Neurodegeneration Nanotechnology in Neurodegenerative Diseases

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Edited by

Shakeel Ahmed

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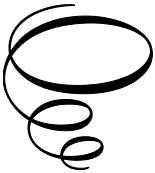

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CHAPTER ONE

NANOTECHNOLOGY IN NEURODEGENERATION

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Abstract

Neurodegenerative illnesses, such as Parkinson's disease, multiple sclerosis, epilepsy, and Alzheimer's disease, affect about 1 million people. Due to the brain's complexity, CNS issues are of the utmost importance. To treat neurodegenerative diseases and address issues with toxicity, specificity, and delivery, a variety of medications are available. The blood-brain barrier (BBB), for example, poses a problem because it prevents therapeutic drugs from passing through and reaching their intended target. The BBB is a barrier that prevents drugs from reaching target sites, so researchers have been looking for ways to open it up. These challenges underscore the necessity of utilizing nanotechnology to manipulate or regulate diverse cellular processes to attain the desired traits. Nanoparticles are a potent substitute for drug administration and other methods because they can cross the BBB due to their nanosize. Nanotechnology has the potential to enhance CNS disorder diagnostic and therapeutic approaches, as well as facilitate efficient drug delivery. With the aid of nanoengineering, medications can be modified to perform tasks such as crossing the BBB, targeting particular cells, modifying signaling pathways, transferring beneficial genes, and promoting nerve cell regeneration and preservation. With a particular emphasis on potential future applications, this chapter

focuses on the most cutting-edge current nanotechnology applications in the treatment and diagnosis of the most prevalent ND.

Keywords: Neurodegenerative diseases; Nanoparticles; CNS issues; Blood-brain barrier; Nanotechnology

Introduction

The progressive loss of a neuron's structure or function, which is frequently accompanied by neuronal death, is the hallmark of neurodegenerative diseases (ND). Examples include prion disease (PrD), Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS).

There are still a few effective early diagnosis and treatment options for many ND, despite notable advancements and a wealth of research on the subject. One of the most important barriers is the blood-brain barrier (BBB), which prevents the majority of drugs and imaging agents from entering and having side effects outside the brain. Current options for diagnosing and treating brain diseases are frequently determined by vascular lesions and BBB leakage (Gabathuler, 2010, 50). An innovative and promising technique is nanotechnology, which makes use of materials or devices that are created on a scale of 1 to 100 billionths of a metre (1-100 nm) (Fernandes et al., 2010, 166). The use of NM (nanofibres, nanotubes, nanoparticles, and nanogels) in biomedicine is currently widespread, with a wide range of physicochemical properties.

Because of their adaptability, engineered nanomaterials (NM) are appealing to the biomedical sector. While chemical functionalization can provide targeting specificity, their physical properties, for instance, can be used for tissue engineering and regeneration as well as diagnosis and/or therapy. NM can function to help drugs and/or contrast agents penetrate the BBB or can cross it on their own (Fernandes et al., 2010, 166). Additionally, NM can be administered orally, inhaled, or parenterally and may contain both hydrophilic and hydrophobic molecules. With a particular emphasis on potential future applications, this chapter focuses on the most cutting-edge current nanotechnology applications in the treatment and diagnosis of the most prevalent ND.

1.1. Neurodegenerative diseases

The term "neurodegenerative diseases" describes a class of inherited or sporadic conditions that are all characterized by progressively worsening nervous system dysfunction brought on by the degeneration of particular CNS neurons. Some of the most well-known neurodegenerative diseases include Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), Alzheimer's disease (AD) and Huntington's disease (HD). Despite the variety of neurodegenerative diseases, recent genome-wide and -omics approaches have revealed new insights into the key molecular pathways of those diseases, revealing that inflammation and microglia activation, oxidative stress, misfolded protein accumulation and aggregation, mitochondrial dysfunction, impaired autophagy-lysosomal activities, apoptosis, oxidatively damaged DNA and impaired DNA repair, and disruption of vesicle trafficking are all involved (Erkkinen et al., 2018).

The dopaminergic and serotoninergic systems, the latter of which is crucial in the pathogenesis of both Parkinson's disease and Alzheimer's disease, are affected by NPs, which can also cause cell death in both of these systems. Additionally, NPs can result in neurodegeneration by impairing autophagy, disrupting vesicle trafficking, causing apoptosis, redox imbalance, disrupting mitochondrial function, and activating microglia. Additionally, there is evidence that suggests engineered NMs can change the expression of genes related to DNA methylation pathways as well as general epigenetic markers like DNA methylation and histone tail modifications in vitro, all of which have the potential to be connected to complex human disorders like neurodegeneration (Lafuente et al., 2019, 263).

Because of their capacity to load drugs, contrast agents, and cellular or intracellular component targeting moieties, biodegradable NMs are now recognized as alternatives for monitoring and treating human diseases, including neurodegenerative disorders. Nanoparticulate drug carriers are being tested to see if they can deliver drugs or contrast materials that are useful in the diagnosis and treatment of AD and other neurodegenerative diseases across the BBB because of their size, surface potential, or surface coatings (Luo et al., 2020, 21).

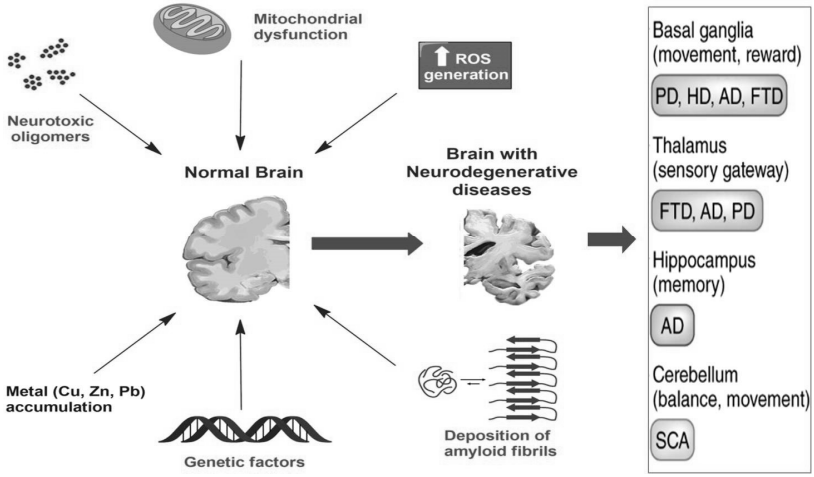

Figure 1: The multifactorial and complex nature of neurodegenerative diseases

1.2. Nanotechnology

A field of science known as nanotechnology deals with things and substances that are smaller than a nanometer. Because it can help avoid some drug delivery issues, improve drug accessibility to target areas, or increase the specificity and selectivity of diagnostic criteria, a number of recent studies have suggested nanomedicine as a promising strategy for the diagnosis and treatment of neurodegenerative disorders (Nie et al., 2020, 257).

1.3. Nanomaterials

Small molecules with distinct biological activity known as nanomaterials have proliferated in a variety of industrial and medical settings over the past 30 years. Little is known about the harmful effects of NMs on the human brain, including the potential induction of neurodegenerative pathways, despite significant advances in nanotechnology. Four categories are used to categorize nanomaterials: Inorganic nanomaterials, carbon nanomaterials, organic nanomaterials, and composite-based nanomaterials (Migliore et al., 2015) (Fig. 1).

Metal and metal oxide nanomaterials are frequently found in inorganic-based nanomaterials. Silver, gold, aluminium, cadmium, copper, iron, zinc, and lead are examples of metal-based inorganic nanomaterials, whereas

metal oxide-based inorganic nanomaterials include iron oxide (Fe3O4), titanium dioxide, magnesium aluminium oxide, zinc oxide, and copper oxide. Graphene, fullerene, single- and multi-walled carbon nanotubes, carbon fibre, activated carbon, and carbon black are examples of carbon-based nanomaterials. Organic materials without carbon, like dendrimers, cyclodextrin, liposomes, and micelles, are used to create organic-based nanomaterials. Composite nanomaterials have complex structures resembling a metal-organic framework and are composed of any combination of metal, carbon, metal oxide, and/or organic nanomaterials as well as carbon- and/or organic-based nanomaterials (Boyes et al., 2020,1121).

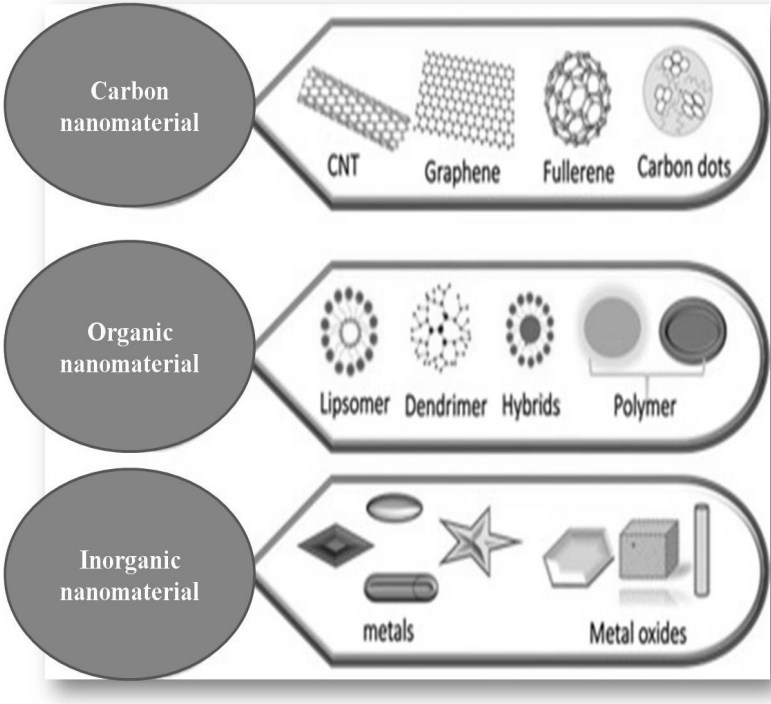

Figure 2: Type of Nanomaterials

1.4. Nanoparticles

The nanoparticles are spherical polymeric particles that can be made artificially or naturally. They come in sizes between 10 and 500 nm. Due to their spherical shape and high surface area-to-volume ratio, these particles have a wide range of potential applications. The nanoparticles are split into two sections: one that encloses the drug, safeguards it from enzymatic degradation, targets particular brain cells, crosses the BBB, and releases it at a particular pH. The distribution of drugs is handled by the other element. One benefit of nanoparticles is their capacity to cross the BBB, which results from a site-specific drug delivery mechanism (Najahi-Missaoui et al., 2020, 385).

1.5. Crossing the BBB with nanotechnology

The blood-brain barrier (BBB), which prevents blood from entering the central nervous system (CNS), is still a dynamic physical and biological barrier. The brain's capillary endothelial cells, which restrict transcellular passage, and its intricate tight and adherent junctions between cells, which restrict paracellular flux, are the main causes of the BBB's functional complexity (Abbott et al., 1999, 277). Using invasive procedures, invasive chemical drug alterations, and in silico creation of molecules with higher permeability, the BBB has been circumvented. The "Trojan horse" method, which combines a substance that doesn't cross the BBB with one that does, has also been applied. Additionally, attempts have been made to circumvent the BBB by using alternative routes (such as intranasal, via the olfactory bulb) (Patel eet al., 2009,35). However, these techniques did not produce obvious outcomes.

Currently, the most promising NM-based strategies aim to interact molecularly with BBB cells while utilizing the physiological transport mechanisms already present to prevent interfering with the barrier's normal function. The most effective mechanisms for facilitating the transcellular movement of NM from the blood to the brain are receptor and adsorptive-mediated transcytosis. There are several considerations that must be made in order to successfully complete this task. Surface functionalization for focusing on and crossing the BBB, as well as an extended half-life in blood to avoid the reticuloendothelial system ("stealth" NM), are the absolute minimum requirements for NM. Additionally, NM needs to be biodegradable, non-toxic, immune-suppressive, and non-inflammatory. The final two criteria are biocompatibility and biodegradability (Bhaskar et al., 2010).

1.6. Application of nanotechnology to the treatment of various NDDs

Thanks to nanotechnology, the problems caused by CNS disorders now have a new solution. Many CNS disorders are nearly incurable and have few effective treatments, including schizophrenia, Huntington's disease (HD), Parkinson's disease (PD), multiple sclerosis (MS), and Parkinson's disease (AD). These conditions might be treated by nanoparticles.

1.6.1. Alzheimer's disease

Memory loss and cognitive decline are signs of Alzheimer's disease. In the hippocampus, amyloid plaques (Amyloid, A) accumulate and fold unevenly, resulting in the formation of tau protein-based senile plaques (SPs) and neurofibrillary tangles (NFTs). This condition is the fifth most common cause of death for people 65 and older and the sixth most frequent cause of disease-related deaths in the United States. Neurotoxicity and an immune-inflammatory response are side effects of Alzheimer's disease, which is characterized by A42 fibrils and is caused by a disproportion in the synthesis and disposal of A in the brain. As a result, some of the many treatments for Alzheimer's disease include removing or reducing A-deposition or protecting the brain's neurons. But there is no total treatment or cure for Alzheimer's disease is currently available (Ma et al., 2022, 1210).

Despite the fact that there are many issues with the current AD treatments, intranasal techniques seem to be the only one that works. The current treatments for Alzheimer's disease alter neurotransmitters or enzymes. Patients who use these medications report unfavourable side effects and discontinue use. Acetyl cholinesterase inhibitors, for example, can make someone feel sick to their stomach and cause them to vomit. Tacrine's short half-life necessitates daily administration. Galantamine and rivastigmine must also be taken twice daily. Memantine, a different medication used to treat Alzheimer's disease, has undesirable effects like nausea, confusion, dizziness, and constipation. Nanotechnology provides a novel approach for the diagnosis and treatment of Alzheimer's disease. Nanoparticles could be used to deliver medications to the brain because they can't reach the intended location. A number of nanoparticles, including liposomes, solid lipid carriers, hydrogels, liquid crystals, microemulsions, PNPs, and SLNs, have been used to treat Alzheimer's disease with success. In a research investigation, poly (n-butyl cyanoacrylate) nanoparticles were synthesized through emulsion polymerization and subsequently loaded with tacrine. These nanoparticles were then coated with polysorbate 80. The

author proposed leveraging the interaction between the endothelial cells of the brain and the polysorbate 80 coating to facilitate the delivery of the drug-coated nanoparticles to the brain. This strategy was suggested due to the inadequate concentration of tacrine observed in the lungs and kidneys (Wilson et al., 2008, 75).

To investigate its effects, the nanoparticle was injected into mice. Coated nanoparticles significantly increased the amount of tacrine in comparison to non-coated nanoparticles or the drug alone. To deliver rivastigmine for the treatment of Alzheimer's disease, the author developed poly(n-butyl cyanoacrylate) nanoparticles coated in polysorbate80. A scientist developed a CPP that altered rivastigmine liposomes as well as all liposomes in order to boost rivastigmine brain absorption while reducing side effects and enhancing pharmacodynamics. Rivastigmine crossed the BBB at a higher concentration when administered in combination with nanoparticles than when administered alone (Wilson et al., 2008, 159; Yang et al., 2013). In a recent study, AD was treated with curcumin using Fe2O3@CDs. The Fe3O4@CDs nanocomposite was made using rat pheochromocytoma (PC12) cell lines, and curcumin was loaded onto the CDs via hydrogen-bonding interaction. The composition's fibril nature was demonstrated (Kuang et al., 2020). Additionally, significant therapeutic effects against AD symptoms were seen when the dipeptidyl peptidase-4 inhibitor sitagliptin (SIT) was combined with nanoparticles and administered orally (Wilson et al., 2021). A recent study that was finished resulted in the identification of a novel AD treatment strategy. When MC11 was applied to brain endothelial cells, P-gp and breast cancer resistance protein transporters were anticipated to be expressed (Arduino et al., 2020). The transferrin-functionalized nanostructured lipid carrier is capable of expressing a protein that is a potential treatment candidate for AD.

1.6.2. Parkinson disease

This is a neurodegenerative disease that over time causes people to lose their ability to move. One methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine exposure, elevated alpha-synuclein levels, and increased oxidative stress are just a few of the numerous factors that contribute to Parkinson's disease (PD) and the degeneration of substantia nigra neuronal cells. Some brain nerve cells (neurons) die or degenerate as a result of Parkinson's disease (Rastegari et al., 2019). The brain's nerve cells can only produce a finite amount of the neuronal transmitter dopamine because of the random or familial degeneration known as Parkinson's disease (PD) (Modi et al., 2010, 154). Some of the symptoms are brought on by the degeneration of

dopamine-producing brain neurons. Reduced movement and other symptoms are caused by abnormal brain activity brought on by dopamine deficiency. A barely perceptible tremor in one arm could be the first symptom, and it might advance quickly. There is a lot of trembling. Stiffness or sluggishness in movement could be additional symptoms of the illness. Parkinson's disease is the second most common NDD, but it is currently incurable and has no certain therapeutic options.

There are numerous ways to make materials on your own, and depending on the material you select, these ways serve a variety of intended purposes or functions. For example, delivery-imaging agents are frequently made from inorganic materials and nanosystem metals or QDs (Lewinski et al., 2008, 26). In order to deliver selegiline (Solupor), Fang et al. developed a novel transdermal device using a hydrogel and a microporous polyethylene membrane. The results suggested that the Solupor barrier may have been the rate-limiting element, even with hydrogel in the formulation (Fang et al., 2009, 33).

The innovative transdermal device created by Azeem et al. offers potential for sustained delivery of ropinirole, potentially delaying the onset of levodopa-related motor complications. The final results of in vitro testing revealed a significant 7.5-fold enhancement in ropinirole penetration through the skin (Azeem et al., 2009, 220). Nanoparticles have been demonstrated to facilitate effective drug administration, improve bioavailability, minimise negative pharmacokinetic effects, reduce drug dose, and increase target delivery in studies on a variety of brain-related diseases (Alonso et al., 2012,3). Biocompatibility of lipid-based nanoparticles has been demonstrated. An analytical hierarchy technique and the microemulsion method were used to create the rasagiline-loaded SLNs, yielding an 83.6% yield (Kunasekaran et al., 2014, 115). Additionally, organic materials have been shown to have higher biocompatibility and lower material toxicity (Yohan et al., 2014, 2371). Some of the events that can start a chain of events that can lead to PD include basal ganglia dysfunctions, which may cause movement issues (Nambu et al., 2015, 2). Another study investigated the in vitro rasagiline release from SLNs. The analysis from the rasagiline-enhanced SLNs in the same group's in vitro release drug study was performed after the initial 20% release of the results, and it showed a biphasic controlled release (Kunasekaran et al., 2015, 300).

As an example, the results of moist heat sterilization of rasagiline-loaded SLNs revealed no changes to the particle size, zeta potential, or drug encapsulation efficiency (Viveksarathi and Kannan, 2015, 87). The scientists also used manganese oxide to make nanoparticles. In a different study, they were created and linked to levodopa in order to be used as a

cutting-edge drug delivery system that incorporates an MRI distinction agent. The analysis found that the MRI contrasts changed from dim to brilliant in a temporally dependent manner as a result of the emission of Mn2+ from the nanoparticles (McDonagh et al., 2016, 301). Levodopa liposomes coated with chitosan were used by Cao et al. to study the responses and effects of various substances in an effort to lessen the adverse effects of levodopa (Cao et al., 2016, 32). Parkinson's disease (PD) is currently managed with transdermal patches, and clinical depression is managed with selegiline (Emsam) and rotigotine (Neupro). Increasing dopamine levels, simulating dopamine action, and decreasing dopamine storage and metabolization are currently the main treatments for motor symptoms. Chitosan nanoparticles were developed by Ray et al. to successfully encapsulate ropinirole and allow it to pass through the BBB. The T80 coating increased brain accumulation when chitosan nanoparticles were compared to those that weren't (Ray et al., 2018, 21). Pramipexole was incorporated into a complex formulation of polymeric nanoparticles based on poly (3-hydroxybutyrate-co-3-hydroxyvalerate) (PHBV), developed by Javan and Hasab (Javan et al., 2018, 82).

Jawanjal et al. developed a graphene oxide for the administration of trihexyphenidyl (Jawanjal et al., 2019, 134). The current pharmacological approach to treating both motor and non-motor complaints is primarily centred on symptomatic relief (Armstrong et al., 2020). Based on preclinical studies, CNM-Au8, an oral suspension of gold nanocrystals, appears to enhance cellular bioenergetic processes and aid in eliminating harmful byproducts of cellular metabolism. These effects could potentially prevent motor neuron degeneration in patients with ALS or PD. Additionally, CNM-Au8 has demonstrated protective effects on motor neurons, reducing severe injury and apoptosis. Currently, it is undergoing Phase 2 clinical trials (Prabhakar et al., 2020, 69).

1.6.3. Huntingtin Diseases

This particular type of neurological disorder is caused by an increase in the CAG trinucleotide repetition in the gene that makes the protein huntingtin (HTT), which is necessary for normal development before birth. Histone acetylation declines as the proportion of HTT mutants increases, and this decline is linked to HD-related neural loss and damage. Incurable HD causes brain cell death, which causes additional motor, cognitive, and psychiatric disorders (Bates et al., 2015). Currently, there is no available treatment capable of halting or decelerating the progression of Huntington's disease (HD). However, given the pivotal role of mitochondria in the onset

of HD, where they regulate energy metabolism and apoptosis pathways, detecting faulty mitochondria and oxidative stress in patient biological samples is straightforward. A recent clinical trial involving individuals with early-stage HD investigated the feasibility, safety, and characteristics of Ionis-HTTRx (Tabrizi et al., 2019, 2307). To disrupt HTT mRNA and diminish the levels of mutant HTT, scientists developed an antisense oligonucleotide. However, a challenge emerged. This therapy necessitates administration at least six times annually throughout the patient's lifetime due to its reliance on a rapid and effective drug delivery mechanism.

Although a lumbar puncture is used in the diagnostic process, the chronic brain portal increases the risk of unfavourable side effects like haemorrhage, local infection, and radiculopathy. Numerous academic institutions are actively developing various siRNA-loaded nanocarriers with the aim of delivering them directly from the nose to the brain, targeting specific areas like the striatum and cerebral cortex. This approach is intended to overcome delivery challenges (Sava et al., 2020). Subsequent research into the same area revealed that treatment with selenium nanoparticles led to a decrease in HDA mRNA levels compared to epidemic levels. Additionally, it reduced HTT aggregation and in vivo ROS levels in a transgenic Caenorhabditis elegans model of Huntington's disease. Selenium nanoparticles functioned as antioxidants, regulating the expression of the HDA family. In stressed C. elegans, concentrations of nano-Se below 2 M mitigated behavioral dysfunction, prevented neuronal death, and provided protection (Cong et al., 2019, 34725). Consequently, Nano-Se holds promise for a significant role in future HD treatment.

1.6.4. Multiple sclerosis

1.6.4.1. Demyelination of the neurons is a hallmark of MS.

The myelin sheath that shields the neurons is harmed during the demyelination process. MS is an autoimmune disease that results in demyelination from T and B cells attacking the nervous system. Younger people are more likely to have this condition, and women are more severely affected than men. Demyelinated neurons and inflamed CNS tissue are signs of this condition (Gurav et al., 2019, 16). The disease is difficult to diagnose because it is non-specific. Although there are many imaging and diagnostic methods available, the agents cannot cross the BBB and lose their potency in the middle of delivery. These traditional techniques for imaging and locating lesions are affected by the effectiveness of the field, imaging-related factors, and contrast agent dosage (Sardanelli et al., 2003, 658).

Nanotechnology is a fantastic alternative for MS diagnosis and treatment. To detect cellular inflammation, smaller contrast agents can now more easily get to the target region. In general, neuroprotective, anti-inflammatory, or both functions are performed by nanoparticles. It was found that liposomes could be used to treat MS. The antibodies production against myelin basic protein (MBP) is one of the main causes of MS. Mannosylation could be applied to liposomes containing MBP fragments to lessen the activity of the anti-MBP. As a result, mannose may be taken up by macrophage receptors (Agrawal et al., 2017, 260). The surface conjugation of glucose, transferrin, specific peptides, lactoferrin, and other compounds may enhance the liposomes' ability to bind to the targeted site. Because of their surface conjugation, liposomes can deliver drugs to the target site while crossing the BBB. Dendrimers are additionally efficient against MS. They are efficient in treating MS because they can influence the astrocytes and microglial cells that cause inflammation (Dai et al., 2010, 1317).

Fluorescent phosphorhydrazone dendrimers may be helpful in the treatment of MS because they have anti-inflammatory properties, claims a study [46]. In addition, gadolinium-DTPA (Gd-DTPA), quantum dots (QDs), and super paramagnetic iron oxide nanoparticles (SPIONSs) have been utilized for the detection of inflammation in MS. When used to target CD4 cells, the LIF-Nano nanoformulation of poly (lactic-co-glycolic acid) (PLGA) has been shown to have a 1,000-fold increase in potency. In a recent study, LIF-NanoCD4 was utilized with the ultimate goal of addressing the inflammatory lesions associated with multiple sclerosis (MS). Additionally, it was found to pass the blood-brain barrier, causing the brain's frontal cortex to launch cargo-specific anti-inflammatory reactions (de la Flor et al., 2021). According to a study (Qiu et al., 2019, 1070), fluorescent phosphorhydrazone dendrimers may be useful in the treatment of MS due to their anti-inflammatory properties. Moreover, nanoparticles like gadolinium-DTPA (Gd-DTPA), quantum dots (QDs), and superparamagnetic iron oxide nanoparticles (SPIONSs) are commonly employed for detecting inflammation in multiple sclerosis (MS). Specifically targeting CD4 cells, the LIF-Nano formulation of poly (lactic-co-glycolic acid) (PLGA) has exhibited a 1,000-fold increase in effectiveness. This LIF-NanoCD4 was utilized in a recent study aiming to address the inflammatory lesions associated with MS. Notably, it was observed to traverse the blood-brain barrier, triggering specific anti-inflammatory responses in the brain's frontal cortex (de la Flor et al., 2021).

1.6.5. Amyotrophic lateral sclerosis (ALS)

ALS is also known as motor neuron disease. It is a neurological condition that affects both lower and upper motor neurons, resulting in firstly weak muscles and then paralysis. Its aetiology is influenced by intricate molecular, cellular, and genetic pathways (Hardiman et al., 2017). ALS can be classified as familial (FALS) or sporadic (SALS) depending on the family history. Normal protein functions can become abnormal as a result of genetic mutations. Over 20 genes have been linked to ALS, with mutations or variations in fus, c9orf72, tardbp, pfn1, or Sod1 accounting for 60–70% of familial ALS (FALS) cases and 10% of sporadic ALS (SALS) cases (Chia et al., 2018, 94).

There is currently no effective treatment for ALS due to a number of difficulties, including the drugs' own significant inherent characteristics and overcoming biological barriers like the blood-brain barrier (BBB) and blood-spinal cord barrier. Nevertheless, nanoparticles offer an effective means to deliver therapeutic agents, surmounting biological barriers, enhancing drug stability, and facilitating interaction with target sites. These materials are employed in nanotechnology-based strategies. Studies on ALS have demonstrated that miRNAs deregulate the pathways, and interventions have been developed to address abnormal miRNA expression (Niccolini et al., 2021, 126).

Numerous viral and non-viral vectors have been developed to overcome biological barriers. However, the non-viral system is preferred due to its lower incidence of side effects and fewer size restrictions on nucleic acids. Despite the higher transfection efficiency of the viral system, non-viral components, such as extracellular vesicles and polymeric, inorganic, and lipid-based vectors, are widely utilized. Nanoparticles stand out as the primary non-viral transporters for delivering exogenous nucleic acids. Among them, two-dimensional graphene emerges as a promising option for treating ALS. Moreover, when nanoparticles are engineered to smaller sizes, like carbon graphene nanoparticles, they can effectively traverse biological barriers such as the blood-brain barrier (BBB) (Niccolini et al., 2021, 126).

1.6.6. Schizophrenia

Psychological symptoms of schizophrenia contribute to the patient's abnormal reality perception. Its hallmarks include hallucinations, delusions, and a clear disordering of the patient's thought process. Insomnia or excessive sleeping, depression, social withdrawal, and strange speech

patterns are some of the illness's early warning signs. Schizophrenia patients frequently need ongoing care because of their disabilities. The aetiology and associated morbidity are still being looked into. The anti-psychotic drug sulpiride, a modified benzamide with specific dopa minergic blocking activity, may be useful in the treatment of schizophrenia, according to a recent study. The study's primary goals were to explain the sulpiride receptor and describe the molecular profile. Another goal was to develop a PNP that uses chitosan as a carrier and provides advantages such as controlled drug release, improved stability and solubility, increased utility, and lower toxicity (Kecel-Gunduz et al., 2019, 104).

1.7. Limitations and future directions

Individualized drugs and intriguing new approaches to the treatment of CNS diseases have both been made possible by recent advancements in nanomedicine. The BBB must be regarded as a successful route for the delivery of medications. The BBB must be regarded as a successful route for the delivery of medications. The BBB can be breached by therapeutic drugs that are carried in carriers designed to diffuse across brain tissue, target specific cells through signalling mechanisms, and penetrate the BBB (Menon et al., 2012; Sharma et al., 2007, 245).

Nanomedicines offer potential for effective drug administration due to their larger surface area, organic or inorganic composition, and possibly ionic surface charge, facilitating favorable drug interactions. They may also provide precision in targeting through intricate formation. Pharmaceutical delivery methods based on nanotechnology have been a primary focus in the treatment of CNS illnesses. Although numerous nanodrugs are under research trials, their delivery methods and safety remain uncertain (Spuch et al., 2012, 2; Dinda et al., 2013, 1264).

Due to oxidative stress, BBB instability, and amino acid breakdown, there may be an increase in brain neurotoxicity as a result of the properties and makeup of nanoparticles. Functionalized nanoparticles still provide efficient therapeutic localization despite having a large surface area and a compact shape that may lead to particle aggregation and limit drug loading. The drug delivery system and dosage of the nanomedicine may cause increased neuroinflammation, oxidative stress, DNA damage, and allergic reactions (Vega-Villa et al., 2008, 929). Understanding how biocompatible and biodegradable nanomedicine is therefore crucial. In order to comprehensively determine the toxicity of nanoformulations in humans, it is crucial to create and execute standardized tests that assess toxicity in both in vitro and in vivo research settings. To be effective, nanomedicine requires

systemic neural communication. The complex cellular interactions and constrained anatomical accessibility at the neuronal level may make drug delivery more challenging. It is very challenging to maintain the vital CNS processes as they were prior to drug administration. For instance, some microbes that are classified as living organisms have characteristics like effectiveness, biological reasonableness, toxic effects, and biocompatibility (Daima et al., 2014, 758). According to research results, a large number of multifunctional nanomaterials have revealed extraordinary challenges that must be quickly overcome both regulating and changing. Research in nanotechnology encompasses a range of intricate subjects, including pharmaceutical cargo packaging, drug delivery to the brain, deep brain stimulation (DBS), implantation stimulation, and the functioning of brain cells (Kumar et al., 2022, 1180).

Characterizing and manufacturing nanomaterials are crucial stages to prevent unintentional toxicity to healthy cells during medication administration. These advancements are anticipated to streamline the development of future treatments, specifically customized to address the extent of neurodegeneration in patients. A few other nanoformulations, like organic or inorganic nanocarriers, are also being researched in preclinical studies to decrease the risk of cancer and lengthen lifespan (Gonzalez-Valdivieso et al., 2021, 599). The NanoTherm® therapeutic, which also utilises ferrofluid made up of SPIONSs, was developed by the German company Magforce. According to claims made by these nanoparticles (Nehra et al., 2021, 224), radiation and magnetic hyperthermia can both kill cancerous cells. The characterization and production of nanomaterials are crucial to avoid unintentional toxicity to healthy cells during medication administration. These advancements are expected to facilitate the development of future treatments, particularly tailored to the level of neurodegeneration present in patients. A few other nanoformulations, like organic or inorganic nanocarriers, are also being researched in preclinical studies to decrease the risk of cancer and lengthen lifespan (Gonzalez-Valdivieso et al., 2021, 599). The NanoTherm® therapeutic, which also utilises ferrofluid made up of SPIONSs, was developed by the German company Magforce. According to claims made by these nanoparticles (Nehra et al., 2021, 224), radiation and magnetic hyperthermia can both kill cancerous cells. Another indication is magnetic-electro nanoparticle-driven neural stimulation, which may eventually play a significant role in implantable DBS therapy. To address tissue and cellular brain functions across different areas, this nanosystem can be engineered to induce magnetothermic, acoustoelectric, magnetoelectric, photothermal, and photoelectric processes. These excitatory and stimulating attributes can be

regulated to match the requirements of brain tissue or cellular responses (Kujawska et al., 2023, 129).

1.8. Conclusions

Rising cases of CNS disorders like ALS, AD, PD, brain tumors, and MS are linked to environmental degradation and lifestyle changes. The impermeability of the blood-brain barrier poses challenges for medication delivery. Developing efficient carriers for targeted drug delivery is crucial. Integrating nanotechnology into neuroscience research offers potential solutions to this problem. Nanomedicine allows precise drug delivery and controlled release, improving treatment efficacy. Despite concerns about adverse effects, advancements in nanotechnology warrant exploration. By adhering to safety guidelines, nanotechnology can revolutionize pharmaceutical delivery, offering more effective treatments.

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CHAPTER TWO

MITOCHONDRIAL CHANGES IN NEURODEGENERATIVE DISEASES

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Abstract

Mitochondria are integral organelles within cells where most energy production occurs via the oxidative phosphorylation system. Alterations in the mitochondrial respiratory chain and mitochondrial genome have been reported in several diseases. Alterations in mtDNA also play a role in age-related neurodegenerative diseases such as Parkinson's disease (PD), Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), and multiple sclerosis (MS). This chapter focuses on an overview of the current state of knowledge on this topic.

Keywords: Mitochondria**,** neurodegenerative diseases

Introduction

The center of energy metabolism is mitochondria. Today, mitochondria, with its role in neurodegenerative diseases, are one of the main research resources. Mitochondrial biogenesis plays a major role in the pathogenesis of diseases caused by problems in the neurodegenerative system such as Parkinson's disease, Alzheimer's disease, Huntingon's disease, and amyotrophic lateral sclerosis, with modifications of nuclear genes encoding mitochondrial proteins (Xu et al., 2021).

Mitochondria are one of the organelles found within the cell and have their own circular genome. The mammalian mitochondrial genome is 16.6 kilobases long and consists of 37 genes. These genes include ribosomal RNAs, transfer RNAs, and proteins important for the electron transport chain. The mitochondrial genome ensures that mitochondria are capable of independent replication. Mitochondria contribute to cellular energy production processes and are an important research topic in genetics (Mercer et al., 2011, Rackham et al., 2011).

Mitochondrial function is regulated by both intrinsic factors in the mitochondrial genome and extrinsic factors in the nuclear genome. The mitochondrial genome, which controls many of the important processes within mitochondria, specifically governs some of the oxidative phosphorylation. However, most mitochondrial proteins are encoded by the nuclear genome located in the cell nucleus. These proteins participate in mitochondrial function by being transported to the mitochondria with specific targeting sequences. Proteins encoded by the nuclear genome regulate mitochondrial function by participating in mitochondrial processes and metabolic pathways. This cooperation creates a balance that affects important functions of the cell, such as energy production, metabolism regulation, and adaptation to cellular stresses (Mottis et al., 2019).

In this section, we will learn about neurodegenerative diseases, the mitochondria associated with these diseases, their structure and functions, and the studies done so far.

2.1. What is Neurodegeneration?

Neuron and glia cells are the two basic cells that make up the central nervous system (CNS). Glia, which are more numerous than neurons, are involved in CNS homeostasis. Neurons are responsible for transmitting information. Neurodegeneration begins due to the deterioration of CNS homeostasis (Guerreiro et al., 2020).