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ROLE OF NANOPARTICULATE DRUG DELIVERY IN THE TREATMENT OF PARKINSON'S DISEASE

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ABSTRACT

Parkinson's disease is a most common neurological disorder (ND), it faces an absence of credible drug delivery,treatment and diagnosis. levodopa is the best drug of choice among the current conventional products designed as anti-parkinson drugs, but it's poor brain transfer and low bioavailability are the most challenging problems for levodopa. To address these drawbacks, drug delivery levodopa. To address these drawbacks, drug delivery nanoparticles (NPs) acted as an outstanding tool for optimising the medicinal effectiveness of anti-parkinson drugs. Nanoparticles enabled the drug to be administered via various routes to eliminate the demand to pass the blood-brain barrier (BBB). Also, the diagnosis of Parkinson's disease(PD)in the early stage is another wing of efficient management of this disease. There are several barriers to the traditional diagnosis of disease. Nanotechnology could provide an insightful solution to this problem. The current study examines the recent innovations in the improvement of nanotechnology diagnosis and treatment platforms for Parkinson's disease. A number of nanoparticles (carbon nanotubes, silver, gold, graphene, etc). Along with different approaches to biosensing and treatment are discussed here which have the potential to be used in Parkinson's disease (PD).

KEYWORDS: Nanoparticles, Blood-brain barrier, Parkinson's disease.

INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disease in the world[1], and destroys neurons in the extrapyramidal dopaminergic pathway in the nigrostriatal region of the basal ganglia in the brain.[2] It was first described clinically by James Parkinson, and the most important symptoms seen in patients with PD are tremor and stiffness in muscles, bradykinesia, and loss of balance.[3] PD is characterized by the presence of Lewy bodies in the midbrain and the loss of activity of dopaminergic neurons, especially in the substantia nigra.[2] It may take many years for the identified neuromotor symptoms of PD to appear so the onset of PD may indicate a long prodromal period. In patients with prodromal period of PD, the most common symptoms are constipation, loss or decrease in sense of smell, and REM (Rapid eye movement) sleep disorder, which are not related to motor movements.[4] However, it has been reported that patients with PD also show non-motor symptoms which is the most important one being pain. And the underlying mechanism of pain is not understood. Some studies have shown evidence that it is related to motor symptoms.[5,6]

PD is generally known as a progressive neurodegenerative disorder that is seen 2 to 3% of the global population aged >65 years and older and much less frequently in young people. PD prevalence is estimated to rise double in 2030.[2] The incidence of PD varies between 40 and 1900 cases per 100000 and the possibility of its incidence increases with age. Even though the onset of PD symptoms is between 60 and 70 years, the incidence peak of the disease is in the 70-79 age range. Men are more affected by PD than women.[7] However, limited data are available on patients with advanced PD prevalence. According to some epidemiological studies, it has been determined that approximately 10% of all PD patients have an advanced PD prevalence.[8] PD creates a huge burden on the population and economy all over the world and this situation is expected to worsen in the future. Today, there are estimated seven to ten million PD patients around the world.[1] The number of patients with PD in Turkey is approximately 150000.[2] A recent report from the World Health Organization shows that over 1.5 billion people worldwide are currently affected by neurological disorders such as Alzheimer's Disease (AD), Parkinson's Disease (PD), stroke, headache, brain injuries, epilepsy, neuro infection, and multiple sclerosis.[3,4] Neurodegenerative diseases are conditions that affect the functioning of neurons in the brain by fluctuations in neurological functions.[5,6] Parkinson's disease (PD), a slowly progressive neurodegenerative disorder[7,8] characterised by bradykinesia associated with tremor, muscular rigidity and postural

instability.[9,10] It affects 7–10 million people worldwide and typically in people over the age of 60.[11,12] medication for its uninterrupted discharge has turned out to be major defies. That's why nanoparticles are being developed to fight this challenge.

Parkinson's disease

More than 250 years after James Parkinson's birth (1755–1824), it is only fitting to introduce this chapter on the history of Parkinson's disease with one of the most famous passages from An Essay on the Shaking Palsy (1817). This celebrated quotation aptly describes clinical signs and symptoms of the eponymous Parkinson's disease but does not capture all features associated with Parkinson's disease today. As the first known published case series, his Essay remains a pivotal piece in the history of Parkinson's disease. Many researchers and clinicians from the 19th century to the present day have heeded Parkinson's pleas, expressed in his Essay, to decipher the nature of this disease, first to understand its pathological basis and then explore treatments for this malady. Since the 19th century, the field of Parkinson's disease has witnessed remarkable discoveries in pathological, neurochemical and genetic substrates and advances in medical and surgical therapeutics.

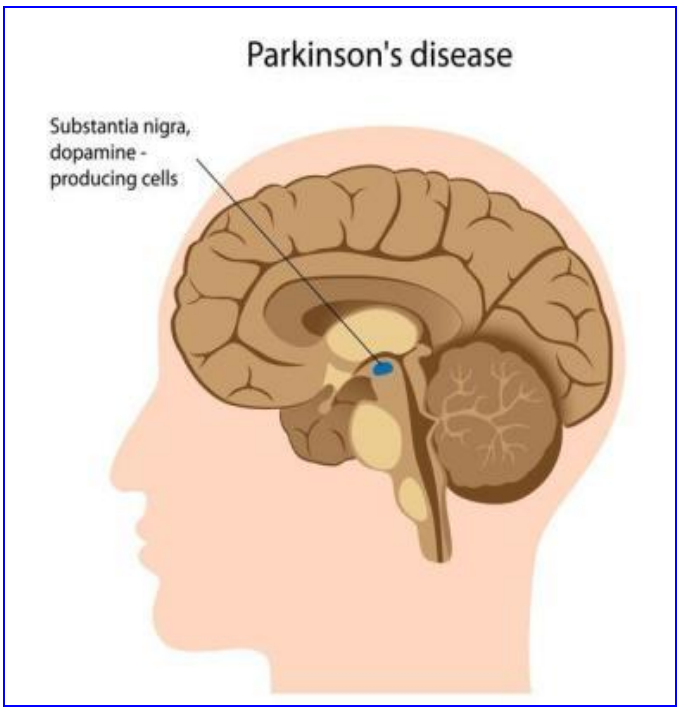

Fig. 1: Parkinson's disease incidence in the brain at substantia nigra region.

This review aims to outline seminal events in the history of Parkinson's disease and expand the topic as last presented in the Handbook of Clinical Neurology in 1986. We hope to provide the reader with a tour of the discoveries related to Parkinson's disease and other

points critical to our current understanding of Parkinson's disease. Since it is only possible within the scope of this chapter to focus on a small selection of events and publications, we regret that we are unable to acknowledge all of those whose contributions have advanced our knowledge of Parkinson's disease.

Neurochemistry of parkinson's disease

Neurochemical changes in Parkinson's disease (PD) is the neurochemical changes noted in the basal ganglia (BG) is summarised. Some of the changes include (1) the profound loss of dopamine and its consequences observed, not just in the striatum, but also in both segments of GP and the subthalamic nucleus (STN), dominate the neurochemical pathology in the BG. Loss of >50%5-hydroxytryptophan (5-HT) in the striatum adds to the clinical spectrum of PD in the later stages of the disease; (2) the melanized dopaminergic neurons of substantia nigra pars compacta (SNPC) and ventral tegmental area (VTA) are selectively more vulnerable to neurodegeneration than the dopaminergic neurons of other areas of the brain, and (3) dopamine denervation and chronic levodopa administration affect the indirect and the direct pathways differently. The neurochemical changes in PD are mostly, but not exclusively, in the BG. Even though dopamine denervation in the BG is the predominant feature of PD, it is emphasised that the decreased levels of monoamines in the cerebral cortex, hypothalamus, brainstem and spinal cord could play an equally formidable role in Parkinson's Disease.

PD pathogenesis

Many processes have been linked to the pathophysiology of Parkinson's disease (PD), with α-synuclein aggregation playing a key role in the disease's progression. Numerous other mechanisms are also believed to be involved; research has revealed a role for aberrant protein clearance, mitochondrial dysfunction, and neuroinflammation in the development and course of Parkinson's disease (PD). But it's still unknown how these routes relate to one another.

Causes: In Parkinson's disease, certain nerve cells called neurons in the brain gradually break down or die. Many of the symptoms of Parkinson's are due to a loss of neurons that produce a chemical messenger in your brain called dopamine. When dopamine levels decrease, it causes irregular brain activity, leading to problems with movement and other symptoms of Parkinson's disease. The cause of Parkinson's disease is unknown, but several factors appear to play a role, including.

Genes: Researchers have identified specific genetic changes that can cause Parkinson's disease. But these are uncommon except in rare cases with many family members affected by Parkinson's disease. However, certain gene variations appear to increase the risk of Parkinson's disease but with a relatively small risk of Parkinson's disease for each of these genetic markers.

Environmental triggers: Exposure to certain toxins or environmental factors may increase the risk of later Parkinson's disease, but the risk is small.

Researchers also have noted that many changes occur in the brains of people with Parkinson's disease, although it's not clear why these changes occur. These changes include:

The presence of Lewy bodies: Clumps of specific substances within brain cells are microscopic markers of Parkinson's disease. These are called Lewy bodies, and researchers believe these Lewy bodies hold an important clue to the cause of Parkinson's disease.

Alpha-synuclein found within Lewy bodies: Although many substances are found within Lewy bodies, scientists believe that an important one is the natural and widespread protein called alpha-synuclein, also called a-synuclein. It's found in all Lewy bodies in a clumped form that cells can't break down. This is currently an important focus among Parkinson's disease researchers. Researchers have found the clumped alpha-synuclein protein in the spinal fluid of people who later develop Parkinson's disease.

Stages of parkinson's disease: Doctors sometimes use five stages to describe the progress of Parkinson’s disease. Each stage presents new or changing symptoms that a person is likely to encounter. It is worth noting that not everyone will reach the advanced stages. Some people find that the symptoms remain mild and that they can continue to live independently and be mobile. Dividing the condition into stages helps doctors and caregivers understand and address some of the challenges a person is experiencing as it progresses.

Stage 1: During the initial stages, the symptoms are not typically severe. A person can perform everyday tasks with minimal difficulty. Some signs and symptoms of this stage include changes in posture, facial expressions, walking A person may not seek or receive a diagnosis at this stage, as the signs and symptoms may not be very noticeable. If a person has received a diagnosis, a doctor might prescribe medication to help control the symptoms.

Stage 2: Tremors, trembling, and stiffness affect both sides of the body and become more noticeable. As stiffness increases, the person may find that daily tasks are harder to carry out and take longer than before Walking, speech, and posture problems are often more noticeable in stage 2 of Parkinson's disease.

Stage 3: During stage 3, a person will experience most or all of the symptoms of stage 2 plus some others, including problems with balance, slow movements, slow reflexes. There is also a higher risk of falling due to coordination problems. Dressing and other self-care tasks may become more difficult. Medication and occupational or physical therapy may help people manage the symptoms and daily living.

Stage 4: daily activities become even more challenging. A person will likely need some form of daily care, as independent living is not usually possible. The person may be able to stand on their own but require a walker or another assistive device to walk.

Stage 5: At stage 5, a person may not be able to stand or move around due to stiffness. Depending on their age and overall health, they may need a wheelchair for mobility. The individual will need constant care to carry out daily activities and protect them from hazards, such as falling.

The person may also experience dementia, confusion, a reduced response to medication. Parkinson's disease is not life threatening, but it can put a strain on the body. A person may become more prone to certain types of infections, and there may be a risk of falling or choking. Advances in treatment now mean that many people with Parkinson's disease can expect to live for as long as a person without the condition.

Symptoms: Parkinson's disease symptoms can be different for everyone. Early symptoms may be mild and go unnoticed. Symptoms often begin on one side of the body and usually remain worse on that side, even after symptoms begin to affect the limbs on both sides.

Parkinson's symptoms may include

Tremor: Rhythmic shaking, called tremor, usually begins in a limb, often your hand or fingers. You may rub your thumb and forefinger back and forth. This is known as a pill-rolling tremor. Your hand may tremble when it's at rest. The shaking may decrease when you are performing tasks.

Slowed movement, known as bradykinesia: Over time, Parkinson's disease may slow your movement, making simple tasks difficult and time-consuming. Your steps may become shorter when you walk. It may be difficult to get out of a chair. You may drag or shuffle your feet as you try to walk.

Rigid muscle: Muscle stiffness may occur in any part of your body. The stiff muscles can be painful and limit your range of motion.

Impaired posture and balance: Your posture may become stooped. Or you may fall or have balance problems as a result of Parkinson's disease.

Loss of automatic movements: You may have a decreased ability to perform unconscious movements, including blinking, smiling or swinging your arms when you walk.

Speech changes: You may speak softly or quickly, slur, or hesitate before talking. Your speech may be more of a monotone rather than have the usual speech patterns.

Writing changes: It may become hard to write, and your writing may appear small.

Risk factors

Risk factors for Parkinson's disease, researchers have identified characteristics that increase a person’s risk of developing Parkinson’s, including gender, age, race, and genetic factors. However, it is worth noting that the vast majority of cases of PD are considered idiopathic Parkinson’s disease. “Idiopathic” means a condition that arises spontaneously or for which the cause is currently unknown. Major advances in research and science are continuing to reveal more underlying causes for PD.

Gender: Many studies have identified that the incidence of PD is more common in men than women. The reasons for the differences in men and women with PD are unclear, although one suggested explanation is the protective effect of estrogen in women. Other theories to explain the difference between PD in men and women include the higher rate of minor head trauma and exposure to occupational toxins in men and genetic susceptibility genes on the sex chromosomes.

Age: Increasing age is a risk factor for PD, as the incidence of PD increases with age. PD affects 1 percent of the population over the age of 60, and this increases to 5 percent of the

population over the age of 85. Only about 5 percent of all people with PD are diagnosed before the age of 60, which is considered early onset PD.

Family history and genetics: Approximately 15 percent to 25 percent of people with PD have a relative with the disease.People with a close family member with Parkinson's have a small increased risk (2 percent to 5 percent) of developing the disease. About 15 percent to 25 percent of people with PD have a known relative with the disease. A number of genetic mutations have been identified that are associated with PD. Some of these appear to be more casual, while others simply increase a person's risk for the disease.

Head trauma: Trauma to the head, neck, or upper cervical spine seems to increase a person's risk of developing PD. While the research is not conclusive, several studies have shown a link between head trauma and an increase in a person's risk of developing the disease.

Environmental pesticides: While there have been theories that rural living may be a risk factor for PD, urban areas have a higher prevalence and incidence of PD.A number of studies have looked at the relationship between exposure to environmental factors, like pesticides, and the development of neurological conditions, including PD and Alzheimer's disease. Several studies have found associations between PD and exposure to pesticides, but there are also studies that have shown no association. At this time, the evidence is inconclusive.

Clinical manifestations and Determinants of parkinson's disease

While the mechanism for the onset of the disease is understood, clinical motor symptoms are only presented following the death of 50–70% of SN dopaminergic neurons, suggesting the need to devise a means of identifying the cause before physical manifestations develop. The motor symptoms include muscle tone rigidity, postural instability, bradykinesia, and resting tremors. Beyond this, nonmotor symptoms may also be seen in patients succumbing to PD, such as dementia, autonomic dysfunctions, sleep disorders, sensory abnormalities, depression, and anxiety.

Similar to cancer, the onset of PD may be due to environmental or genetic factors. Factors such as head injuries or exposure to toxic chemicals may significantly increase a person's susceptibility to PD. While environmental factors play a crucial role in PD, they can also further trigger patients who are already genetically predisposed to the disease. This was noted

in a study on monozygotic and dizygotic twins. The comparison of the concordance rates, which estimated the heritability rate of PD, was found to be 30%, indicating that most PD risk is related to behavioural and environmental factors.

Environmental or external factors that pose a risk to individuals predisposed to PD include, but are not limited to, vigorous exercise, plasma urate, smoking, ibuprofen, and high consumption of coffee. Beyond this, certain pesticides and trauma to the brain have also been recognized as determinants of PD. Further studies have provided greater insight into pesticide exposure and its positive correlation to PD onset in farm workers and rural residences. Laboratory studies have portrayed the use of several dithiocarbamates, rotenone, organochlorines, paraquat, and 2,4-D as causative agents in PD. It has further been observed that mild to moderate head injuries, which may have occurred decades before disease onset, are associated with greater risk of PD. The number of injuries and the trauma, together with genetic susceptibility, was proposed to increase the risk two- to five-fold.

Current therapeutics

Because the current treatment of PD remains palliative, a cure lies in treating the primary causes, such as genetic defects or mutations. To date, dopaminergic administration has been effective for short periods in movement disorders, while antipsychotic medications treat the psychosomatic symptoms. the currently utilised medications for PD treatments and their functions. The major drawback to these medications is their poor ability to efficiently permeate the blood–brain barrier (BBB), causing their localization in the CNS. This often results in low-dose concentrations being administered.

Nanocapsules are vesicular systems in which a drug is confined to a cavity surrounded by a polymer membrane, whereas nanospheres are matrix systems in which the drug is physically and uniformly dispersed. Nanoparticles are solid, colloidal particles consisting of macromolecular substances that vary in size from 10 nm to 1000 nm. However, particles >200 nm are not heavily pursued and nanomedicine often refers to devices <200 nm (i.e., the width of microcapillaries). Typically, the drug of interest is dissolved, entrapped, adsorbed, attached and/or encapsulated into or onto a nano-matrix. Depending on the method of preparation nanoparticles, nanospheres, or nanocapsules can be constructed to possess different properties and release characteristics for the best delivery or encapsulation of the therapeutic agent.

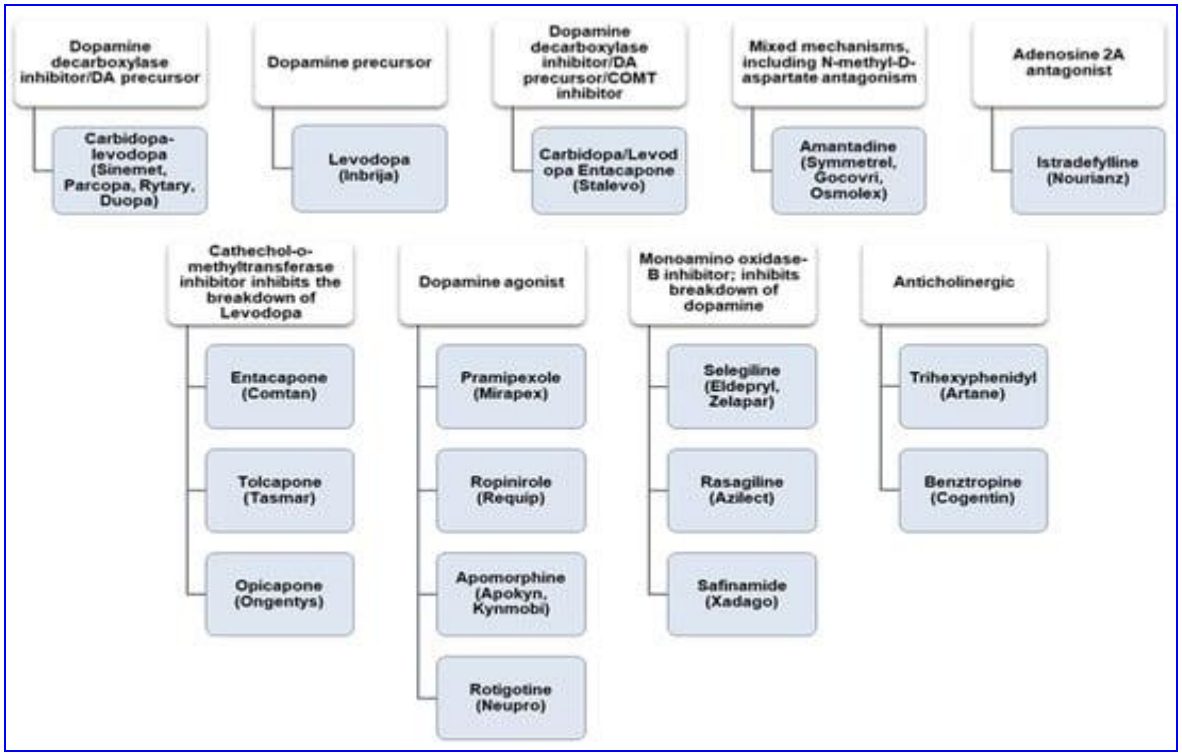

Fig. 2: Nanoparticles delivery system for Parkinson's disease.

Current treatment for Parkinson's disease

Overview of available PD treatments: Due to the inability to slow, stop or reverse the progression of dopaminergic neuronal degradation, current PD treatments focus on the reduction of both motor symptoms and NMS. The 4 main treatment strategies include: physical therapy (e.g. physiotherapy, treadmill exercise and flexibility training), rehabilitating therapy (e.g. speech therapy), pharmacological therapy (e.g. L-DOPA) and surgery (e.g. deep brain stimulation, DBS). Because of the high variability in symptom severity per patient, one or more of the above-mentioned treatments are generally applied. Moreover, due to the risk of the procedure, surgical treatments like DBS are only applied when other treatment options fail as a result of induced tolerance or severe motor symptom fluctuations.[6]

Out of the 4 main treatment strategies, pharmacological therapy is most effective at treating motor symptoms and is therefore nearly always included in treatment of PD. Although intravenous (IV) administration by means of infusion is the most effective method for sustained and constant systemic drug levels, most drugs are delivered via the oral route because of patient compliance.[23,24] There are three main classes of drugs that are used in PD therapy: 1. L-DOPA, a precursor of DA that increases DA levels within the SNpc, 2. DA agonists (e.g. apomorphine and ropinirole), which are drugs that act on DA receptors on the

postsynaptic terminal, 3. monoamine oxidase type B (MOAB) and catechol O-methyltransferase (COMT) inhibitors, (i.e. selegiline and entacapone) that inhibit DA degradation and catabolism.

Early-stage PD treatment is usually started with relatively mild drugs including MOAB and COMT inhibitors. These drugs are administered daily and can cross the blood-brain barrier (BBB) thereby allowing them to reach the brain where they inhibit DA degradation. This approach preserves available DA storages and increases overall DA concentrations, resulting in slight motor symptom reduction with little to no side effects. However, as PD progresses and motor symptom severity increases, these inhibitors are unable to sufficiently suppress disease symptoms, and therefore DA agonists are often added to the treatment regime. DA agonists, like apomorphine and ropinirole, are small drugs with lipophilic properties, allowing them to readily cross the BBB.

DA agonists are able to mimic DA function through activation of D1-like and D2-like receptors in various brain regions and are therefore moderately effective at the reduction of motor symptoms.[26] Depending on the type of DA agonist prescribed, oral administration or transdermal patches are used. While DA agonists generally show a higher efficacy compared to MAOB and COMT inhibitors, they can cause several side effects including nausea, hallucinations, sleep disorders, impulse control disorders and psychosis.

Levodopa treatment (L-DOPA): Dopaminergic neurons can store L-DOPA, as PD progresses and more dopaminergic neurons die this buffer function is lost, resulting in depleted brain DA storage. Eventually brain DA concentrations will then resemble blood DA ones, resulting in so-called “L-DOPA tolerance”. Therefore, higher and more frequent L-DOPA/carbidopa dosages are required to induce symptom relief as PD progresses. Due to this dosage increase, the “on-off phenotype” is developed, where DA levels spike just after treatment and are low between two consecutive treatments.[28] It is now believed that these swings in DA concentrations between treatments are causative for severe adverse effects like dyskinesias, stressing the importance of a continuous and constant DA supply.[30] The severity of these adverse effects increases with time, ultimately surpassing the beneficial effect of the treatment. Recent research indicated that L-DOPA/carbidopa treatment sustained long-term benefits in only 20% of patients after 2 years, while >75% of these patients experienced serious adverse events.

The Blood-brain barrier: To reduce side effects and improve patient compliance, increased L-DOPA bioavailability and brain delivery is required in order to minimise free systemic DA. One major hurdle for the effective and targeted delivery of any therapeutic compound to the brain is the BBB, which is responsible for the discontinuation of approximately 95% of potential therapeutic molecules for treatment of brain disorders. The BBB is the gatekeeper of the CNS and maintains a strictly controlled brain microenvironment by selection of molecules that can enter the brain. The BBB consists of multiple cell types, including non fenestrated endothelial cells (ECs) which are connected through tight junctions (TJs), pericytes, astrocytes and microglial cells. While the BBB is highly selective, certain molecules like nutrients and amino acids (AAs) are able to cross it through two main pathways: the transcellular pathway and the intracellular pathway. Due to the high number of TJs and adherens junctions (AJs), transcellular transport is mainly utilized by small hydrophobic molecules (MW <400 Da), while intracellular transport is mainly employed by hydrophilic macromolecules. Examples of intracellular transport across the BBB are the carrier-mediated transport (CMT) of glucose through glucose transporters GLUT1 and GLUT3, receptor-mediated transcytosis (RMT) of larger macromolecules through for example the low-density lipoprotein receptor, and adsorptive-mediated transcytosis (AMT), allowing transport of charged proteins through electrostatic interactions between the proteins and the ECs.

Additionally, recent research has illustrated that BBB permeability is altered in diseases involving inflammatory, traumatic or degenerative conditions becoming disrupted and allowing the passage of more and larger molecules. While the exact mechanisms of BBB disruption are still unknown, disrupted EC junctions are believed to be at the base of this phenomenon. Though the high selectivity of the BBB limits the effective L-DOPA delivery to the brain, insight into the mechanisms responsible for the facilitation of BBB transport in combination with altered BBB permeability in PD, opens a window for precise L-DOPA targeting to the CNS, with the potential to increase L-DOPA bioavailability and reduce free systemic DA.

Nanoparticles improved L-DOPA brain delivery

Nanoparticles composition: Improved L-DOPA targeting to the CNS as well as protection from systemic conversion by AAAD is required to decrease the L-DOPA dosage, increase bioavailability and reduce systemic side effects. The use of nanoparticles (NPs) for the

encapsulation and targeting of PD drugs to the BBB or the CNS has been explored in the past decades. NPs are small colloidal nano-sized carriers (usually between 10 and 200 nm in size) that can either be of inorganic, or organic origin or a hybrid of both. Inorganic NPs, usually consist of metals or quantum dots and display low batch-to-batch variability. They are easily controlled in size, easy to modify and to track using different imaging techniques and are therefore mainly utilised for imaging rather than drug delivery. Organic NPs can consist of virtually all biological products, but usually contain either lipids, polymers or proteins. Unlike inorganic NPs, organic NPs display high biocompatibility, low toxicity and are easily modified for better BBB targeting. Organic NPs can successfully encapsulate L-DOPA, thereby preventing its systemic degradation and increasing its circulation time. This potentially results in increased brain uptake through the BBB, leading to a decreased required L-DOPA dose. Additionally, organic NP properties can be tailored to increase specific BBB targeting and facilitate targeted uptake into the CNS. First, NP size is an important feature to overcome the BBB, where BBB penetration decreases as NP size increases. Secondly, zeta potential (surface charge) strongly influences the biological fate of NPs.

A negative zeta potential increases NP circulation time while reducing protein absorption, and a positive zeta potential facilitates AMT across cellular barriers through interactions with negatively charged plasma membranes. Although positively charged NPs have been associated with increased brain uptake, positive charges which are too high have been linked with immediate BBB toxicity. Thirdly, nanoparticles' hydrophobicity impacts the pathway of NP passage across the BBB, where hydrophobic NPs tend to utilise the receptor/carrier mediated paracellular pathway, and the hydrophilic NPs employ transcellular diffusion. Therefore, NP biomaterial composition should be carefully considered and optimised to ensure appropriate size, hydrophilicity and zeta potential to facilitate BBB penetration.

Lipid based and polymeric nanoparticles: While there are virtually endless configurations for organic NPs, lipid nanoparticles (LNPs) and polymer-based NPs are mostly studied because of their high biocompatibility, stability, low toxicity, potential to customise to control biological fate (e.g. targeting to the BBB) and drug release capability . Due to the nature and composition of these NPs, polymers and polymeric micelles are mostly used for delivery of hydrophobic drugs, while liposomes and LNPs are more suitable for the delivery of hydrophilic drugs and oligonucleotides. Even though there are limited NP-based

treatments currently on the market, numerous lipid and polymeric NPs have been developed and investigated and are currently tested in clinical pipelines.

Polymeric nanoparticles: Polymeric NPs are composed of one or more synthetic or natural polymer(s) which are assembled to form vesicles that are biocompatible, biodegradable and exhibit controlled and sustained release properties. The simplest type of polymeric NP is the nanocapsule, in which a drug is encapsulated by a single polymer vesicle. While there are practically endless polymeric NP configurations, the most widely investigated FDA approved polymers include poly(ethylene glycol) (PEG), poly(trimethylene carbonate) (PTMC), poly(lactic-co-glycolic acid) (PLGA) and chitosan, due to their sustained-release properties in combination with their low toxicity and favourable safety profiles.[40,55] Examples of currently explored co-polymer-based NPs for brain delivery of PD drugs are PEG-PTMC NPs, developed by Wang and co-workers.[55] They demonstrated that PEG-PTMC NPs, 78 nm in size with a surface charge of approximately −10 mV, could be efficiently loaded with PD drugs which showed a partial rapid release over 4 h in vitro, as well as sustained release properties for up to 48 h. In vivo pharmacokinetic experiments in rats demonstrated a significantly increased plasma concentration as well as brain concentration of the PD drug Ginkgolide B (GB), compared to free drug after oral administration, which was sustained for up to 48 h.[55]

More sophisticated copolymers include the utilisation of amphiphilic copolymers, which can assemble into NPs consisting of a hydrophilic shell and a hydrophobic core, called polymeric micelles. These polymeric micelles are generally stable, can be modified to facilitate targeting to the BBB, and enable sustained drug release which can be tailored to respond to external stimuli. Liu et al. studied polymeric micelles for the use of increased and sustained brain delivery, through the generation of PEGylated micelles modified with cell penetrating transactivator of transcription (TAT) peptides. These micelles self-assembled into NPs of 180 nm or smaller, showed efficient drug loading and illustrated an in vitro sustained drug release for 6 h in PBS at body temperature. Moreover, increased cellular uptake in an in vitro human astrocytic model was also found upon addition of these micelles.

Interestingly, these PEGylated micelles showed significantly increased BBB targeting and brain delivery after IV administration in rats, which was visualised by imaging of fluorescein 5-isothiocyanate (FITC)-loaded micelles and compared to free injected FITC.Although none of the polymeric NPs have received FDA approval yet for treatment of PD, some of these

polymers are already applied in other treatments, where they are used to coat NPs, stabilise proteins and facilitate controlled hormone release in the treatment of for example prostate cancer.The main advantage of polymeric NPs over other carrier systems is the variety of available polymers in combination with the possibility to modify their surfaces. This allows fine-tuning of NP composition to accurately control NP properties like size, hydrophilicity, surface charge, circulation time, drug release profile, degradation rate, and stimuli to external responses.

However, polymeric NP disadvantages include toxicity from degradation products, premature or incomplete drug release upon in vivo administration, batch-to-batch variation and difficulties in upscaling production.Additionally, specific antibodies are formed against polymers used to coat the NP surface, such as PEG, upon multiple administrations. These antibodies induce faster clearance, leading to shortened circulation times. This process is referred to as the accelerated blood clearance (ABC) phenomenon.

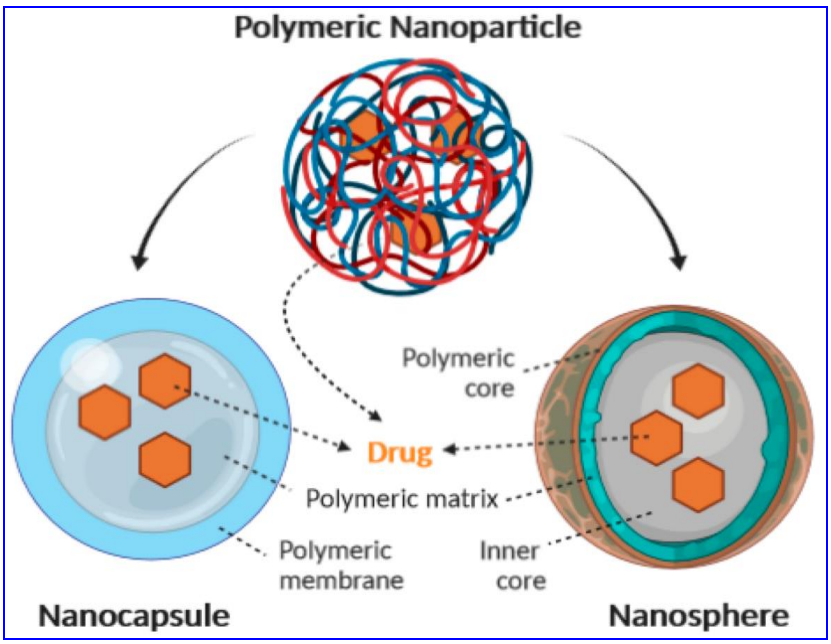

Fig. 3: Polymeric Nanoparticles drug polymer matrix.

Lipid based nanoparticles

Lipid-based NPs comprise carriers composed of one or more types of lipids. The most used and studied lipid-based NPs are liposomes, consisting of a bilayer of phospholipids with a hydrophilic aqueous core, micelles, consisting of a single layer of phospholipids with an aqueous core, and solid lipid NPs (SLNs) containing a solid hydrophobic core. Liposomes and micelles are mostly used for the encapsulation and delivery of hydrophilic compounds

entrapped in their aqueous core. However, hydrophobic and lipophilic payloads could also be loaded to some extent within their hydrophobic lipid (bi)layer(s). Compared to polymeric NPs, lipid-based NPs are more biocompatible and show decreased toxicity, and several liposomal formulations are currently on the market for applications including treatment of specific cancers, delivery of viral vaccines and treatment of fungal diseases.

Additionally, because of their relatively small size and composition, they can readily pass the BBB without any functional modifications, through either the hydrophobic transcellular pathway or the lipophilic paracellular pathway. Additionally, these lipid NPs are more cost effective and easier to scale up compared to polymer-based NPs. Functional liposome modifications can aid direct targeting to the BBB through liposome modifications with BBB-specific antibodies or ligands to facilitate RMT and CMT. Examples of surface modifications employed for targeting of the BBB include specific antibodies, mannose and the CPPs penetratin and rabies virus glycoprotein (RVG) peptide.[66]

Additionally, the circulation time of lipid-based NPs can be increased through surface modifications including PEG coating and modifications neutralising liposome charge, disguising liposomes from the reticuloendothelial system (RES), creating so-called “stealth liposomes”. Although these modifications are essential for effective liposome-mediated L-DOPA delivery to the brain, they also induce specific antibody production leading to accelerated clearance. While recent research has demonstrated that encapsulation of PD drugs in NPs can improve circulation kinetics and targeting to the CNS, there are some shortcomings and questions to be answered regarding this strategy. First, there is an ongoing debate whether entire NPs can penetrate the BBB or whether the drug is released in the BBB before reaching the CNS.Additionally, oral administration of NPs is very challenging.

The major hurdles that orally administered NPs face are digestion within the GI tract, EC barriers and TJs, as well as extensive first pass metabolism in case of reaching the circulation. The natural barriers result in the excretion and degradation of 85–90% of orally administered NPs, with only 2–3% of orally administered drug reaching the bloodstream after 30 min, highlighting the inefficiency of this delivery route. Hence, modifications to protect NPs in the GI tract and to facilitate crossing of cellular barriers are required to optimise oral NP delivery. To circumvent these issues, most polymeric and lipid-based NP formulations are designed for IV administration. However, current NP formulations improve drug release for no more than a few days at best, which would result in frequent hospital visitations for PD

patients, thereby drastically reducing patient compliance.[55] Therefore, alternative strategies are required to enable delivery of PD drugs to the CNS.

Although the previously described oral and IV administration routes are able to increase drug delivery to the CNS and reduce PD symptoms, these routes are limited by either low oral bioavailability or frequent hospital visits, respectively. An alternative administration route entails the delivery of PD drugs through transdermal patches. These patches facilitate sustained drug release through the skin, thereby reducing treatment frequency while enabling self-administration by PD patients and increasing patient compliance. Obaidat et al. designed L-DOPA loaded xanthan gum and Carbopol 971 transdermal patches, which were lined with b-cyclodextrin to increase L-DOPA stability. These patches were shown to provide sustained L-DOPA release for up to 6 h.

Similarly, Nair et al. formulated polyvinylpyrrolidone transdermal patches loaded with L-DOPA/carbidopa and spread on a polyester release liner. Transdermal delivery of L-DOPA and carbidopa by transdermal patches in healthy rats illustrated increased L-DOPA plasma concentrations compared to transdermal delivery of naked L-DOPA, sustaining for up to 8 h. While these papers illustrated the possible advantages of transdermal L-DOPA delivery, therapeutic concentrations of systemic L-DOPA were significantly below therapeutic range, and steady-state drug concentrations were not maintained. A likely explanation is the instability of L-DOPA, causing degradation within the transdermal patch as well as after systemic absorption, resulting in low L-DOPA brain concentrations.

Additionally, the transdermal delivery of naked L-DOPA is limited by poor permeability through the skin and high BBB selectivity, as describedpreviously. A possible solution could be the encapsulation of L-DOPA in NPs, protecting L-DOPA from degradation and decarboxylation both in the transdermal patch and after systemic absorption, while enabling modifications for improved BBB targeting. Therefore, Sintov et al. designed a self-assembling nanomicellar hydrogel system loaded with 2% L-DOPA and 1% carbidopa for transdermal delivery. In vivo pharmacokinetic studies in healthy rabbits revealed that L-DOPA plasma levels of this self-assembling nanomicellar hydrogel peaked at about 0.6 μg/ml after 12 h, which was fully cleared after 24–28 h. Interestingly, the self-assembling nanomicellar liquid patch resulted in 0.8–1 μg/ml peak plasma concentrations after daily patch application, which increased to 3–4.5 μg/ml when applied twice-daily, reducing dosing frequency while simultaneously avoiding fluctuating plasma L-DOPA concentrations, which

are linked with severe side effects as described earlier. While no further publications describe the transdermal delivery of NP-encapsulated L-DOPA, the NP-encapsulated transdermal delivery of other PD drugs has been studied.

Nikhil et al. described the generation of selegiline-loaded polymeric PLGA NPs embedded in ethylene vinyl acetate transdermal films, which were transdermally delivered in reserpine-induced PD rats. In vivo pharmacokinetic studies showed increased selegiline half-life and mean residence time after transdermal delivery in PLGA NPs compared to plain drug, and a 13-fold increase in area under the curve (AUC) when comparing transdermal PLGA NP delivery to IV administration, being detectable for up to 72 h after transdermal delivery. Additionally, biodistribution studies illustrated a 137% increase in brain drug-targeting efficiency and a 27% increase in brain drug-targeting potential. In vivo experiments in reserpine-induced PD rats illustrated a slight reduction of cataleptic activity after transdermal delivery of selegiline PLGA NPs, with no alterations in an open field test.In another study, the authors embedded rasagiline mesylate loaded polymeric PLGA NPs in gellan gum transdermal films and observed undetectable initial rasagiline mesylate concentrations after transdermal delivery, which increased over time and showed sustained release for 72 h, peaking at 24 h, with stable brain-drug concentrations for up to 70 h. Behavioural tests in reserpine-induced PD rats showed reduced cataleptic activity for up to 24 days as well as increased number of crossovers and overall movement in an open field test after transdermal PLGA NP delivery.

Mechanisms explaining functional improvement include brain dopamine concentration restoration, prevention of neuronal damage caused by oxidative stress and inhibition of dopamine catabolizing MAOB enzyme . While the usage of polymeric NPs is effective, Prabhu et al. generated curcumin-loaded solid lipid NPs that were transdermally delivered in a dissolvable microneedle patch. Neuroprotective studies in PD mice illustrated a significantly decreased degree of bradykinesia in a pole test and improved motor coordination and balance ability in a rotarod test, while showing no signs of skin irritation or sensitivity. These studies suggest that transdermal delivery of NP-encapsulated L-DOPA is feasible, however limited evidence of therapeutic L-DOPA concentrations reaching the brain exists, likely as a result of poor skin permeability and L-DOPA instability as described before.

Intranasal delivery of PD drugs

Intranasal delivery routes: While the previously described transdermal and IV administered NPs focus on targeting to – and facilitation of crossing the BBB, an alternative strategy is to avoid the BBB altogether. Over the past decade, increasing evidence supports the existence of a more direct delivery route between the nose and the CNS. Direct nose-to-brain delivery is a non-invasive and easy to self-administer pathway which circumvents some of the major flaws of IV administration or oral and transdermal delivery. These advantages include, evasion of degradation in the GI tract and hepatic first-pass metabolism, and reduction of free systemic drugs and DDC inhibitors. Upon intranasal administration, drugs are deposited on the respiratory and olfactory epithelium, and for the nose-to-blood-to-brain pathway, the drug deposited on the respiratory epithelium can be absorbed through the fenestrated nasal epithelial cells of the well-vascularized lateral walls of the nasal cavities. From there, the drug can enter the peripheral circulation, after which it may pass to the CNS in case the drug can cross the BBB or the more permeable blood-cerebrospinal fluid barrier (BCSFB).

Alternatively, drugs deposited in the olfactory region of the nasal cavity can be directly transported to the CNS in a matter of minutes via the olfactory or trigeminal nerves, which are the only direct connection between the brain and the rest of the body. These direct nose-to-brain routes can be crossed via intracellular and extracellular transport pathways. During the intracellular route, therapeutics are internalized within the olfactory and trigeminal neurons via endocytosis, after which they are transported within the endosome towards the neuronal axons where they are released in the olfactory bulb via exocytosis before finally reaching the brain stem.

During the extracellular route, drugs penetrate the olfactory epithelium and trigeminal nerve, after which they migrate through the paracellular space of the nasal epithelium along the length of the neuronal axon before reaching the CNS. After reaching brain stem, therapeutics are either absorbed in blood/lymphatic vessels or further distributed to other parts of the brain through the perivascular pump driven by arterial pulsation or transported back to the nasal cavity via P-glycoprotein (P-gp) efflux proteins (ATP-binding cassettes present in cell membranes able to export foreign substances) Unlike systemic route, direct nose-to-brain delivery facilitates fast transport to the CNS, reaching the target site within minutes.

Salameh and coworkers demonstrated the presence of labelled insulin in and around the olfactory bulb only 5 min after nasal administration in rats, with the insulin reaching all parts

of the brain within 30 min. Additionally, Chao and coworkers demonstrated the rapid effect of intranasally administered L-DOPA on PD rats, where intranasal L-DOPA treatment illustrated mild reductions of modelled PD symptoms like turning behaviour, foot slips and motor asymmetry 10 to 20 min after treatment administration, which could be sustained for approximately 60 min.

We believe that these nanoscale coordination polymers as promising future candidates for efficient nasal delivery of drugs to the central nervous system, and thus for the symptomatic treatment of people affected by Parkinson's and other neurodegenerative disorders. This type of nano-formulation and administration route may also pave the way to the development of other platforms able to deliver a wide range of drugs into the brain in a controlled manner, for the treatment of other diseases, such as brain tumours, Alzheimer's and Epilepsy.

The NP encapsulation of L-DOPA is a promising new treatment strategy for PD which has been demonstrated to improve drug delivery to the CNS while reducing dose, treatment frequency and systemic side effects. Moreover, due to problems with oral and transdermal delivery and IV administration, intranasal NP delivery offers a non-invasive and easy to self-administer alternative which has the potential to increase therapeutic efficacy through direct brain delivery via the olfactory and trigeminal nerves, which could be of interest for various brain diseases. Nevertheless, before intranasally delivered drug-loaded NPs can be tested in patients, further research into optimal NP composition and characteristics, systemic methodology for intranasal delivery devices, more representative in vivo model systems, improved NP-mediated brain targeting and delivery, and long-term safety of NP formulations are required.

CONCLUSION

Aging will cause an increase in the number of individuals with PD. Since PD cannot be cured currently, the development of new anti-PD drugs is required. Nanotechnology based anti-PD drugs can provide precise and well-controlled brain-targeted delivery and therefore have been receiving extensive attention in recent years. In this review, we highlight various strategies for crossing the BBB and shed light on the nanomaterials with anti-parkinson's nano-biological effects to provide a new reference for their clinical application. The BBB makes it difficult for anti-PD drugs to enter the brain parenchyma, but there are various receptor- and carrier-mediated pathways that allow the movement of molecules as observed in the simple

diffusion of lipophilic substances. However,common anti-PD nanomedicines have focused on brain-targeted delivery.

Overall, these drug delivery paltform certainly demonstrate nanotechnology in the treatment of brain disorders. one of the main neurotransmitters active in the central nervous system.

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