lamina propria. Three characteristics set them apart from the tracheobronchial tree's vasculature. The nose's venous sinusoids come first. Secondly, the nose has arterio-venous anastomoses. Third, the nasal cycle is caused by periodic variations in congestion in the nasal vasculature[26].

a. Arterioles: The endothelial basement membrane is continuous with the smooth muscle cell's basement membrane system since the arterioles aredevoid of the internal elastic membrane. Additionally, it has been stated that a feature of nasal blood vessels is the porosity of the endothelial basement membrane[27,28]. Due to these anatomical features, the subendothelial musculature of these veins may be more susceptible than blood vessels elsewhere to the effects of chemicals

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circulating in the bloodstream, such as hormones, medications, and mediation molecules**.**

b. Capillary: The fenestrated kind of capillaries surround the glands and lie slightly beneath the surface epithelium. These capillaries are ideal for allowing fluid to pass through the vascular wall quickly[27,29]. This will permit evaporation in the air inspired by conditioning and water to escape into the airway lumen.

c. Venous sinusoids: The nasal mucous membrane is characterized by large venous cavernous sinusoids, which are primarily located in the inferior turbinates. They are typically observed in a semi-contracted state brought on by smooth muscle tone regulated by the sympathetic nervous system. When it comes to heating and humidifying breathed air, the cavernous sinusoids are thought of as specialized blood veins that have been developed to meet the functional requirements of the nasal airway.The mucosa will swell and tend to partially (in the case of normal) or fully (in the case of illness) restrict the airway lumen when they distend with blood[20].

d. Post-capillary venules: Extravasation of plasma occurs during mucosal inflammation through the walls of postcapillary venules, where holes in the intercellular connections between endothelial cells open. Interstitial liquid volume and pressure will rise as a result, and the latter will tend to push liquid that resembles plasma into the lumen as exudate. Many humoral mediators, including histamine, bradykinin, different prostaglandins, and neuro-peptides from sensory nerves like substance P, are responsible for the extravasation of plasma[28].

e. Arterio-venous anastomoses: Arteriovenous anastomoses allow blood to travel through the capillary bed. These anastomoses can be seen in the nose, lips, nail beds, and skin of the fingertips and toes. Arterio-venous anastomoses most likely have a part in controlling water and temperature. Arteriovenous anastomoses typically redirect at least 50% of the blood flow in the nasal mucosa[30], and the upper airway mucosa has a higher total blood flow per cm3 of tissue than the liver, brain, or muscle[31].

1.4 Submucosal glands

There are two different kinds of glands in the nose: seromucous and anterior serous glands. On each side, there are just 100–150 anterior serous glands. Large apertures can be found in the upper portion of the internal ostium of their lengthy excretory canals. The secretory capacity of the seromucous glands is significantly greater. However, compared to secretions produced in the posterior region of the nose, those produced in the anterior part of the nose are more watery and have a significantly lower viscoelasticity[32].

The tracheobronchial glands and the nose's seromucous glands are nearly structurally identical. The human nose has over 100,000 seromucous glands, and this quantity seems to stay consistent throughout life[21]. Since nasal glands are smaller than tracheal glands, the number of glands per unit surface area in the nose is significantly larger than that of the trachea (eight against one per mm2). However, this difference may not be directly related to secretory capacity[21].

1.5 Mucus and mucociliary clearance

a. **Mucus:** Water makes up 95% of airway mucus, followed by mucus glycoproteins (2%), other proteins (1%), inorganic salts (1%), albumin, immunoglobulins, lysozyme, and lactoferrin, and lipids (less than 1%)[33]. The primary source of the mucus glycoproteins that give mucus its distinctive viscoelastic qualities is the submucosal glands, and to a lesser extent, the goblet cells. Mucus glycoproteins are made up of a 20% protein core and 80% oligosaccharide side chains that are connected by hydrogen and disulfide bonds [33]. To create a viscoelastic gel that can mechanically couple with cilia and be conveyed by them, mucus can cross-link. Compared to tracheobronchial secretions, nasal secretions are much less viscous but have a similar elasticity. Elasticity is more crucial for mucus transmission than viscosity[34].

b. **Mucus layer:**The mucus layer is most likely a double layer with an aqueous periciliary sol phase in which the cilia beat and a superficial blanket of gel that is moved forward by the tips of the cilia; both layers are about 5 mm thick. The composition and thickness of the double layer play a crucial role in mucociliary transport; if the sol layer is too thin, the viscous surface layer will inhibit ciliary beating; if it is too thick, the gel layer will lose its contact with the cilia and mucociliary clearance will be hampered[20].

c. **Measurement of mucociliary transport rate**: Every minute, Cilia beats roughly 1,000 times. The cilia in the nose beat in a backward

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direction, which helps the mucus with its trapped inhaled particles go down the throat where it is swallowed. The saccharin-dye method is a useful tool for measuring mucociliary transport rate[20].

d. **Other clearance mechanisms**: There are other ways besides mucociliary clearance to remove secretions and debris from the nose. Airway secretions can be moved with the aid of sniffing and nose-blowing. A burst of air is produced when you sneeze, and watery nasal secretions increase as well. You can then blow your nose and sniff to get rid of them. Particles that have become stuck and secretions that have been inspissed can be removed with nasal sprays and washes[20].

1.6 **Nerves**

The trigeminal nerve contains afferent nerve fibres, the vidian nerve contains efferent parasympathetic nerve fibres, and the blood vessels are followed by efferent sympathetic nerve fibres. The glands are richly innervated by the parasympathetic nervous system. Marked hypersecretion results from the nervous activation of glandular cholinoceptors, which is frequently a component of a reflexarc. On the other hand, blood vessels are primarily regulated by sympathetic fibres despite possessing both parasympathetic and sympathetic innervation. Because the vasoconstrictor action of alpha-adrenoceptor stimulation is more pronounced than the vasodilatation effect of beta-2 receptor activation, continuous noradrenaline release maintains the sinusoids partially constricted.

Peptide neurotransmitters, which are rapidly proliferating, have joined the conventional neurotransmitters noradrenaline and acetylcholine in recent years[35,36]. They are released from efferent parasympathetic nerve endings (vasoactive intestinal peptide (VIP), peptide histidine methionine, and from efferent sympathetic nerve endings (neuropeptide Y), as well as from afferent unmyelinated C fibres (substance P, calcitonin gene-related peptide (CGRP), neurokinin A (NKA), and gastrin-releasing peptide)[17]. The exact function of peptide neurotransmitters in the human nose remains unclear as there are no particular drugs that inhibit their receptors

1.7 Nasopharynx

The upper and lower portions of the nasopharynx are covered by ciliated and squamous epithelium, respectively. When swallowing, the uvula and soft palate come into contact with the posterior and lateral walls of the pharynx, causing a change in epithelial type. Because of the flexible shape of the epithelium lining the adenoids, the immune system of the adenoids and inhaled antigens in the mucus surface layer can more easily come into touch. It is important to remember that the majority of foreign particles that are transported by mucociliary action through the nasal filter end up in the adenoidal area. The adenoids in the nose most likely perform the same role as the BALT (bronchi-associated lymphoid tissue) in the lower respiratory tract[20].

II. Physiology of nose

The nose has two primary purposes in addition to being the initial segment of theairways.

1.Aroma(Olfaction)

2.Preparing the inspired air for inhalation, which includes heating, humidification, and cleansing.

a. Nasal airways

For the majority of animals, including nearly all newborns in their first few weeks of life, nasal breathing is essential. Life can then be sustained by breathing through the mouth, but as the nose's ability to regulate temperature is lost, suspended nasal outflow is uncomfortable and may even be dangerous. The slit-like tubes that make up a typical nose facilitate the effective exchange of moisture and heat. The sympathetic innervation and tone in the venous sinusoids actively control the width of the nasal cavity. This alternates every two to four hours from one side to the other. Only individuals with a deviated septum and those suffering from rhinitis perceive the nasal cycle. It might cause problems for intranasal medicine. Few studies have been done on the topic of sufficient patency and airflow in the nasal cavity to guarantee appropriate medication distribution in the nose. Depending on the inhaler device being utilized, that is. Rhinomanometry, nasal peak flow measurement, and acoustic rhinometry can all be used to study nasal patency[37].

b. Heating and humidification

The nasal cavity's slit-like shape ensures close contact between the inhaled air and the mucous membranes; (ii) the cavity's width can adapt quickly to changing needs by changing the sinusoid contraction; (iii) heat exchange is facilitated by a large amount of arterial blood flowing in arteriovenous anastomoses, which is similar to hot water in a radiator; and (iv) the nasal mucosa has a high secretory capacity. These factors

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make the nose a good choice for its air conditioning function. Ingelstrdt investigated the upper airway's (primarily the nose's) capacity to regulate temperature as early as 1956[38]. He discovered that when ambient air (238°C, 40% relative humidity) entered the subglottic region, it was already conditioned to 328°C and 98% humidity. The corresponding values for oral breathing varied depending on how wide the mouth was opened, and they were 308C and 90%. Following the inhalation of cold air at 08°C, the results showed 318°C and 98%. N.G. Toremalm paraphrases this as follows: "A single sniff transforms Scandinavian winter into Florida summer." In summary, the upper respiratory tract (pharynx, larynx, and notably nose) sufficiently heats and moisturizes inspired air at room temperature, but mouth-breathing circumstances inspire air less successfully at room temperature than the nose does cold air[39].

c. Filtration

The more proximally the inhaled particles are deposited, the faster they are eliminated (nose, minutes; bronchi, hours; alveoli, days to weeks). This is in contrast to the lower airways, where damage to the epithelial lining from inhaled noxious agents is unlikely to have serious consequences. Consequently, it is convenient for inhaled particles to deposit in the nose. The way the nasal canals are shaped favors it because turbulence and impaction allow particles to settle farther away from constriction sites and locations where airflow direction changes. The primary location of particle deposition in the airways is typically the nose; however, the effectiveness of the nasal filter is primarily dependent on the size of the particles that are inhaled.When breathing at rest, the majority of particles less than 2 mm (mould spores) can pass through the nose, but almost all particles larger than 10 mm (pollen grains) are kept in the nose. Additionally, the nose serves as a barrier against water-soluble pollutants including formaldehyde and sulfur dioxide. Even when the percentage of sulfur dioxide is higher than in the most polluted city air, almost 99% of the irritating and tissue-damaging gas is contained in the "nasal gas mask." Mucociliary transport removes inhaled particles that are caught in the nasal filter from the nose in less than 30 minutes. The speed of the inhaled airstream, the particle size, and the aerosol velocity from the spray device all affect how much of a medicine is deposited in the nasal cavity. Intranasal deposition is favoured by rapid drug velocity and high particle size inhalation[20].

3.Intra-nasal drug delivery system

Direct delivery of pharmacological formulations from the nose to the brain is beneficial because it involves an uncomplicated and simple transport process [40]. William H. Frey II first proposed intranasal administration as a non-invasive method of delivering medication from the nose to the brain in 1989. This method makes use of the olfactory bulb, which facilitates the direct link between the olfactory nerve and the frontal area of the brain, as well as the trigeminal nerve's entrance through the pons and trigeminal ganglion. Through these links, it is possible to avoid intestinal enzyme degradation, avoid hepatic first-pass effects, and circumvent the BBB [41].

Pathway of Intranasal Transport to the Brain

The difficulty of getting medications to the brain through the Blood-Brain Barrier (BBB) is what spurred the development of intranasal drug administration[42]. Direct paths to the brain are provided by the olfactory and trigeminal nerve pathways, which are the two main delivery mechanisms for intranasal administration [41].

a. Olfactory pathway

Drugs are delivered to the olfactory nerve axons through intracellular axonal transport by olfactory receptors in the olfactory epithelium, where they are absorbed by endocytosis or passive diffusion. Because of the size of the olfactory nerve axon, small-molecule medications that are less than 200 nm are extraordinarily acceptable[42]. Drug delivery from the peripheral nervous system (the olfactory epithelium) to the central nervous system (the brain) may be possible due to the special structure of the axons that are enclosed by the olfactory ensheathing cells and extend to the olfactory bulb across the cribriform[43]. Substances are transported to the perineural space, which connects the subarachnoid region, via transcellular or paracellular transport processes after they reach the lamina propria of the olfactory epithelium [42].
The absorption of drugs through the epithelium occurs via two pathways:

1. Trans/paracellular pathway: use endocytosis to enter and support epithelial cells. Drug molecule absorption by this route is contingent on several variables, including molecular weight, water solubility, lipophilicity, and bioavailability.
2. Olfactory nerve pathway: medication is taken up by endocytosis or pinocytosis in nerve cells and then delivered by nano-carriers via an

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intracellular axonal pathway to the olfactory bulb [44,45].

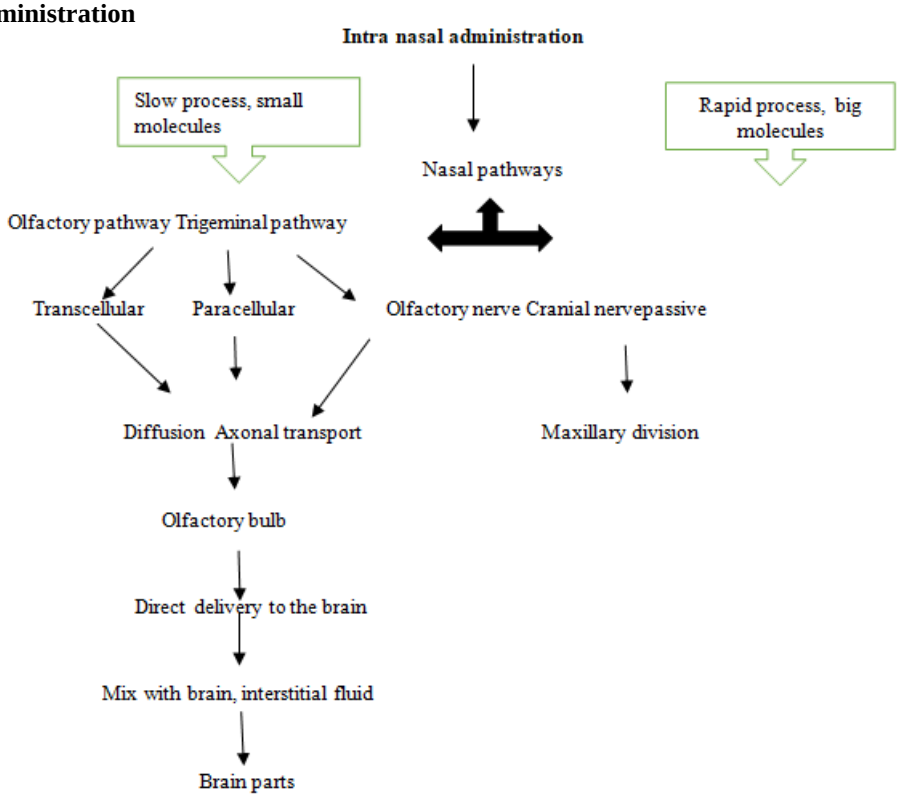
b. Trigeminal pathway

Drugs are delivered to the brain through the trigeminal nerve route in the respiratory system. The ocular, maxillary, and mandibular nerve branches innervate the fifth cranial nerve, the trigeminal nerve, and they converge at the trigeminal ganglion. Given that the trigeminal nerve arises from the brainstem's pons, it may serve as a target nerve for the transfer of drugs into the central nervous system. Drugs that are absorbed in the ophthalmic and maxillary nerve branches, in particular, can be administered brain-targeted to the brainstem through the pons. Like the olfactory nerve pathway, the trigeminal nerve pathway enables transportation from the nose to the brain by extracellular and intracellular axonal transport.Compared to the olfactory nerve system, the trigeminal nerve pathway has a slower intracellular transportation rate [41].

c. Glymphatic pathway

The lymphatic system manages the exchange of CSF and ISF, which includes solute transport and the removal of metabolites that have accumulated. When the glymphatic system is compromised, there is an increase in CSF influx but not ISF efflux, which leads to an accumulation of extracellular solutes and cognitive impairment. In the treatment of disorders associated with the central nervous system, changing the CSF-ISF exchange may be beneficial in promoting solute and metabolite clearance [46,47].

Intra nasal administration



Overview of pathways for direct nose to brain delivery[40]

Mechanism of drug absorption

The drug's journey through mucus is the main stage in its absorption from the nasal cavity. Larger particles could have some trouble getting past the mucus layer, but fine particles do so with ease[48]. Mucin, a protein found in mucus, can bond with solutes and influence the diffusion process. The mucus layer may undergo structural alterations as a result of physiological or environmental modifications[49]. There are several methods for medication absorption through the mucosa once it has passed through the mucus. These consist of paracellular transport through cell-to-cell migration, transcytosis by vesicle carriers, and

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transcellular or simple diffusion across the membrane. Although many mechanisms have been suggested, paracellular and transcellular pathways are the most common[50].

Transport within cells is passive and sluggish. The molecular weight of water-soluble substances and intranasal absorption are inversely correlated. It has been found that medications with a molecular weight larger than 1000 Daltons have poor bioavailability[58].

The second mechanism, which is also referred to as the transcellular process, entails the transport of lipophilic medicines that exhibit a rate dependence on their lipophilicity through a lipoidal pathway. Moreover, drugs can traverse cell membranes actively through carrier-mediated transport or by opening tight junctions[50]. Potential metabolism before entering the systemic circulation and insufficient time spent in the nasal cavity can be barriers to medication absorption. Numerous medications with high water solubility may not have enough bioavailability due to their limited permeability through nasal epithelia. Enhancers are commonly used to improve the penetration and bioavailability of materials. Permeation enhancers, in theory, cause reversible changes to the epithelial barrier's structural makeup[51].

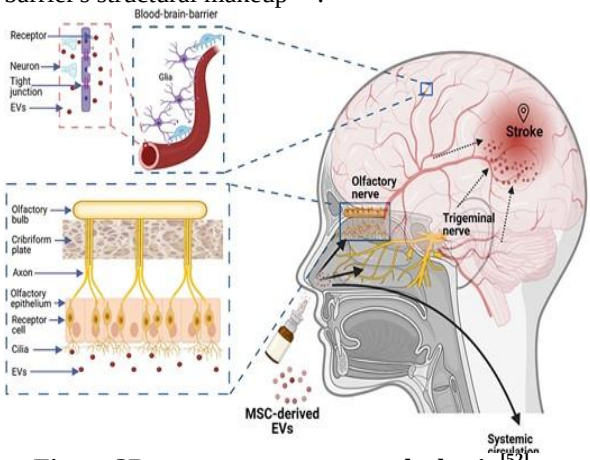

Figure 3Drug transport nose to the brain[52]

Ideal drug candidate for nasal delivery

The following characteristics make up an optimal nasal medication candidate:

• Appropriate aqueous solubility to provide the required dose in a 25–150 ml volume of formulation administration per nostril.
• Proper qualities of nasal absorption.
• The medication does not irritate the nose.
• A good therapeutic justification, such as a quick beginning of action, for nasal dose forms.
• Minimal dosage. usually less than 25 mg for each dosage.
• No harmful byproducts in the nose.
• The medicine has no unpleasant smells or aromas attached to it.
• Adequate stability attributes.[53]

Limitation of nasal drug delivery system

• The nasal cavity's delivery volume is limited to 25–200µL.
• This method is not suitable for delivering high molecular weight drugs (mass cut off ~1kDa).
• Affected negatively by medical disorders.
• This pathway exhibits significant interspecies diversity.

The permeability of drugs is impacted by regularlydefined mechanisms such as ciliary beating and mucociliary clearance.
• Drug irritation of the nasal mucosa caused by azilactine and budesonide.
• At this point, models are less established, and mechanisms are not fully understood.
• There is currently no proof that absorption enhancers cause systemic toxicity.
• Less absorption surface area in comparison to the GIT.
• Inconvenient when compared to the oral route due to the potential for nasal discomfort.
• The enzymatic barrier to the drug's permeability.[54]

Advantage

• Enhanced pharmacokinetic profile, Quick absorption of medication
• With regard to oral administration, drug breakdown is restricted.
• Preventing first-pass metabolism
• Direct brain targeting prevents BBB crossing and potential drug side effects that could affect the whole body.
• Painless and non-invasive method
• Adherence to treatment[55]

Disadvantage

• Risk for local side effects, such as irreversible damage to cilia
• Nasal cavity has less absorption surface area than the gastrointestinal system
• Potential irritation to the nasal mucosa, especially with repeated administrations;
• Nasal epithelial cells may experience harmful effects from surfactants or penetration enhancers.

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• Potentially occurring partial drug dosage loss in the gastrointestinal and respiratory systems while being administered
• The nasal cavity's limited capacity (23 cm3 in humans receiving about 400 L formulation)
• Quick mucociliary removal. [55]

Factors affecting intranasal drug delivery

Biological factors

- Mucin secretion
- Mucociliary clearance
- Enzymatic degradation
- P-glycoprotein PH of the nasal cavity

Physicochemical factors

- Molecular weight
- Lipophilicity
- Solubility

Formulation factors

- Osmolarity
- PH
- Viscosity

Mucin secretion

The nasal mucosa serves as the main drug barrier after intranasal administration, guarding the nasal epithelium from external objects and controlling humidity and temperature. Mucus, which is made up of mucin proteins released by goblet cells, coats the nasal mucosa. Other chemicals that can break down living entities and have immunomodulatory and antibacterial properties are also present in mucus. Mucin is composed of proline, threonine, and serine residues arranged in elongated, flexible domains called "PTS" domains. The majority of the PTS domains' serine and threonine residues are connected to glycan molecules. These glycans end in negatively charged carboxyl groups that include sialic acid, which leaves the PTS domains significantly negatively charged.Mucin monomers are linked end-to-end with one another by disulfide bonds, and each monomer is roughly 0.2–0.6 μ m long.

Uncharged hydrophilic molecules can pass through the mucin mesh very quickly, with smaller molecules traveling nearly as fast as water, but hydrophobic or charged hydrophilic molecules diffuse poorly through mucus. Although nasal mucus is typically thin and not a major factor in most clinical instances, its thickness can vary depending on its water content.

Mucociliary clearance

The passage of ciliated hairs within the nasal mucosa makes it easier for inhaled particles trapped in mucus to be expelled from the nasal cavity and into the nasopharynx. This procedure, called nasal mucociliary clearance, keeps dangerous materials out of the nose as a form ofself-defense. But it also has an impact on how long medications stay in the nasal mucosa, which has a direct bearing on how well nose-to-brain drug delivery works. The olfactory region has a slower rate of mucociliary clearance than the respiratory region, with a nasal mucociliary clearance rate of roughly 10–20minutes.

Because powders tend to stick to the moist nasal epithelial surfaces, liquid dose forms typically have a shorter residence period in the nasal cavity than powder forms due to mucociliary clearance.

One of the main obstacles to medication absorption during intranasal administration is mucin secretion and flow. To get over these mucin-related restrictions, techniques like changing the size of the nanoparticles, balancing their hydrophilic and lipophilic characteristics, and employing mucolytic agents have been suggested. The formulation's viscosity rises as a gel forms inside the nasal cavity. Consequently, this increases the duration of contact between the medication and the nasal membrane, leading to a longer retention period and a potential decrease in the drug loss rate. Although mucociliary clearance may still have an impact on this strategy, it is thought to be an efficient formulation method because it is comparatively more successful in getting over this drawback.

Enzymatic degradation

Enzymatic Deterioration Despite the fact that medications delivered to the nasal cavity can avoid the hepatic first-pass effect and gastrointestinal degradation, the nasal cavity's defense mechanism against xenobiotics includes hydrolytic enzymes, which cause enzymatic drug degradation. As a result, this causes a pseudo-first-pass impact that impedes drug absorption and adversely alters the medications' pharmacokinetic and pharmacodynamic characteristics.

P-Glycoprotein

Because it lacks motile cilia, the olfactory epithelium has a slower mucociliary clearance time than the respiratory epithelium. However, this effect might be offset by the olfactory epithelia's high expression levels of p-glycoprotein pumps.

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Molecular weight and Lipophilicity

Medication absorption through the nasal epithelium is dependent on the molecular weight and lipophilicity of the substance. Regardless of their lipophilicity, drugs with molecular weights less than 300 Da are quickly absorbed and readily pass through the nasal epithelium. On the other hand, lipophilic compounds are usually absorbed by passive diffusion, while hydrophilic molecules can be absorbed by the mucosal epithelia paracellularly or via carrier-mediated transport.

Lipophilicity is especially important for medications whose molecular weights fall between 300 and 1000 Da. Hydrophilic medications use a paracellular route, while lipophilic pharmaceuticals pass by passive diffusion. Lipophilic high molecular weight medications, however, show less absorption. Hydrophilic macromolecules (> 1000 Da), on the other hand, are absorbed by endocytosis and have relatively limited bioavailability. Examples of these macromolecules are proteins and peptides.

Solubility

Due to the watery nature of nasal secretions, appropriate aqueous-soluble drug forms can remain in molecular dispersion or solution form to enhance their dissolution; however, drugs with poor aqueous solubility or those administered at high doses may find it difficult to dissolve in the nasal cavity due to its low volume. Various strategies to improve drug solubility for nose-to-brain delivery have been studied, including the use of prodrugs, salt forms, co-solvents, cyclodextrins (as solubilizing excipients), and nanoparticle systems.

Osmolarity

Because hypertonic and hypotonic nasal formulations can interfere with normal ciliary activity and impair nasal medication absorption, osmolality is an important consideration in nasal formulation design. As a result, isotonic nasal formulations that lie between 290 and 500 Omol/kg are considered appropriate. Isomaltonizing excipients that are frequently utilized include dextrose, glucose, sodium chloride, and glycerine.

PH

It is recommended that the nasal formulation's pH be adjusted to a range of 4.5–6.5 to minimize nasal irritation. This will help to ensure effective medication absorption and inhibit the growth of germs.

Viscosity

By changing ciliary beating and mucociliary clearance, improving the viscosity of nasal formulations can change the therapeutic effect and increase drug permeation. Nevertheless, this can also decrease drug diffusion from the formulation, therefore it might be problematic to increase viscosity too much.[41]

Devices for nasal administration

For effective treatment, it is essential to increase drug deposition on the olfactory epithelium since the nasal epithelium plays a critical role in modulating the nose-to-brain connection. Droppers and spray pumps, two common intranasal devices for liquid formulations, have difficulties reaching the olfactory epithelium due to their placement in the upper nasal cavity and the limitations placed on them by the nasal turbinate. For instance, a spray pump delivers less than 3% of the medicine to the olfactory region, while a dropper necessitates a precise patient posture. As a result, the medication may be eliminated by mucociliary clearance or absorbed systemically by blood vessels. To overcome the disadvantages of conventional devices, researchers have developed devices capable of delivering drugs in different forms (powders or liquids).[41] e.g.,

Nasal Device	Dosage form
Via Nase (electronic atomizer)	Liquid
Precision olfactory delivery (semi-disposable unit dose delivery)	Liquid and powder
Sip Nose (pressurised delivery)	Liquid and powder

Excipients used in nasal formulation

a. **Bio-adhesive polymers**: Bio-adhesive polymers are compounds that can interact with biological material through interfacial forces and remain on it for extended periods of time; they are also referred to as mucoadhesive

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materials if the biological material is a mucus membrane. At the molecular level, the process of mucoadhesion can be explained by attractive molecular interactions involving forces like Van Der Waals, electrostatic interactions, hydrogen bonding, and hydrophobic interactions. The bio-adhesive force of a polymer material is dependent on the nature of the polymer, the surrounding medium (pH), swelling, and physiological factors (mucin turnover, disease state, etc.). Examples of these include cellulose derivatives:

- ✓ Soluble: hydroxypropyl cellulose (HPC), methyl methylcellulose, cellulose (MC), hydroxypropyl carboxymethyl cellulose (CMC)
- ✓ Insoluble: ethyl cellulose, microcrystalline cellulose (MCC) Polyacrylates
- ✓ Carbomers, Polycarbophils

b. Penetration enhancer: Chemical penetration enhancers are frequently utilized in nasal medication delivery. Classification of chemical penetration enhancers comprises, the following 1) Solvents 2) Alkyl methyl sulphoxides 3) Pyrrolidones 4) 1- Dodecyl azacycloheptan-2-one 5) Surfactants.

c. Buffers: The most frequent dose volume for nasal formulations is 100 µ L, and they are often provided in tiny quantities ranging from 25 to 200 µ L. Therefore, nasal secretions may change the administered dose's pH, which may impact the amount of unionized medication that is available for absorption. Therefore, to maintain the pH in-situ, a sufficient formulation buffer capacity could be needed.

d. Solubilizers: Nasal medication administration in solution is always constrained by the drug's aqueous solubility. To improve the solubility of medications, one can employ conventional solvents or co-solvents like glycols, trace amounts of alcohol, Transcutol (diethylene glycol mono ethyl ether), medium chain glycerides, and Labrasol (saturated poly glycolyzed C8–C10 glyceride). Additional chemicals such as cyclodextrins or surfactants, such as HP-ß-Cyclodextrin, can be employed in conjunction with lipophilic absorption enhancers to act as a biocompatible stabilizer and solubilizer. Their effect on nasal irritancy must be taken into account in these situations.

e. Preservatives: Because most nasal treatments are aqueous in nature, preservatives are necessary to stop microbiological development. Nasal preparations frequently contain parabens, benzalkonium chloride, EDTA, benzyl alcohol, and phenyl ethyl alcohol as preservatives.

f. Antioxidants: It could be necessary to use a tiny amount of antioxidants to stop medication oxidation. Tocopherol, sodium metabisulfite, butylated hydroxytoluene, and sodium bisulfite are examples of commonly used antioxidants. Antioxidants typically don't irritate the nasal passages or alter how well drugs absorb.

g. Humectants: A sufficient amount of moisture in the intranasal cavity is necessary to prevent dehydration; therefore, humectants can be added, especially in gel-based nasal products; humectants prevent nasal irritation and do not affect drug absorption. Common examples of humectants include glycerin, sorbitol, and mannitol. Cracks and drying of the mucous membrane can result from allergic and chronic diseases. Certain preservatives/antioxidants are also likely to cause nasal irritation, especially when used in higher quantities.

h. Surfactants: By altering the permeability of nasal membranes, surfactants can be added to nasal dosage forms, potentially facilitating medication absorption through the nose.[54]

Nasal drug formulations

Nasal drops

Among all formulations, nasal drops are among the easiest and most practical delivery methods. The primary constraints are the potential for contamination during usage and the impreciseness of the amount delivered[56]. Nasal drops can be administered via a squeezy container or pipette. Though there are certain drawbacks, such as microbial growth, mucociliary dysfunction, and non-specific loss from the nose or down the back of the throat, these formulations are typically advised for the treatment of local disorders [57,58].

Nasal sprays

The components of a nasal spray system include an actuator, a piston, and a chamber. Nasal sprays produce precise doses (25 - 200 µl) per spray and are somewhat more accurate than drops. Nasal sprays have been demonstrated in numerous experiments to be able to deliver reliable doses of plume geometry. Viscosity, surface tension, and thixotropy are examples of formulation characteristics that may have an impact on dosage accuracy and droplet size. The droplet size, which affects the sprays' nasal deposition, can also be influenced by other elements such as the applied force, pump design, and orifice size [13].

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Nano suspensions

Klang et al. [59]targeted the brain through the nose using a nano-suspension. For particles with a size range of 1 to 500 nm, formulation as a nanosuspension made it easier to go beyond the blood-brain barrier (BBB). Typical drug-loaded nanoformulations called nanosuspensions are stabilized by non-ionic surfactants or lipid mixes. Improved pharmacokinetics, easier manufacture, increased drug loading, and surface modification possibilities are just a few benefits of using polymeric nanosuspensions. Unfortunately, due to their unstable shelf life, polymeric nanosuspensions are not thought to be the best formulations for the treatment of chronic diseases because their manufacture takes a very long time [60]. Ando et al. researched the commercially available nasal suspension used to administer insulin (1998). As absorption enhancers, steryl glycoside and sterol combinations generated from soybeans were utilized in this case, resulting in pharmacological bioavailability of 6.7% and 11.3%, respectively. Suspensions help make poorly soluble medications more bioavailable [13].

Nanoemulsion

Comparable research has not been done on intranasal emulsions as it has on other liquid nasal administration techniques. Because of its viscosity, nasal emulsions have advantages for local application [54].

Nano gels

A gel is a material that is soft, firm, or semi-solid-like that is made up of two or more components, at least one of which is a liquid and is present in significant amounts. Elastic modulus G' and viscous modulus G" are two dynamic mechanical variables that can be used to characterize the semi-solid properties of gels [11]. The cross-linked hydrophilic or amphiphilic polymers used to create polymeric nanogels are produced by emulsification and solvent evaporation. The basis of the nanogel formulation is the idea that ionic and non-ionic polymers will combine to form cross-linked networks [61]. The kind of polymer, concentration, and physical condition of the gel all affect its rheological characteristics [13]. Compared to other nanoformulations, polymeric nanogels are thought to offer entrapped medications greater protection during the transport phase [61]. Bio-adhesive polymers can regulate the rate and amount of medication release, which reduces the frequency of drug administration and has demonstrated good potential for nasal formulations [13].

Nano liposomes

Polymeric nanoliposomes are a type of vesicle that have an outside layer of single or many lamellar lipid layers and an interior aqueous compartment. Nanoliposomes' structural makeup enables improved stability, drug encapsulation, and reticuloendothelial system evasion [61]. One of the many benefits of liposomal drug delivery systems is their ability to efficiently encapsulate both big and small molecules with a variety of hydrophilicity and Pka values. It has been discovered that they increase the membrane penetration of peptides like calcitonin and insulin, improving their nasal absorption. This has been linked to peptides' growing nasal retention. shielding the peptides inside the entrapment from enzymatic breakdown and damage to the mucosal membrane [54]. A study has demonstrated that curcumin nanoliposomes were particularly effective against amyloid aggregates, despite the fact that the stability of nanoliposomes for brain illnesses is still up for debate [61].

Microspheres

The use of microsphere technology in the creation of nasal medication delivery formulations is widespread. Mucoadhesive polymers, such as chitosan and alginate, are the common basis for microspheres and offer benefits for intranasal medication delivery. Moreover, the drug's action may be prolonged by microspheres' ability to maintain drug release and shield it from enzymatic metabolism [54].

Nanoparticles

Solid colloidal particles having dimensions ranging from 1 to 1000 nm are known as nanoparticles. They are made of macromolecular components and can be applied therapeutically as drug carriers, where the active ingredient is chemically attached, dissolved, encapsulated, or trapped, or as adjuvants in vaccines. Because of their small size, nanoparticles may have several benefits. However, because tight junctions range in size from 3.9 to 8.4 Å, only the tiniest nanoparticles can pass through the mucosal membrane in a paracellular manner and small quantities [54].

Nanospheres and Nanocapsules

The solid polymeric matrix known as nanospheres is created by the micro-emulsion polymerization technique, while the drug-filled oil-

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filled compartment of nanocapsules is encapsulated in a thin, harmless polymer. The benefits of enhanced drug stability, simple surface modification, and evasion of systemic breakdown are shared by nanospheres and nanocapsules. They do, however, have several drawbacks, including difficult storage and purifying processes and incorrect drug release patterns [61].

Metal Nanoparticles

Recent studies have concentrated on metal nanoparticles because of their potential uses in the sciences and biomedical engineering. Many structural and surface alterations can be added to metal nanoparticles during their synthesis, opening up new possibilities for their use in targeted gene and medication delivery, magnetic separation, and diagnostic imaging in particular [61].

Gold nanoparticles

AuNPsor gold nanoparticles, are frequently employed as nanomaterials for imaging and medication administration. According to studies, the lack of a selective moiety in AuNPs causes them to have limited specificity when it comes to differentiating between targeted and non-targeted cells. Researchers have paired AuNPs with cell-targeting ligands to deliver medicinal chemicals to specific cells or organs. There are two primary ways to use AuNPs for neuronal uptake: via the olfactory nerves and by bridging the blood-brain barrier [61].

Silver nanoparticles

Human skin, lungs, and fibroblast cells have all been demonstrated to become cytotoxically exposed to silver nanoparticles (AgNPs). It has been demonstrated that AgNPs breach the blood-brain barrier (BBB) in the brain after being inhaled or ingested and collected there. After a 6-hour treatment, Patchin et al. observed that 20 nm AgNPs moved quickly into the olfactory bulb while 110 nm silver particles moved more slowly and ineffectively. Silver observed in the blood was caused by silver ion release from Ag NPs, according to a study that found relatively little absorption of AgNP (measured as total silver) into the blood following intranasal treatment and much higher blood concentrations following AgNO3 delivery. AgNPs have also been demonstrated to cause neuronal cytotoxicity in vitro [61].

Dendrimers

Dendrimers are a novel kind of highly branching nanoparticles that can target particular cells, and they have a distinctive design made up of molecular hooks. Dendrimers have been shown to have two basic structures: one kind has a central core surrounded by radiating polymer branches, while the other type only displays many branches in the absence of the core. Dendrimers have a special branching structure that makes it very simple to modify their surface by covalent conjugation or adsorption, which increases their ability to transport a variety of medications. It has been demonstrated that poly amidoamine dendrimers can be utilized to create adjustable drug delivery systems that may target intracellular components in both vitro and vivo settings. Dendrimers can also be employed as scaffolding in vitro to transport therapeutic and diagnostic entities [61].

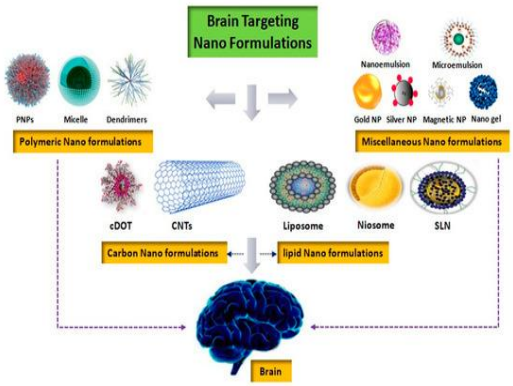

figure 4Brain Targeting Nano Formulations[61]

4.Neurodegenerative disorders

Conditions known as neurodegenerative disorders are defined by the progressive loss of particular neuronal populations as a result of oxidative stress, neuro-inflammation, and proteotoxic stress, which ultimately results in the malfunction and death of neurons. More than 50 million people worldwide suffer from neurodegenerative illness, and if no practical preventive or therapeutic measures are discovered, this figure will nearly treble to 152 million in2050[62].

A variety of disorders known as neurodegenerative diseases (NDD) are distinguished by continuing loss and selective malfunctioning of neurons, glial cells, and neural networks in the brain and spinal cord. As a result, they can lead to a variety of issues, such as those involving mobility (known as ataxias), mental function (known as dementias), and the capacity to breathe, speak, and move. NDDs are crippling, incurable diseases that are growing more common,

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partly because of the aging of the world's population[63,64]. Many families are affected by NDD; neither the person with the illness nor their loved ones find it easy.NDDs can be classified according to:

1. Primary clinical features, include:
✓ Alzheimer's disease (AD)
✓ Dementia
✓ Parkinson's disease (PD)
✓ Motor Neurone disease
✓ Huntington's disease
2. Anatomic distribution of neurodegeneration, include:
✓ Frontotemporal dementia
✓ Extrapyramidal disorders
✓ Spinocerebellar ataxia spinal muscular atrophy (SMA)
3. Principal molecular abnormality, include:
✓ Prion disease
✓ Synucleinopathies
✓ Amyloidoses[62,63]

Classifications have moved away from the clinical presentation in favor of the underlying pathological processes as more and more NDDs are understood at the biochemical level.

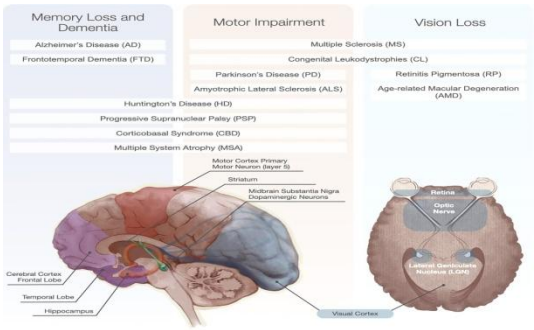

Figure 5Primary function impact of neurodegenerative diseases and affected brain regions [65]

Alzheimer's disease

A common kind of neurodegenerative disease, Alzheimer's disease (AD) affects 60% to 80% of cases. Although there are several possible etiologies for AD, which were first identified in 1907, the precise origins of the illness are still unknown. Furthermore, even after more than a century of research, no curative remedy has been created. There are two types of AD: (1) the sporadic form; (2) the genetic form, also known as autosomal-dominant AD (ADAD), which affects fewer than 1% of cases and manifests before the age of 65. The average age at which sporadic Alzheimer's disease (SAD) manifests itself is over 65, and the disease's risk doubles every five years. Here, we review AD that occurs occasionally. AD disease is caused by aberrant protein aggregation in the nervous system, neurodegenerative processes, and structural as well as functional damage to the central nervous system (CNS).

Alzheimer's disease (AD) is a neurological illness that gradually impairs behavioral and cognitive abilities. Memory, comprehension, language, focus, logic, and judgment are some of these abilities. Although AD does not directly cause mortality, it does significantly increase a person's susceptibility to additional issues that may ultimately result in death. In the United States in 2022, AD is ranked as the seventh largest cause of death, whereas COVID-19 is placed fourth, according to data from the Centers for Disease Control and Prevention (CDC). However, after stroke, during the COVID-19 pandemic, AD was the sixth most common cause of death.[66]. Late-onset AD (LOAD) is the term used to describe AD that usually appears after age 65. On the other hand, early-onset AD (EOAD), which manifests before the age of 65, is less prevalent and affects 5% of AD patients.Because EOAD is typically diagnosed later in life and frequently presents with unusual symptoms, the disease tends to progress more quickly.[67].

The symptoms of AD can change according to the disease's stage. Depending on the degree of cognitive impairment and disability that each person experiences, AD is divided into several phases. These phases comprise moderate cognitive impairment, dementia, and the preclinical or presymptomatic stage. There are three categories for dementia stages: mild, moderate, and severe.

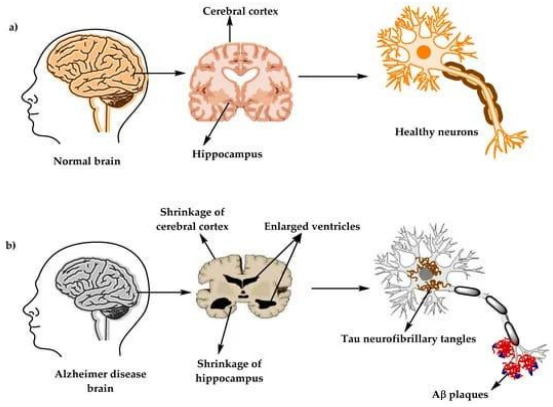

Figure 6Normal brain and Alzheimer's disease brain [68]

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Etiology

Neurodegeneration brought on by the death of neurons gradually and progressively is the hallmark of Alzheimer's disease. The entorhinal cortex of the hippocampal region is where the neurodegenerative process usually starts. It has been determined that genetic factors have a role in both early and late-onset AD. One risk factor linked to dementia with an early start is trisomy 21. AD is a complex illness linked to numerous established risk factors. Age is the most important component, and becoming older is the main cause. Beginning at age 65, the prevalence of AD about doubles for every five years of age increase.

It is known that cardiovascular illnesses (CVD) are a risk factor for AD. They also raise the chance of dementia from strokes or vascular dementia, as well as the chance of acquiring AD. There is growing recognition that one controllablerisk factor for AD is CVD.

Diabetes and obesity are two more significant modifiable risk factors for AD. Obesity raises the risk of type II diabetes and can impede glucose tolerance. Chronic hyperglycemia can cause beta-amyloid (A-bata) buildup and neuroinflammation, which can both result in cognitive impairment. By encouraging insulin resistance and inducing the release of pro-inflammatory cytokines, obesity raises the risk even more. [69]

A traumatic brain injury, depression, cardiovascular and cerebrovascular disease, smoking, higher paternal age at birth, a family history of dementia, elevated homocysteine levels, and the APOE e4 allele are additional possible risk factors for AD. Having an AD first-degree relative raises one's chance of getting the illness by 10% to 30%. The risk of late-onset AD is three times higher in those with two or more siblings who have the disease than in the general population. [70]

There are a number of known factors that may lower the chance of acquiring AD. Higher education, oestrogen use in women, anti-inflammatory medications, reading and music-making as hobbies, eating a balanced diet, and frequent aerobic activity are a few of these.[71]

Pathology

Extracellular neuritic plaques in the cerebral cortex and the walls of the meningeal and cerebral bleeding arteries are indicative of the pathophysiology of Alzheimer's disease. Reactive astrocytes, microglia, and dystrophic neurites—axons and dendrites—encircle a thick core of amyloid material in these plaques. The development of intraneuronal neurofibrillary tangles, loss of neurons and synapses, reactive astrocytosis, and microglial proliferation are other structural alterations. Paired helical filaments made of hyperphosphorylated tau, a microtubule protein, make up neurofibrillary tangles[72].

Pathophysiology

a. **Amyloid β-peptide:** Amyloid β-peptide (Aβ) is the primary protein seen in neuritic plaques. It is produced by proteolysis of the membrane protein known as the β-amyloid precursor protein (APP), which is encoded by a gene located on chromosome 21q21.3-22.05. In neuronal cells, APP interacts with the extracellular matrix to promote neurite development**.**

b. **Presenilins:** Current research is focusing on the enzyme pathways that control the generation of Aβ, which could result in new treatments. The membrane-anchored protease beta-amyloid precursor protein cleaving enzyme (BACE), sometimes referred to as beta-secretase, cleaves APP at the amino terminus of the Aβ sequence. A 99-amino acid carboxyl-terminal fragment was produced by this cleavage. This fragment is cleaved to generate Aβ by γ-secretase, a second enzyme activity. Missense mutations in the gene PS-1/S182, on chromosome 14q24.3, which encodes a seven-trans-membrane protein (presenilin 1), have been associated with nearly 70% of familial instances of Alzheimer's dementia. Twenty percent more instances have been connected to mutations in the chromosome 1q31-42 gene STM2 (presenilin2). Presenilins with mutant versions linked to familial Alzheimer's disease produce more Aβ42. Therefore, neurodegeneration in patients with presenilin mutations may be exacerbated by γ-secretase insufficiency.

c. **Apolipoprotein E**: Apolipoprotein E (apoE4), a 34-kDa protein that facilitates lipoprotein binding to the LDL receptor-related protein (LRP) and low-density lipoprotein (LDL) receptor, is associated with risk. It is believed to be crucial for mobilizing lipids throughout normal nervous system development and during the regeneration of damaged peripheral nerves. It is produced and secreted by astrocytes and macrophages. It's unclear how apoE alleles affect the likelihood of developing a disease. When very low-density lipoproteins are present in cultured neurons**,** apoE3 promotes neurite development while apoE4 inhibits it. Compared to those homozygous for the e3 allele, those with Alzheimer's disease

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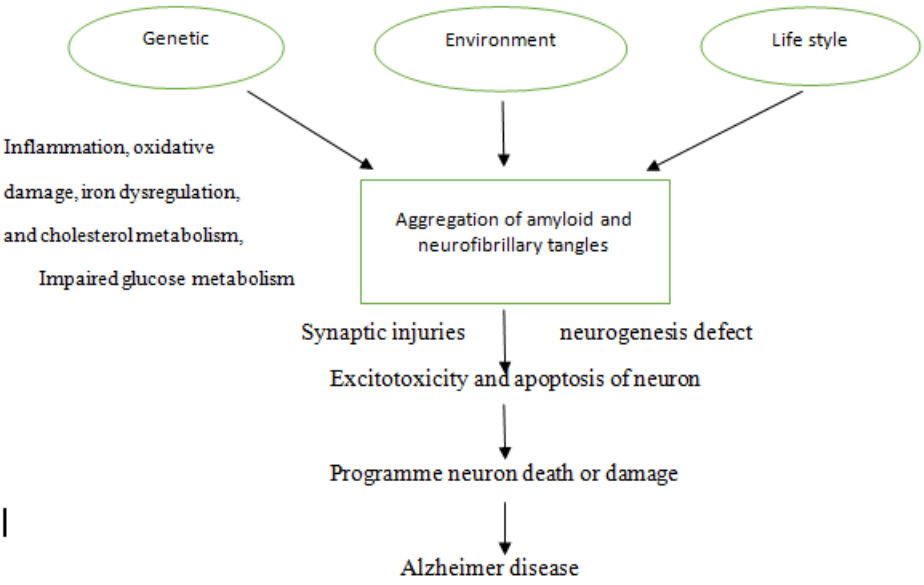
homozygous for the e4 allele had thicker and larger senile plaques. Neuritic plaques include apoE, and apoE4 binds Aβ more quickly than apoE3. Consequently, apoE4 might promote plaque development or lessen the amount of Aβ that is removed from brain tissue. Furthermore, the microtubule-associated protein tau, a primary component of neurofibrillary tangles, is bound by apoE upon entering neurons[72].



Pathogenesis of Alzheimer's disease [40]

Nanoparticles based strategies [40]

Carrier	Characteristics	Example
Liposomes	- Spherical, concentric, bi-layered, phospholipids vesicles -Size range between 50 and 100µm -Can trap hydrophilic and lipophilic drugs - Have different surface changes like uni, di, or multi Laminar, non-toxic, biocompatible - Prepared by film hydration, heating or micro fluidization	Galantamine, Rivastigmine, folic acid, Donepezil, Ropinirole
Polymeric Nanoparticles	-Matrix type, size range 100-200nm higher polydispersity index, good stability, biodegradability, low-toxicity - Natural polymer: chitosan, alginate, albumin, gelatine - Synthetic polymer: polyacrylates, polycaprolactones	BuspironHCL, Didanosine, Estradiol
Lipid Nanoparticles	- Colloidal carriers, size range between 10 to 200nm - Able to cross tight junctions of endothelium cells -Higher drug loading efficiency, biodegradable - Control releasing for several days	Bromocriptine, Duloxetine

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Drugs[40]

1. Rivastigmine

A semi-synthetic derivative of phytostigmine, rivastigmine is used to treat dementia symptoms. By blocking the activity of the enzymes acetylcholinesterase and butyrylcholinesterase, it stops the hydrolysis of acetylcholine in the brain, increasing acetylcholine levels. The Herbrew University of Jerusalem developed the first rivastigmine that was approved by the USFDA [32]. Rivastigmine comes in skin patches, liquid, pill, and oral solution forms. The bioavailability (36%) of the oral route is a drawback, because it is significantly impacted by food. Aside from this, it metabolizes about 97% in the kidney and has a poor capacity for binding proteins (40%). Acetylcholinesterase hydrolyzes it to render it inactive.

a) **Brijesh Shah et al.,** and colleagues developed mucoadhesive microemulsion (RHT ME) and intranasal chitosan laden microemulsion (CH-ME). Their formulations have been compared to oral tablets to improve penetration and bioavailability.
b) **Morgan Temothy M et al.,** and others When nasal spray formulations are compared to transdermal patches and capsules, a greater absolute bioavailability is achieved. They found that the nasal mucosa had a high rate of rivastigmine absorption and a high Cmax. Rivastigmine nasal spray had a plasma half-life that was nearly twice as long as the IV dosage.
c) Rivastigmine liposome was produced for intranasal delivery by **Kartik Arumugamet al.** It may be possible to lower the frequency of administration by using this regulated release of rivastigmine from liposomes.

2. Tacrine

Under the brand name Cognex, tacrine, a centrally acting anticholinesterase, was distributed for the treatment of Alzheimer's disease.

a) According to research by **Jogani VV et al.,** tacrine can be administered directly to the brain by the intranasal route, increasing its bioavailability and decreasing its nonspecific distribution to untargeted locations. The frequency of dosage, dose required, and dose-dependent systemic side effects may all be decreased by this selective localization in the brain. Additionally, compared to oral, the intranasal concentration of tacrine was higher. This proved that tacrine could be directly transported from the nasal cavity to the brain.
b) **Shuai Qian et al.** used the thermosensitive polymer Pluronic F-127 to create an in- situ gel formulation for tacrine intranasal administration. When they tested their product on rats, comparing it to an oral solution, they found that the in-situ gel was more potent than the oral formulation, which showed enhanced mucociliary retention time and pseudoplastic fluid behaviour at its Tsol-gel (28.5 °C).

Parkinson's disease (PD)

More than 85,000 articles about Parkinson's disease (PD) and associated conditions have been published in worldwide journals since 1915. After Alzheimer's disease, the clinical entity that James Parkinson (1755–1824) named "paralysis agitans" in his 1817 "Assay on the Shaking Palsy" is currently the second most significant neurodegenerative illness affecting the aged population. With yearly incidence estimates ranging from 1.5 per 1,00,000 in various countries and prevalence rates ranging from 35.8 per 1,00,000, Parkinson's disease (PD) is emerging as a significant age-related health issue. A meta-analysis of data from around the world shows that the prevalence of Parkinson's disease (PD) increases with age (41 per 1,00,000 at 40–49 years; 107 at 50–59 years; 173 at 55–64 years; 428 at 60–69 years; 425 at 65–74 years; 1087 at 70–79 years; and 1903 per 1,00,000 at over 80 years). The data also shows a characteristic distribution by geographic location, with patients from North America, Europe, and Australia having a prevalence of 1602 per 1,00,000, while patients from Asia have a prevalence of 646 per 1,00,000. Males are more likely than females to have Parkinson's disease (1729 instances per 1,000,000, >65 years), with a high prevalence of 4633 cases per 1,000 in the over 90 age group and a mean prevalence of 1680 cases per 1,000 in the over 65 age group.

Parkinson's disease (PD) is a complicated neurological illness that worsens with time and is characterized by bradykinesia, tremor, and rigidity. As the condition worsens, some individuals may also experience postural instability. We are still learning more about Parkinson's disease (PD), which was initially identified by James Parkinson in 1817 and later extensively defined by Jean-Martin Charcot. After Alzheimer's disease (AD), Parkinson's disease (PD) is the second most common neurological illness. Its prevalence ranges from approximately 0.3-1% in people 65 to 69 years old to 1-3% in people 80 years of age and above. The aging population is predicted to cause

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both the prevalence and incidence of Parkinson's disease (PD) to rise by over 30% by 2030. This will have an impact on society and the economy directly as well as indirectly[72].

Etiology

Genetic and environmental variables are involved in Parkinson's disease (PD), which is a complex disease. With a median age of onset of 60 years old, aging is the largest risk factor for Parkinson's disease (PD). In age groups between 70 and 79 years, the disease's incidence increases with age, reaching 93.1 (per 1,0,000 person years). Furthermore, there exist cross-cultural disparities, wherein countries in Africa, Asia, and the Arab world have lower prevalence rates than those in Europe, North America, and South America.

1. **Cigarette smoking:** Parkinson's disease (PD), cigarette smoking has been well examined, with generally reliable findings. Larger cohort studies concur with the majority of epidemiological research, which are case-control studies demonstrating a lower chance of acquiring Parkinson's disease. Smoking and Parkinson's disease (PD) were found to be inversely correlated in a major meta-analysis that included 44 case-control studies and 8 cohort studies from 20 different countries. The pooled relative risk for current smokers was 0.39. With a pooled odds ratio ranging from 0.23 to 0.70, two further meta-analyses also found an inverse relationship between smoking and Parkinson's disease (PD)—indicating a preventive mechanism against the disease. Additionally, they found that there was an inverse relationship between the number of years of smoking, the number of pocket years, and the risk of Parkinson's disease (PD), with heavy or long-term smokers having a much lower chance of getting PD than nonsmokers.
   We don't fully grasp why there is a correspondingly lower danger. In animal models of Parkinson's disease, it has been demonstrated that selective agonists or nicotine can activate nicotinic acetylcholine receptors on dopaminergic neurons in a neuroprolective manner. However, nicotine can also trigger the production of dopamine, which is involved in reward systems; as a result, it is challenging to determine whether PD stops smoking or smoking itself becomes less habitual.Patients with Parkinson's disease (PD) may have lower levels of dopamine, which makes them less inclined to engage in addictive behaviors like smoking. The fact that prodromal PD and PD patients were able to stop smoking significantly more easily than controls lends credence to the theory that this link may be caused by a reduced response to nicotine.
2. **Caffeine**: Numerous research has examined the impact of caffeine on Parkinson's disease development and found that coffee consumers have a lower chance of developing Parkinson's disease. An adenosine AZA receptor antagonist, caffeine is thought to be protective against Parkinson's disease (PD) and has demonstrated neuroprotective effects in a PD-affected mice model (28). Coffee consumers have been shown to have a 25% lower chance of acquiring Parkinson's disease (PD). Numerous retrospective studiesand two sizable prospective epidemiological studies have also demonstrated a lower risk of Parkinson's disease (PD) among coffee consumers compared to non-drinkers, with a relative risk ranging from 0.45 to 0.80.A meta-analysis of eight case-control studies and live cohort studies also revealed that coffee consumers had a significantly lower risk of Parkinson's disease (PD) (RR0.69). Those who regularly drink tea have also been linked to a decreased risk of Parkinson's disease (PD).
   Similar to smoking, it is unknown what causes coffee to prevent Parkinson's disease. Moreover, variations concerning gender were observed in the research. Coffee consumption was found to be strongly inversely correlated with the development of Parkinson's disease (PD) in males, but not in women, according to two cohort studies. Furthermore, whether or not post-menopausal women were receiving hormone replacement treatment, which includes oestrogens, affected how caffeine affected them. The competitive inhibition of caffeine metabolism by oestrogens suggests that the dependence of postmenopausal women's PD risk on hormone replacement therapy may be partially explained by the interactions between oestrogen and caffeine.

Additional elements such as:

- ✓ Pesticides, herbicides, and heavy metals
- ✓ Genetics
- ✓ Autosomal dominant PD
- ✓ Autosomal recessive PD[72]

Pathology

The primary characteristic morphological alteration in Parkinson's disease (PD) brains is shown in transverse sections of the brainstem,

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where the loss of the darkly pigmented region in the locus coeruleus and substantia nigra pars compacta (SNpc) is found in nearly all instances. The loss of pigmentation is directly associated with the demise of noradrenergic neurons in the locus coeruleus and dopaminergic (DA) neuromelanin-containing neurons in the SNPC. The A9 neurons, a subset of neuromelanin-containing dopaminergic neurons, are primarily responsible for cell death in the SNPC; other neuronal and glial cell types are mainly spared. The emergence of the cardinal motor symptom in Parkinson's disease (PD) is thought to be caused by a decline in dopaminergic signaling.There is an impact on several non-dopaminergic neurotransmitter systems, including the glutamatergic, cholinergic, adenosinergic, GABAergic, noradrenergic, serotonergic, and histaminergic systems. Some of the non-motor symptoms of Parkinson's disease (PD) that do not improve with dopamine replacement therapy are believed to be caused by degeneration in those systems. It is still not entirely understood, nevertheless, what specific pathogenic pathways underlie the non-motor symptoms of Parkinson's disease.

Lewy body pathology

The appearance of aberrant cytoplasmic deposits within neuronal cell bodies that are immunoreactive for the protein α-synuclein is the pathological hallmark of Parkinson's disease (PD) under a microscope. Lewy bodies (LBs) are abnormal protein aggregates that are frequently accompanied by dystrophic neurites (Lewy neurites), which are primarily axonal.

Intracytoplasmic inclusions known as LBs have a granular and fibrillar core around a halo. A protein that is widely expressed in the brain called filamentous α-synuclein is the main structural element of LBs. It develops an amyloid-like filamentous form, becomes aberrantly phosphorylated, and aggregates in Parkinson's disease (PD) and other synucleinopathies. α-synuclein is the main component of an LB's halo.

α-synuclein and Lewy body distribution outside the brain

Raises the question of whether peripheral or cerebral sources of α-synuclein disease are involved. A full truncal vagotomy is linked to a lower risk of developing Parkinson's disease (PD) in the future, according to a Danish epidemiological study. This finding has sparked attention to the potential involvement of the gut-brain axis in the pathogeneses of PD.

Interaction of α-synuclein with other proteins

Tau can become inappropriately hyperphosphorylated in pathological circumstances, resulting in intracytoplasmic aggregates known as neurofibrillary tau tangles (NRTS). Both the aggregates and the amyloid-β plaques are indicative of AD. But aberrant tau protein has also been connected to Parkinson's disease. Both in vitro and in vivo tau hyperphosphorylation can be induced by increased α-synuclein expression. Additionally, a substantial correlation between MAPT and the risk of Parkinson's disease (PD) was discovered by genome-wide association studies, and later longitudinal research revealed that the H1/H1 haplotype of MEPT is a powerful predictor of the early onset of Parkinson's disease dementia. Additionally, it has been observed that amyloid-β and α-synuclein work together to cause amyloid-β plaque formation in a subset of Parkinson's disease patients[72].

Pathogenesis

α-synuclein misfolding and aggregation

α-synuclein takes on an amyloid-like, β-sheet-risk form that is prone to aggregation in Parkinson's disease. Indeed, 5–10 nm long filaments of misfolded α-synuclein are seen within LBs. Numerous mechanisms, including as serine 129 phosphorylation, ubiquitination, and C-truncation, have been postulated to explain the conformational alterations that cause aberrant α-synuclein aggregation. As a result, several α-synuclein species, such as unfolded monomers, soluble oligomers, protofibrils, and high molecular weight insoluble fibrils, are discovered in the PD brain.

Mitochondrial dysfunction

An essential part of the electron transport chain, mitochondrial complex-I, was shown to be lacking in the SNPC of Parkinson's disease (PD) brains in early postmortem investigations. In comparison to healthy individuals, complex-I deficit was also discovered in the skeletal muscle and platelets of PD patients. The finding that the drug MPTP usage resulted in long-term Parkinsonian symptoms (34) and the observation that dopaminergic cells were lost during postmortem examination provided more evidence. Subsequent research revealed that oxidized MPTP is absorbed by DA neurons and inhibits complex-I. other poisons and insecticides, like as paraquat and rotenone, that reduce mitochondrial complex-I activity. Mitochondrial homeostasis is impacted by

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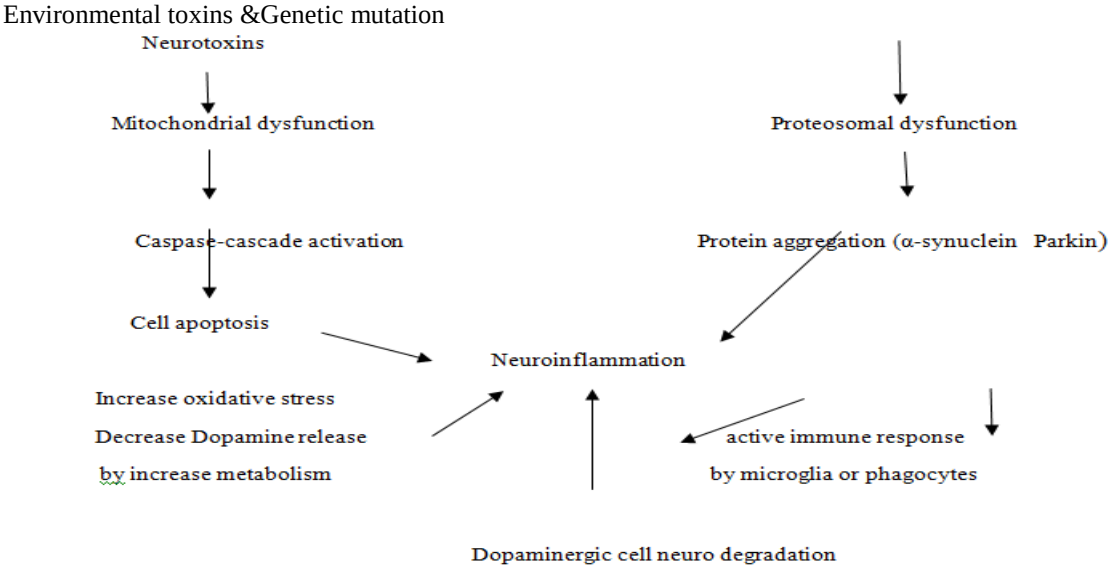
the genes that produce familial Parkinson's disease. Mitochondrial homeostasis is impacted by the genes that produce familial Parkinson's disease. As an illustration, consider the roles played by PINK1 and parkin (PARK2 and PARK6, respectively), which are essential elements of the pathway controlling the elimination of unhealthy mitochondria, or mitophagy. Lastly, it is recognized that α-synuclein can disrupt mitochondrial activity on its own. As an example, α-synuclein can interact with the membrane of the mitochondria and gather inside the organelles. Complex-I activity is harmed as a result, which eventually causes mitochondrial malfunction and elevated oxidative stress.

Dysfunctional protein clearance systems

The ubiquitin-proteasome system (UPS) and the autophagy-lysosome pathway are the two key protein clearance processes in cells that eliminate malfunctioning proteins. The UPS is principally in charge of "tagging" aberrant proteins with ubiquitin and delivering them to the proteasome for eventual destruction. There are three components to the autophagy-lysosome pathway: chaperone-mediated autophagy (CMA), microautophagy, and macroautophagy. In short, macroautophagy involves the autophagosome consuming intracellular components, such as cytosolic proteins, fusing with the lysosome to break down its contents. However, in microautophagy, cytoplasmic components are only consumed and destroyed by the lysosome. Molecular chaperones target particular proteins in CMA, a more selective process, and transfer them to the lysosome where they are degraded. Monomeric α-synuclein is typically eliminated by the UPS and the autophagy-lysosome pathway. Any malfunction in one of these systems is linked to the development of Parkinson's disease (PD) by causing the build-up of faulty proteins, specifically soluble misfolded α-synuclein.

Neuroinflammation

In the SNPC and striatum of PD patients compared to healthy persons, postmortem brain investigations have reported higher concentrations of pro-inflammatory cytokines, T-lymphocyte infiltration, and microglial and complement activation. Early research using rodent models of Parkinson's disease (6-hydroxydopamine and MPTP) showed that microglia-induced inflammatory processes may be a factor in the degeneration of these cells. This was demonstrated by the significant attenuation of DA cell death in the SNPC following pre- and post-neurotoxic insult microglial activation inhibition with minocycline. Numerous pieces of evidence also point to the possibility that α-synuclein can directly cause microglial activation and start inflammatory processes. For example, α-synuclein induces a dose-dependent activation of microglia in primary cultures. The discovery of a high correlation between the risk of acquiring Parkinson's disease (PD) and the human leucocyte antigen (HLA) class II region, a crucial immune system protein, provides genetic hints that immunological activation may play an etiological role in PD [72].



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Parkinson's disease pathogenesis[40]

Drugs that are available for the treatment of Parkinson's disease (PD) include cholinesterase inhibitors, dopamine agonists, and monoamine oxidase type B inhibitors. Out of all of them, levodopa is the most often used medication. It provides symptomatic relief but also has some negative side effects, including response variations and levodopa-induced dyskinesia (LID). It also eventually develops tolerance. Because of all of these factors, it is essential to create alternative controlled-release delivery methods to enhance the benefits of dopamine stimulants and reduce the prevalence of LID. As a result, researchers are investigating cutting-edge PD treatment methods. Among these, researchers are becoming more interested in enhancing patients' lifestyles through the use of intranasal delivery routes. The medications used to treat Parkinson's disease (PD) and their patent-related publication through the intranasal route are covered in the section that follows.

Drugs

1) Rotigotine

As a dopamine agonist that enhances dopaminergic actions in the central nervous system, rogabine was first used to treat Parkinson's disease symptoms. The first synthetic molecule of rotigotine was created in 1985 by a team at the University of Groningen under the name N-0437. Later on, Aderis Pharmaceuticals began working on its development and continued to market it. It has been widely used for restless leg syndrome since August 2008.

To control Parkinson's (PD), **Chenchen Bi et al.** developed nanoparticles that increase rotigotine absorption through the intranasal route. They contrasted their formulation with nanoparticles devoid of lactoferrin for this purpose, using biodegradable lactide-co-glycolide (PEG-PLGA) with lactoferrin (Lf). They found that the accumulation and effective concentration of lactoferrin-containing nanoparticles were higher than those of lactoferrin-free nanoparticles based on cellular absorption assays. Furthermore, a large distribution of rotigotine was noted in the impacted locations. Each of these outcomes demonstrated the efficacy of Lf-NPs in the treatment of Parkinson's disease. Furthermore, findings showed that Lf-NPs may be used as a vehicle to transfer rotigotine from the nose to the brain in the treatment of Parkinson's disease.

2) Glutathione

Glutathione (GSH) is a peptide that works with GSH-S-transferase, a neuronal defense mechanism, to detoxify free oxygen radicals. The primary cause of the initial metabolic disruptions in Parkinson's disease (PD) is a deficiency of GSH. Age-related increases in oxidative stress result in a reduction in the synthesis of glutathione hormone, which is the primary cause of neurodegenerative disorders. Furthermore, it is believed that GSH supplementation may be utilized to treat Parkinson's disease symptoms and prevent them from spreading. GSH is not extremely bioavailable when taken orally. Intravenous injection of GSH exhibits good outcomes for increasing GSH concentration when compared to other delivery routes. The intranasal route is a handy and non-invasive way to provide synthesized GSH or GSH precursors. GSH was created for intranasal administration by **Laurie K**. **Mischley et al.** Studies using proton magnetic resonance spectroscopy (1H-MRS) revealed higher GSH concentrations in the brain and proved that this hormone is absorbed through the nasal cavity. Nevertheless, they encountered challenges while conducting observational studies to identify the primary reason for uptake.

3) GDNF (Glial cell line-derived neurotrophic factor)

Similar to GSH, GDNF has neuroprotective qualities that help keep dopaminergic neurons safe. However, because GDNF cannot penetrate the blood-brain barrier, it must be injected surgically into the brain, making a delivery to the brain-challenging.

Aly AE et al. attempted to administer GDNF intravenously. They used plasmid DNA and gene recombinant technology for this. They created plasmid nanoparticals containing human GDNF and gave them to rats via their noses. They noticed transgenic expression protecting dopamine neurons. Rats with pre-existing 6-hydroxydopamine-related lesions were treated for one week to determine whether the transgene was sufficiently expressed. The rats' rotating behavior improved, their lesion size decreased, and the density of dopaminergic fibers in the brain increased. Finally, it was determined that recombinant pGDNF-DNA NPs administered intranasally can provide a method of gene therapy for early-stage Parkinson's disease (PD) that is non-invasive and non-viral [40].

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II. CONCLUSION

The development of novel delivery routes for neurological disorders represents a significant paradigm shift in therapeutics, offering unprecedented opportunities to overcome the limitations of traditional treatment approaches. By leveraging innovative delivery strategies such as intranasal, transdermal, microneedle-based, and nanoparticle-based approaches, researchers and clinicians can enhance drug targeting, increase bioavailability, and reduce systemic side effects. These advancements have the potential to revolutionize treatment paradigms for debilitating neurological conditions, including Alzheimer's disease, Parkinson's disease, and epilepsy.

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