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REVIEW ARTICLE

Recent Advances in Nanoparticles in Diagnosis and Treatment of Neurodegenerative Disorders

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ABSTRACT

Neurodegenerative disorders (ND) are defined by the rapid losses of neuronal structure or function. Alzheimer's disease, Parkinson's disease, and prion disease are a few examples of neurodegenerative disorders. Finding appropriate medicines is critical in the treatment and prevention of ND disorders. The blood brain barrier (BBB) is the main restriction to reach the drug at the site of action in the brain. Because of passive diffusion, small molecules such as ethanol, CO2, and barbiturates can easily flow through the BBB. The use of specialized medication carriers, such as nanoparticles (NP), can increase cargo passage across the brain barrier.in this paper various nanoparticles have been investigated which can cross the BBB so that there is proper drug delivery at the exact site of action in the brain. Some engineered NP with size less than 100 nm provide beneficial potential for fixing these biomedical and pharmacological concerns due to their special physicochemical characteristics and strength to cross BBB. Several inventions have done in last few decades that helps to improve CNS drug delivery. Various systems have remarkable potential for clinical applications. Metallic Nanoparticles have received a huge attention because of their ability to quickly pass through BBB and accumulate in the brain. These NPs are commonly used for imaging CNS delirium. They are well-known for their anti-inflammatory and theranostic properties. Organic compounds and lipids can also be used as nanomedicines delivery vehicles. Nanoparticles are ideal for immunotherapy due to their opposition to extremely high pH and their ability to bind to specific targets.

Keywords*: Neurodegenerative disorders, Nanoparticles, Treatments, Diagnosis, BBB*

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INTRODUCTION

ND are feature by a gradual losing of neuronal structure or function., which is frequently accompanied by neuronal loss. Alzheimer's disease (AD), Parkinson's disease (PD), prion disease (PrD), and amyotrophic lateral sclerosis (ALS) are only a few of the diseases [1]. WHO estimates that the people diagnosed with ND diseases will triple in coming 30 years because of fast expansion of the senior people [2,3]. In treatment and prevention of neurodegenerative illnesses, finding effective therapeutics is crucial. NP, which are very tiny particles (1–1000 nm), have been used to diagnose and cure cancers and neurological illnesses, resulting in new therapeutic strategies [4,5]. In the culinary, electronics, and medical industries, nanoparticles offer a wide range of applications [6] Nanoparticles with a surface area of less than 100 nm have a greater surface area and are better able to react with organic and inorganic compounds [7]. NP has increased their applications in tumor imaging, cancer biomarkers and biomolecules, nerve cell inflammation, and targeted medication administration [8]. Drug stabilization, particularly enzymatic drug stabilization, improves the stability of polymeric nanoparticles against heat, pH, proteases, and other

structurally damaging stimuli. Nanoparticles are now proven to be capable of eliminating inflammatory molecules in normal cells without causing any negative effects [9]. Several NDs have been thoroughly explored, but despite significant advances, effective early diagnostic and treatment techniques remain limited. Among the most prominent barriers is the BBB, which restricts chemicals from entering the brain. Inside the current level of disease imaging and treatment options, the majority of drugs and imaging agents have negative side effects in the peripheral area [10]. To have the greatest impact on illness results, immune activators or drug should access CNS and thereby cross BBB. The BBB is substantial hurdle to medication delivery because of its structure and functional complexity [11,12]. The aims of the study are to develop therapeutic approaches that delay or stop the progression of human CNS illness. It will require expertise in biomedicine such as (neuroscience, immunology, pathology and imaging of molecules)) as well as materials, biomaterials, and pharmaceutical sciences [13]. Despite the fact that there has been numerous analysis of administrated drug to brain in current days, none of latest important research use cell or nanomaterial with polymer incorporation in central nervous system delivery are described. Talks have been undertaken in this regard to explain illness and requirements, and also novel nanoparticle - based research activities. This was done in the aim of enhancing neurodegenerative disease detection and therapy [14,15].

NEURODEGENERATIVE DISORDERS

As neurons are involved in communication, they are important for the healthy functioning of the brain [16,17,18]. Although the majority of neurons originate in the brain, they can be found throughout the body [19,20]. Most neurons are generated by neural stem cells during childhood, but their number decreases dramatically as adults [21]. As neurons are not eternal, neurodegeneration, or Chronic loss of neurons, neuron structures, or functions has serious Issue for healthcare system and is at core of the pathophysiology of a variety of brain illnesses [22]. Synapse dysfunction, neuronal dysfunction, as well as adhesion of modified protein variations in brain have all been related to neurodegeneration [23,24]. Neurodegenerative disorders (NDs) are a collection of illnesses that all have neurodegeneration as a common trait [25,26]. The most prevalent neurodegenerative illnesses are AD prion disease, ALS, HD, motor neuron disease, spinal muscular atrophy, PD, and spinocerebellar ataxia [25,27,28]. Millions of people around the world suffer from neurodegenerative diseases. A person's age is the most important risk factor for developing Neurodegenerative Disorder. But a person's genetic profile and environmental factors can also increase the risk of developing ND, according to new research [29]. The speed and severity of neurodegeneration are largely determined by their immediate surroundings [30]. Recent research suggests that a single neurodegenerative disorder may be characterised by multiple pathologies [31,32]. As a result, NDs can be very serious, even life-threatening in some cases; however, this is solely dependent on the stage and type of the disease. Because the brain is in charge of so many aspects of body function, neurodegenerative diseases are common. As a result, diseases affect many facets of human functions, reducing one's ability to execute both simple and complex tasks (e.g., speech, movement, stability, balance, bladder or bowel functions, as well as cognitive abilities). The majority of NDs make progress without any remission, while in some cases, treatments are aimed at improving symptoms and relieving pain. If pain is present, it may be treated, as well as the restoration of balance and mobility [33]. Neurodegenerative diseases and the types of neurons affected is shown in figure 1.

Alzheimer Disease (AD)

It is the most prevalent neurological illness that results in progressive loss of cognitive functions. This disease is defined by the presence of two neuropathological brain lesions: intracellular hyperphosphorylated tau protein deposits and extracellular A protein [34,35]. According to new research, the accumulation of amyloid-β and tau proteins is essential in progression of the illness [36,37]. The production of Aβ—containing plaques in the brain, coupled to hyperphosphorylated tau of which neurofibrillary tangles (NFTs) is composed, which has been recognized as a characteristic hallmark of AD [38,39]. Plaque development impairs hippocampal circuitry, resulting in poor consolidation of short-term memories which generate long period signs [40]. Alzheimer disease is characterized by neuronal loss, impairment of the essential neurotransmission that is required for brain processes, incorrect synaptic connections, and, particularly memories. As a result, selective memory impairment is the most prevalent clinical sign in early-stage AD. Activities requiring the hippocampal and middle temporal lobes, such as declarative episodic memory, are frequently impaired. Other pathological changes that commonly appear early in the illness process include, judgement, executive function dysfunction, and dilemma [41]. There is presently no treatment for Alzheimer's disease, just palliative methods (tacrine, rivastigmine, etc.) slows the growth and enhance the patient’s performance, which opens way in nanosciences, particularly PLGA NPs [42].

Parkinson Disease

Muscle spasms, muscle rigidity, a shaky gait, and difficulties with postural control are all symptoms of this degenerative neurological condition. PD is caused by both genetic and non-genetic factors. The primary risk factor for Parkinson's disease is age [43,44]. Other factors that have been linked to the development of this disease include high coffee consumption, cigarettes, and being exposed to environmental pollutants [45,46]. Despite the fact that the exact mechanism is still unknown [47,48]. Deterioration of frontal pallium and hypertrophy of the ventriclest are two important common symptoms of Parkinson disease. In Parkinson's disease, cell destruction causes nigrostriatal pathway's impairment, resulting in lower dopamine levels in the striatum and also cardinal motor illnesses [49]. Cell destruction causes non-motor symptoms in PD. Misfolding and aggregation of synuclein, mitochondrial failure, defective protein clearance systems, neuroinflammation and neuroprotection are all implicated [50]. Cell loss in raphe nuclei, nucleus basalis of Meynert, the locus coeruleus, pedunculopontine nucleus, hypothalamus, dorsal motor nucleus of the vagus nerve, and olfactory bulb is main hallmarks in disease [51]. The occurrence of Lewy bodies within neuronal cell bodies, as well as neuronal loss, are microscopically indicative of PD [52,53].

Amyotrophic Lateral Sclerosis (ALS)

ALS or Lou Gehrig's disease, also known as motor neuron disease, is a degenerative neurological and spinal cord disease ultimately causes paralysis and muscle weakening [54,55]. Motor neurons deteriorate gradually before dying in ALS. Messages that should be transmitted to the brain aren't getting through when motor neurons are damaged or dead. ALS has been related to more than 30 genes, whereas mutations in 4 key gene such as (C9orf72, TARDBP, SOD1, and FUS) responsible over seventy percent patients [56]. 4 of this genes code for proteins which help in, homeostasis, mitochondrial functioning, DNA repair, and glial cell activity, among other things. Both of this defective mechanism is believing as cause for formation of motor neuron seen in this. The formation of intraneuronal protein aggregates is a pathogenic characteristic of disease. In many ALS patients, the TAR DNA-binding protein is the most abundant protein [57].

Huntington's Diseases

HD is a congenital and inherited condition as a result of a genetic changes in IT15 gene which causes the CAG trinucleotide, usually specified for the huntingtin protein, to spread. George Huntington was the first to describe it in 1872 [58]. Progressive motor example (involuntary jerking called as Chorea, stiffness, Muscle contraction etc.) behavioral (memory loss, complication in organizing and acquisition of knowledge), mental illnesses (irritability, insomnia) this HD symptom usually occur in the age of 30 and 50 years old [59,60]. In advanced cases of HD, these issues are the loss of striatal neurons in the striatum hippocampus, cortex and in different brain areas such as subthalamic nucleus, thalamus, *substantia nigra* and pars reticulate has been linked to this problem [61,62].

Multiple Sclerosis

MS is neurodegenerative illness that affect the CNS, mostly brain, spinal cord and nerves [63]. A number of bioactive molecules limiting threats and postponing the growth of disease have now been authorized by government organization. Indications vary by region of the attack: leg paralysis, visual issues, electric startle like feelings in body parts, loss of coordination, and so on. PLGA NPs may be used to vectorize a few of them to treat some MS symptoms [64].

CHALLENGES OF BRAIN-DRUG DELIVERY [BDD]

Instead of addressing the fundamental causes, ND treatment aims at reducing the disease's progression. The ability of NDs to act successfully is restricted by their ability to deliver adequate dosages to the brain [65].

Blood–brain barrier (BBB)

The diffusion barrier i.e. BBB stops the molecules or compounds present in the blood from reaching the brain, allowing for healthy brain function and homeostasis [66]. The BBB, which is a physically tight brain capillary, is formed by the fusion of several brain cells [67]. Tiny molecule protein diffusion is restricted within brain capillary endothelial cells due to a lack of openings [68,69]. Inter-endothelial junctions connect the endothelial cells to a continuous barrier, preventing the transport of water-soluble substances [70,71]. The basal lamina, astrocytes, and pericytes surround the endothelial cells, preventing drug compounds from reaching the brain through the blood [72]. Efflux transporters, which are found in the brain capillaries, add to the barrier's strength by returning molecules that return to the circulation after entering the brain [73]. Gap junctions, tight junctions and adherens junctions are examples of inter-endothelial junctions, which are protein complexes, that also regulate the BBB's permeability function. Molecules that cross the BBB travel in one of two ways: paracellular or transcellular [74]. The physicochemical features of substances that allow them to cross the blood brain barrier are size, surface

activity, lipid solubility, molecular weight, and charge. Small substances (including ethanol, CO2, and barbiturates) can effortlessly traverse the blood brain barrier due to passive diffusion. Transferrin receptor, Insulin transporters, and glucose transporter-1(GLUT-1) are examples of receptor-mediated transport mechanisms and also aid hydrophilic molecules like peptides and proteins in their transport [75]. Furthermore, a few pathological conditions are well known for causing problems in BBB's tightness, allowing substances to leak into the brain. Finally, using specialised drug carriers like nanoparticles can improve cargo transport throughout the blood brain barrier [76]. Different types of transporters and drug transport ways are shown in figure 2 of BBB

Pharmacokinetic effect on BDD

The effectiveness of routinely delivered medicines substantially shown by pharmacokinetic properties [77]. Trip from the site of delivery to the site of action (in this example, the brain) is long and usually does not provide any benefit to bioactive agent. Presence of distinct plasma proteins contained is initially focused. Some medications bind firmly to these proteins, reducing the quantity of free drug accessible for delivery to the brain and hence decreasing the quantity of drug in circulation [78]. The amount of drug that can be absorbed is limited by the interaction between the drug and the target cells. Small lipid soluble compounds are appropriate for BDD [79]. The inhibition of channels, an alteration in membrane permeability, can all occur as a result of drug components acting on cells [80].

NANOPARTICLES APPROACHES IN NEURODEGENERATIVE DISEASE

As a result of advancement in nanomedicine, a range of technologies that increase medication transport across the BBB have been developed. In stroke, PD, ALS, HD, AD, and spinal muscular atrophy, nanotechnology can assist in improving sensory motor and cognitive skills. Because of the nanomaterial's unique features, as used with another treatment help to boost effectiveness of cell-based therapy. In stem-cell niche, nanoparticles interact with proneurogenic factors, boosting endogenous and exogenous brain stem cell self-renewal, proliferation, and differentiation. Nanotechnology techniques have significant effects in stem-cell investigations, leading to the huge proliferation of stem cells, which is one of the key advantages of nanotechnology techniques. The progress of neurodegenerative disease therapies is governed by the amplification of neuronal cells, which is a vital indicator [81].

Commonly studied np types for the treatment of neurodegenerative illnesses are shown in figure 3

Inorganic Nanoparticles

Metal nanoparticles have attracted a lot of attention because of their capacity to easily pass BBB to further accumulate in brain. Because of their propensity to smoothly pass the blood brain barrier and pile up in the brain, they have piqued researchers' curiosity. For effective brain targeting, their numerous features, including surface changes, size, and stability, can be smoothly controlled. Metal NP are routinely prepared with different ligands, example proteins etc. to increase medicine administration to the central nervous system. These NPs were renowned as anti-inflammatory and theranostic capabilities. Silver, Gold, and cerium NPs are commonly used metallic nanoparticles for imaging CNS delirium [82].

Gold Nanoparticles

In CNS imaging and targeting, gold nanoparticles (AuNPs) have been widely exploited [91]. Because the core has plasmonic properties, they are well suited for Micro-CT scanning or X-rays used in imaging applications. AuNPs are more effective than traditional materials at absorbing and reducing X-rays. In a recent study, Poly-L-lysine (PLL) and Rhodamine B isothiocyanate (RITC) were chelated with gold nanoparticles of 40 nm NP absorption in patient mesenchymal stem cells was increased as a result of these changes (hMSCs). This Au-labelled hMSCs was injected in brains of rats and examined for 30 minutes using micro-CT. When used in addition with cell imaging, they have showed huge effect for identifying, eliminating amyloid clumps in vitro. The AuNPs' cores were coupled with apolipoproteins E3 (ApoE3), which enhanced their coupling with amyloid clumps and increased their penetration of brain. Researchers employed curcumin as a sensor to monitor these AuNPs [83].

Silver Nanoparticles (AgNPs)

The researched has been done on use of AgNPs for medication delivery to brain. After administration, silver NPs deposits in the hippocampus, called as key location for neurodegenerative disorders. In mice's brain cells, a 5g/mL dosage of these nanoparticles induced an inflammatory and neurodegenerative gene expression response. Silver nanoparticles helps to target range of therapeutic agent to the brain, including alisertib, which is used to treat glioblastoma, and anti-amoebic pharmaceuticals, which are used for treatment of amoebae that eat the brain. Another study found that citrate-capped AgNPs have anti-inflammatory and antioxidant activities in the brain immune cells. Microglia absorbs these AgNPs preferentially, resulting in the development of enzymes that reduced oxygen species which is reactive and had anti-inflammatory effects. AgNPs, on the other hand, have the drawback of disrupting the blood brain

barrier by loosening the tight junctions. By collecting inert silver over time, they appear to trigger ND and necrosis in brain [84].

Cerium Oxide Nanoparticles

The effect of cerium oxide nanoparticles on decreasing oxygen species (ROS), which has been related to neuronal death and NDs, is well-known. The remarkable antioxidant property of these nanoparticles is due to the change in state of oxidation between Cerium+3 and Cerium+4. When combined metal chelators or polyethylene glycol coats, these nanoparticles have been demonstrated to diminish A-aggregation and delay the impact of apoptotic in AD in cells of neuronal via modifying the neurological factor and pathway of signal transduction. In addition, cerium oxide nanoparticles have been found to efficiently absorb peroxynitrite ROS in stroke models in ischemic to repair motor functioning of the legs in MS as well as amyotrophic lateral sclerosis mouse model. Many preparations based on nanoparticles with neurogenesis potential has recently been reported. The neurogenesis efficiency of cerium dioxide (CeO2) nanoparticles was investigated by Zavvari et al., 2020. They reported that a single dose of CeO2 nanoparticles was sufficient to trigger neurogenesis in the hippocampus area. This is attributed to cerium oxide's anti-inflammatory and neuro-regenerative properties [85]

Organic Nanoparticles

Due to their greater biocompatibility to inorganic materials, naturally found substances, like organic compounds and lipids, could be employed as nanomedicine delivery vehicles. Furthermore, a lipid nanocarrier is more successful than free-drug delivery at preventing degradation of the medicinal substance, lowering toxicity, and improving biocompatibility [86].

Liposomes

Liposomes have been the most widely studied of the many lipid carriers for targeted brain delivery. Phosphatidic acid and mApoE containing liposomes were created for improvement in transport across the blood brain barrier and target A accumulates with strong affinity. In vitro, this liposomal preparation was not able to accumulate A fibril. The amino acid residues with positively charged on the A engage with the negatively charged phosphatidic acid, on the other hand mApoE reacts with area of the same which is negatively charged. In current work, surface-modified liposomes were created by group for brain-targeted administration of plasmid DNA with ApoE2-encoding. Mannose was utilised as a targeting ligand, combined with a CPP to improve brain targeting and cell level internalisation. In same way, when compared to plain liposomes, transferrin and RVG modified liposomes showed improved absorption in brain, neurons, astrocytes and endothelial cells. Rodriguez et al. found that modification of surface of liposomes with transferrin and CPP is enough for increasing liposome permeability in brain in mice after an injection given intravenously [87].

Optimised Brain-Targeting Liposomes: In vivo animal models and in vitro blood brain barrier models, optimal brain-targeted liposome modified by mannose or RVG, penetratin or CGN peptide provided VGF. Researchers discovered increasing about from 1.5–2 folds in mice treated by in functionalized -liposomes than control mice (a group of mice that were not given any treatment) [88].

Solid Lipid Nanoparticles (SLN)

In addition to liposomes, solid lipid nanoparticles (SLN) have been employed to transport medicines to the brain to treat a variety of NDs. Intranasally given Rosmarinic acid-loaded SLNs were used to treat the behavioural dysfunction in HD [89].

Nanomicelle

For delivering a variety of therapeutic drugs polymer coated nano micelle as a vehicle have proven promising effect. Functionalized chitosan nanomicelles have recently been shown to be capable of introducing cells in the brain at an appropriate dose. Easily disposable, nontoxic at the doses utilised, versatile in terms of surface modification are all advantages of this delivery Because of these benefits, medicines, proteins, DNA, and even antibodies can all be delivered to the brain via this transporter [99]. Xue et al. has shown that chitosan conjugated NP is greatly reduced in vitro by-syn aggregation, as well as this chitosan can be utilised in a variety of applications to improve distribution across the BBB by conjugation with other polymers [90].

Polymeric Formulations

Among the various polymeric formulations used to create NPs, (PLGA) have seen widespread use in brain-controlled and targeted drug administration. This biocompatible, disposable polymer is an ideal carrier system for treating NDs because it has customizable degrading rates, a large drug carrying ability, and the ability to penetrate from blood brain barrier to reach the brain. In an investigation, TET1 peptide-coated PLGA NPs were utilised for encapsulation and distribution nattokinase, a hydrophilic medicine to brain. The peptide TET1 has a strong affinity for neurons and that it increased reverse transport. This

preparation enhanced consistency of nattokinase protein, decreased protein accumulation, showing as important treatment for alzheimer disease [90,91].

RECENT DIAGNOSIS AND TREATMENTS FOR NEURODEGENERATIVE DISORDERS

Treatments for Alzheimer disease (AD)

Recently, NP-based techniques for treating Alzheimer's disease have primarily focused on interfering with A aggregation of peptide, in the blood as well as centrally with intention for lowering its brain level (the 'sink effect'). NLs modified with phosphatidic acid or cardiolipin can be used for sink effect which has been found by Gobbi et al. These NL, according to the author, in vitro, has a strong affinity for A and reduces its toxicity. Canovi et al. created NL that was coated with an anti-A monoclonal antibody that had strong affinity for A and ex in vitro in vivo on brain samples with post-mortem from Alzheimer's patients. In vitro, Mourtas et al. created nanoliposomes coated with derivative of curcumin, which bound A with great affinity to inhibits its accumulation [91].

Diagnosis for AD

Nanotechnology also provides methods for early detection of Alzheimer's disease in vitro by assessing recognised pathogenic indicators (such as ADDLs or tau protein) in human CSF at proportions undetectable by standard techniques. Georgeakopoulos et al. developed an ultrasensitive assay, based on gold nanoparticle bio-barcode that determines concentration of ADDL. The Neely et al. used 2 photons scattering with antibody-coated surfaces found that gold nanoparticle is used to detect tau protein. For CSF phospholipid profiling, nano-HPLC-MS has recently become popular and has been utilised for CSF phospholipid profiling, allowing researchers to track lipid changes as a possible new pathogenic factor. Nanotechnology has been used in vivo to identify A deposits in the AD brain. A-coupled iron oxide nanoparticles such as monocrystalline or superparamagnetic, has been studied. MRI was used to identify amyloid accumulation in Alzheimer disease transgenic mice. Roney et al. produce polymer containing n-butyl-2-cyanoacrylate NPs by which 125I-CQ, a radiolabelled amyloid affinity medication, is encapsulated. They show that this nanoparticle has the ability to penetrate from BBB, resulting in increase in their effectiveness and brain absorption in Alzheimer disease transgenic mice with by taking under consideration of controls. Detection of amyloid-beta aggregation in cerebrospinal fluid and serum is done by using fluorescent peptide nanoparticles for AD diagnostic testing as well as growth controlling [92].

Treatment for Parkinson disease (PD)

The treatments of PD are reported using nanotechnology-based techniques to dopamine delivery and release in the brain. Trapani et al. made chitosan NPs with dopamine adhesion. Experiments with animals in a live environment .NP-loaded DA is less effective in rats after i.p. administration. toxin, reaches the brain, and causes an increase in striatum dopamine by itself is less effective. NP has also been used as a vector for transfection. As an alternative to viruses, gene therapy for Parkinson's disease is being investigated. Excessive immune response and mutagenesis are both possible side effects. Using human neurotrophic factor-encapsulated Lactoferrin-modified NP Huang et al. found that the gene improved locomotor performance significantly. Reduced dopaminergic neuronal loss, and increased dopaminergic neuronal activity in brains of PD rats [93].

Diagnosis for PD

Yu and Lyubchenko developed a method for detecting synuclein. A new technique for describing the misfolding and self-assembly of alpha-synuclein that is based on nanomanipulation of a molecule of alpha-synuclein. AFM Baron et al. had previously found in vitro diagnostic test for neurotransmitters involved in the pathophysiology of Parkinson's illness that takes advantage of Au NP and plasmon absorbance. There is currently no information in vivo application of nanomedicine for Parkinson's disease diagnosis [106]. Immune sensing of alpha-synuclein protein in human plasma samples utilizing Au NPs coated with graphene: a novel immuno-platform for early stage PD identification via point of care (POC) analysis [94].

Treatment for amyotrophic lateral sclerosis (ALS)

The transport of various medicines, nutritive agents, and bio macromolecules to the CNS via the BBB/BSCB is a hurdle for ALS treatment. Nanotechnologies may be able to help overcome these limitations. Nanomaterials could be used to provide new DNA, antisense oligonucleotides (ASOs), and RNA for gene therapy, as well as glutamate inhibitors, anti-oxidants, anti-inflammatory agents, Iron chelators, SOD1-loaded (PLGA). HDAC6 inhibitor-encapsulated nanoparticles, stem cell delivery, neurotrophic proteins and chemical molecules help neurons survive and regenerate. To increase therapeutic index of therapeutics, New methods to the difficulty of breaching the blood brain barrier have been developed: Exosomes, glycosylated nano carriers, virus-mimic nanomaterials [95]

Diagnosis for ALS

Some of the techniques used are diffusion tensor imaging (DTI), tractography analyses fractional anisotropy (FA) and proton magnetic resonance spectroscopy (1H-MRS). These techniques have been utilized to acquire a better knowledge of alterations in different regions of brain and in order to determine prognostic and clinical outcome. Decision making is done by neuroimaging. Less fractional anisotropy measurement in the corticospinal tract (CST) and ALS patients with hypermetabolism have a shortest lifespan. Preconditioning (PC) is phenomena in which minor factor causes tolerance to develop later in response to a more severe damage. A sub toxic dose of L-BMAA is employed as a preconditioning stimulus, and NCX3 can used as a new therapeutic target due to its protective impact. Last but not least, iron is regarded as a biomarker. Excess ferritin levels have been shown to worsen muscle deterioration and shorten patients' lives [96].

Therapeutic application of nanosystems in neurodegenerative disorders is shown in table no. 1[97-99]

NANOMEDICINES UNDER CLINICAL TRIAL

A new review of current clinical studies against NDs showed only ten nps formulations in various stages of development. Only one clinical trial for transthyretin-mediated amyloidosis using a lipid nanoparticle-based formulation was already completed and is now available for sale to the general public. The purpose of this research is the use of nanoparticles to deliver APH-1105 against cancer is an exciting new approach. This clinical trial will begin in 2023 and will be open to patient with mild-to-moderate AD. AuNPs-mediated CNM-Au8 technique of delivering, is recently in phase-2 of a clinical investigation. A number of CNM-Au8-Au nanocrystals-based study are at the early phases of development. Phase 2 clinical trials for ALS are also underway [16A]. Nanocarrier-mediated formulation under clinical studies against various NDDs is shown in table no.2 [99,100].

Table 1: Therapeutic application of nanosystems in neurodegenerative disorders [97-99]

Nanocarrier platform	Bioactive agent	Active targeting ligand	Composition
A. Alzheimer disease-			
Liposomes	Amyloid beta binding llama single-domain antibody fragments (VHH-pa2H)	GSH	PEG-EYPC, PEG-DMPC
Polymeric micelles	R-flurbiprofen	FBA, RNA aptamers	PEG-PLA
Polymeric NPs	IAβ5 peptide, Aβ aggregation inhibitor	Anti-TfR mAb OX26 and anti-Aβ mAb DE2B4	PLGA NPs with pluronicF127
Gold NPs	Curcumin	-	Silica-coated Au NPs
Polymeric NPs	Curcumin	Tet-1 peptide	PLGA NP
B. Parkinson disease-			
Polymeric nanoparticles	Urocortin	Lactoferrin	PEG-PLGA NPs, PLGA
Liposomes	L-DOPA, dopamine precursor	Chlorotoxin peptide	HSPC/Chol/DSPE-PEG 20:10:2 molar ratio
SLNs	dopamine agonist Ropinirole	-	Dynasan-114 (solid lipid), soy lecithin (primary surfactant) and poloxamer 188(secondary surfactant)
Zwitterionic polymers	Non-Fe hemin, iron chelators	TAT peptide	PMPC-coated acrylated BSA
C. Huntington disease			
PLGA NPs	Cholesterol	g7 glycopeptide	Polymeric NPs
SLNs	Thymoquinone	-	Stearic acid (solid core), lecithin and taurocholate (co-surfactant)

Table 2: Nanocarrier-mediated formulation under clinical studies against various NDDs [99,100].

Nanocarrier (Composition)	Product (Active Molecules/Class)	Clinical Phase, NCT Number	Indications
NPs	APH-1105 (an α-secretase modulator)	Phase 2, NCT03806478	Dementia, Mild-to-moderate AD,
LNPs (DLin-MC3-DMA; PEG2000-C-DMG; DSPC; and cholesterol)	ALN-TTR02 (Patisiran)	Approved for marketing, NCT02939820	Transthyretin mediated amyloidosis
Au nanocrystals	CNM-Au8 (Nanocrystalline gold)	Phase 1, NCT0408171	Amyotropic lateral sclerosis
Au nanocrystals	CNM-Au8 (Nanocrystalline Au)	Phase 2, NCT04098406	Amyotropic lateral sclerosis
Au nanocrystals	CNM-Au8 (Nanocrystalline Au)	Phase 2, NCT03815916	Parkinson disease

DSPC—distearoylphosphatidylcholine, PEG2000-C-DMG—1,2-dimyristoyl-rac-glycero3-methoxypolyethylene glycol- 2000, DLin-MC3-DMA-dilinoleylmethyl-4-dimethylaminobutyrate.

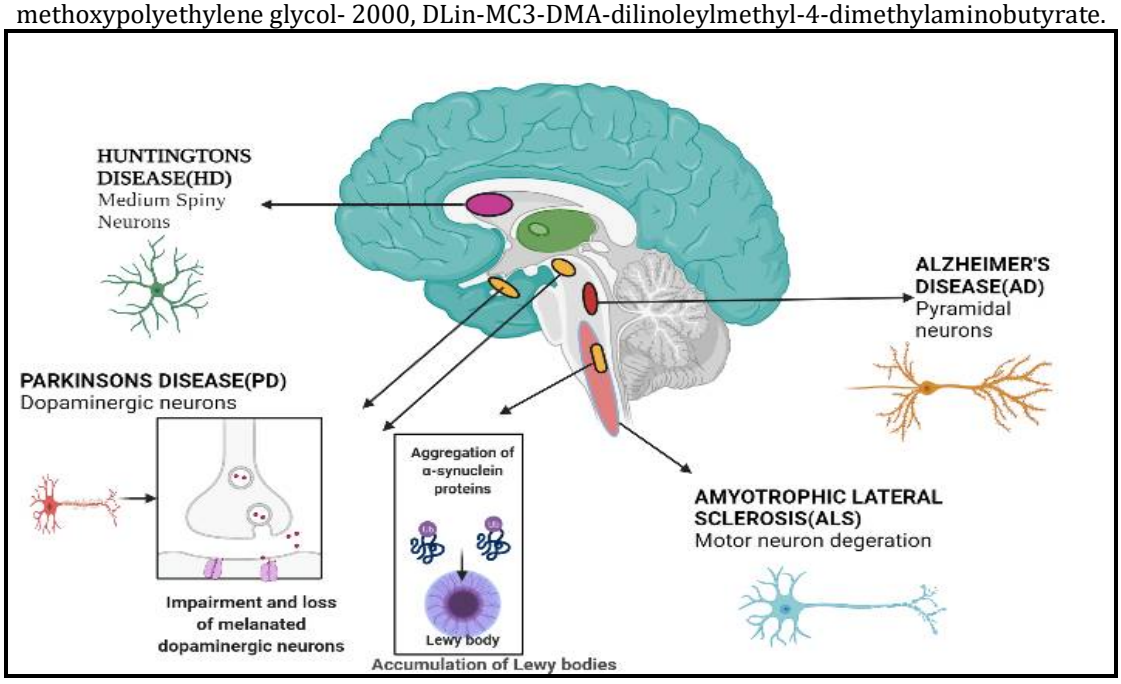
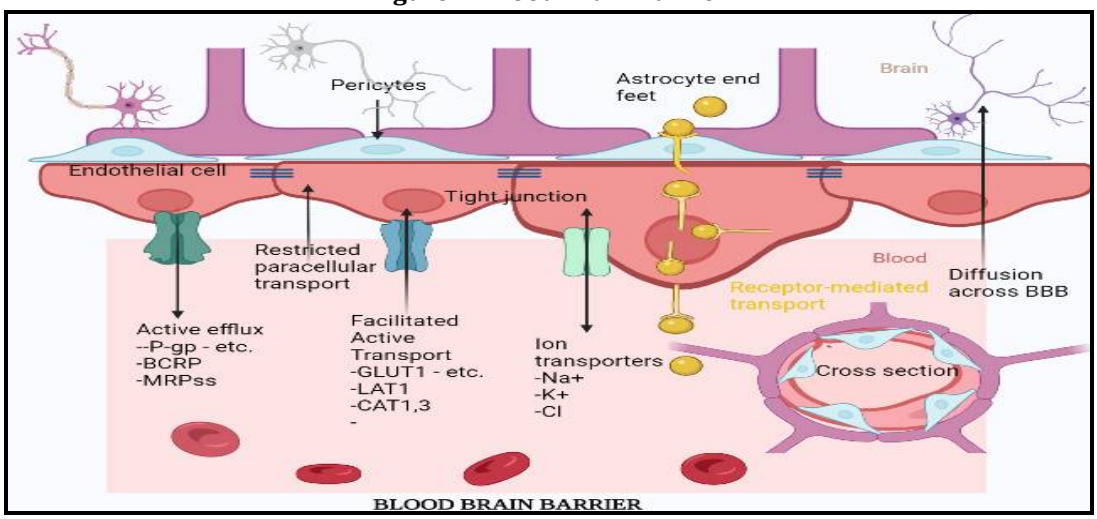


Fig 1: Neurodegenerative diseases and the types of neurons affected

Figure 2: Blood Brain Barrier



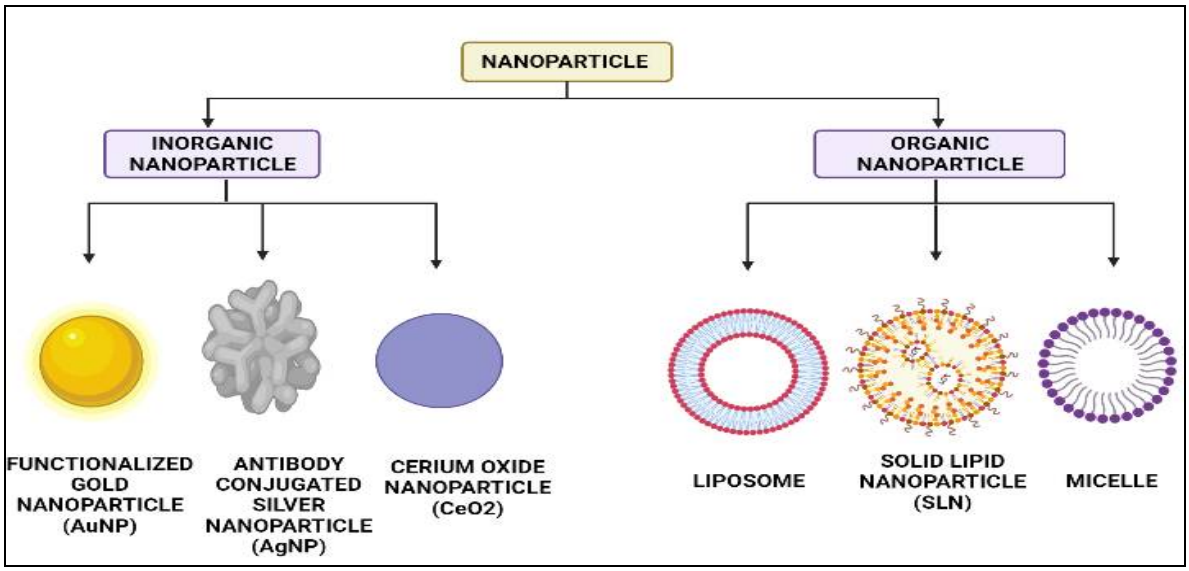


Figure 3: Types of Nanoparticles.

CONCLUSION

Application of nanoparticles is source of hope for NDs, and it has potential to be powerful resource for overcoming the constraints of present and conventional methods of treatment**.** The primary feature of NDs, for example AD and PD, is death of neurons. As a result, so most extensively discussed therapy approach for these illnesses is neurogenesis. Yet, medication transport to brain remains challenging because of some factors such as the blood brain barrier, lipid solubility, and the drug's molecular mass. These factors restrict therapeutic options. Drug potency is reduced, making NDs more difficult to treat. As a result, nanoparticle-mediated nanoparticle-medicine, as targeted delivery of drug to the brain has been investigated for neurogenesis currently. It also provides a potential basis for future therapeutic techniques. Nanoparticles are ideal for immunotherapy as a result of their opposition to extremely high pH and their ability to bind to specific targets. As inflammation plays a crucial role in the development of neurological diseases, there is currently no treatment. There has been no effective therapy for uncontrollable behaviour. Controlling inflammation, rather than suppressing inflammation, will show to be a much effective therapy choice.

REFERENCES

1. Munjar, V. (2021). Ramifications of Nanotechnology on Common Human Disorders. Spectrum of Emerging Sciences, 1(1), 56-60. 10.55878/SES2021-1-1-12
2. Asefy, Z., Hoseinnejhad, S., & Ceferov, Z. (2021). Nanoparticles approaches in neurodegenerative diseases diagnosis and treatment. Neurological Sciences, 42(7), 2653-2660. https://doi.org/10.1007/s10072-021-05234-x
3. Waris, A., Ali, A., Khan, A. U., Asim, M., Zamel, D., Fatima, K., ... & Abourehab, M. A. (2022). Applications of various types of nanomaterials for the treatment of neurological disorders. Nanomaterials, 12(13), 2140. https://doi.org/10.3390/nano12132140
4. Upton, D. H., Ung, C., George, S. M., Tsoli, M., Kavallaris, M., & Ziegler, D. S. (2022). Challenges and opportunities to penetrate the blood-brain barrier for brain cancer therapy. Theranostics, 12(10), 4734. 10.7150/thno.69682
5. Vissers, C., Ming, G. L., & Song, H. (2019). Nanoparticle technology and stem cell therapy team up against neurodegenerative disorders. Advanced drug delivery reviews, 148, 239-251. https://doi.org/ 10.1016/ j.addr.2019.02.007
6. Eftekhari, A., Maleki Dizaj, S., Sharifi, S., Salatin, S., Rahbar Saadat, Y., Zununi Vahed, S., ... & Cucchiarini, M. (2020). The use of nanomaterials in tissue engineering for cartilage regeneration; current approaches and future perspectives. International Journal of Molecular Sciences, 21(2), 536. https://doi.org/10.3390/ijms21020536
7. Namdeo, P., Mathew, J., & Garg, A. (2022). Nanoparticle-mediated delivery of AChE inhibitors for the treatment of Alzheimer's disease. In Nanomedical Drug Delivery for Neurodegenerative Diseases (pp. 223-242). Academic Press. https://doi.org/10.1016/B978-0-323-85544-0.00004-6
8. Caracciolo, G., Vali, H., Moore, A., & Mahmoudi, M. (2019). Challenges in molecular diagnostic research in cancer nanotechnology. Nano Today, 27, 6-10. https://doi.org/10.1016/j.nantod.2019.06.001
9. Tierney, T., Bodnár, K., Rasmuson, Å., & Hudson, S. (2017). Carrier particle design for stabilization and isolation of drug nanoparticles. International journal of pharmaceutics, 518(1-2), 111-118. https://doi.org/ 10.1016/j.ijpharm.2016.11.045

10. Hasannejad-Asl, B., Pooresmaeil, F., Choupani, E., Dabiri, M., Behmardi, A., Fadaie, M., ... & Kazemi-Lomedasht, F. (2022). Nanoparticles as Powerful Tools for Crossing the Blood-brain Barrier. CNS & Neurological Disorders-Drug Targets (Formerly Current Drug Targets-CNS & Neurological Disorders). https://doi.org/10.2174/1871527321666220222092655
11. Modi, G., Pillay, V., Choonara, Y. E., Ndesendo, V. M., du Toit, L. C., & Naidoo, D. (2009). Nanotechnological applications for the treatment of neurodegenerative disorders. Progress in Neurobiology, 88(4), 272-285. https://doi.org/10.1016/j.pneurobio.2009.05.002
12. Dai, R., Zhang, W., Tang, W., Wynendaele, E., Zhu, Q., Bin, Y., ... & Xia, J. (2021). BBPpred: sequence-based prediction of blood-brain barrier peptides with feature representation learning and logistic regression. Journal of Chemical Information and Modeling, 61(1), 525-534. https://doi.org/10.1021/acs.jcim.0c01115
13. Tripathi, P., Shukla, P., & Bieberich, E. (2022). Theranostic Applications of Nanomaterials in Alzheimer's Disease: A Multifunctional Approach. Current Pharmaceutical Design, 28(2), 116-132. https://doi.org/10.2174/1381612827666211122153946
14. Ahmad, M. S., Batool, S., Islam, A., Jabeen, A., Noureen, A., Shamshad, S., ... & Ahmed, W. (2021). Neurological Disorders: Biochemistry of Drug Resistance and Future Challenges. In Biochemistry of Drug Resistance (pp. 255-277). Springer, Cham. https://doi.org/10.1007/978-3-030-76320-6_9
15. Ramanathan, S., Archunan, G., Sivakumar, M., Selvan, S. T., Fred, A. L., Kumar, S., ... & Padmanabhan, P. (2018). Theranostic applications of nanoparticles in neurodegenerative disorders. International journal of nanomedicine, 13, 5561. 10.2147/IJN.S149022
16. Lamptey, R. N., Chaulagain, B., Trivedi, R., Gothwal, A., Layek, B., & Singh, J. (2022). A Review of the Common Neurodegenerative Disorders: Current Therapeutic Approaches and the Potential Role of Nanotherapeutics. International Journal of Molecular Sciences, 23(3), 1851. https://doi.org/10.3390/ijms23031851
17. Rosendale, N. (2022). Social Determinants of Health in Neurology. Neurologic Clinics, 40(1), 231-247. https://doi.org/10.1016/j.ncl.2021.08.012
18. Shephard, E., Batistuzzo, M. C., Hoexter, M. Q., Stern, E. R., Zuccolo, P. F., Ogawa, C. Y., ... & Miguel, E. C. (2022). Neurocircuit models of obsessive-compulsive disorder: limitations and future directions for research. Brazilian Journal of Psychiatry, 44, 187-200. https://doi.org/10.1590/1516-4446-2020-1709
19. Xu, C., Fan, W., Zhang, Y., Loh, H. H., & Law, P. Y. (2021). Kappa opioid receptor controls neural stem cell differentiation via a miR-7a/Pax6 dependent pathway. Stem Cells, 39(5), 600-616. https://doi.org/10.1002/stem.3334
20. Pino, A., Fumagalli, G., Bifari, F., & Decimo, I. (2017). New neurons in adult brain: distribution, molecular mechanisms and therapies. Biochemical pharmacology, 141, 4-22. https://doi.org/10.1016/j.bcp.2017.07.003
21. Pinto, M., Silva, V., Barreiro, S., Silva, R., Remião, F., Borges, F., & Fernandes, C. (2022). Brain Drug Delivery and Neurodegenerative Diseases: Polymeric PLGA-Based Nanoparticles as a Forefront Platform. Ageing Research Reviews, 101658. https://doi.org/10.1016/j.arr.2022.101658
22. Sultana, S., Mitra, R. D., Gawai, J., & Singh, S. (2021). Impact of Exosomes Serving as a Tool for Nano-Science in Neurotherapeutics: Anti-Alzheimers. SAMRIDDHI: A Journal of Physical Sciences, Engineering and Technology, 13(SUP 1), 7-9. https://doi.org/10.18090/samriddhi.v13iS1.3
23. Rahman, M. M., Islam, M. R., Akash, S., Harun-Or-Rashid, M., Ray, T. K., Rahaman, M. S., ... & Wilairatana, P. (2022). Recent advancements of nanoparticles application in cancer and neurodegenerative disorders: At a glance. Biomedicine & Pharmacotherapy, 153, 113305. https://doi.org/10.1016/j.biopha.2022.113305
24. Kovacs, G. G. (2019). Molecular pathology of neurodegenerative diseases: principles and practice. Journal of clinical pathology, 72(11), 725-735. http://dx.doi.org/10.1136/jclinpath-2019-205952
25. Voet, S., Srinivasan, S., Lamkanfi, M., & van Loo, G. (2019). Inflammasomes in neuroinflammatory and neurodegenerative diseases. EMBO Molecular Medicine, 11(6), e10248. https://doi.org/10.15252/emmm.201810248
26. Mitchell, M. J., Billingsley, M. M., Haley, R. M., Wechsler, M. E., Peppas, N. A., & Langer, R. (2021). Engineering precision nanoparticles for drug delivery. Nature Reviews Drug Discovery, 20(2), 101-124. https://doi.org/10.1038/s41573-020-0090-8
27. Gautam, A. (2022). Towards modern-age advanced sensors for the management of neurodegenerative disorders: current status, challenges and prospects. ECS Sensors Plus. 10.1149/2754-2726/ac973e
28. Bouvier, D. S., Fixemer, S., Heurtaux, T., Jeannelle, F., Frauenknecht, K., & Mittelbronn, M. (2022). The Multifaceted Neurotoxicity of Astrocytes in Ageing and Age-Related Neurodegenerative Diseases: A Translational Perspective. Frontiers in Physiology, 467. https://doi.org/10.3389/fphys.2022.814889
29. Li, S., Liu, B., Li, Q. H., Zhang, Y., Zhang, H., Gao, S., ... & Wang, K. (2022). Evaluating the Bidirectional Causal Association Between Daytime Napping and Alzheimer's Disease Using Mendelian Randomization. Journal of Alzheimer's Disease, (Preprint), 1-8. 10.3233/JAD-220497
30. Radhakrishnan, D. M., & Goyal, V. (2018). Parkinson's disease: A review. Neurology India, 66(7), 26. 10.4103/0028-3886.226451
31. Singh, A., Kukreti, R., Saso, L., & Kukreti, S. (2019). Oxidative stress: a key modulator in neurodegenerative diseases. Molecules, 24(8), 1583.https://doi.org/10.3390/molecules24081583
32. Chi, H., Chang, H. Y., & Sang, T. K. (2018). Neuronal cell death mechanisms in major neurodegenerative diseases. International journal of molecular sciences, 19(10), 3082. https://doi.org/10.3390/ijms19103082

33. Corti, O., Blomgren, K., Poletti, A., & Beart, P. M. (2020). Autophagy in neurodegeneration: New insights underpinning therapy for neurological diseases. Journal of Neurochemistry, 154(4), 354-371. https://doi.org/10.1111/jnc.15002
34. Yang, C., Yang, Q., Xiang, Y., Zeng, X. R., Xiao, J., & Le, W. D. (2023). The neuroprotective effects of oxygen therapy in Alzheimer's disease: a narrative review. Neural Regeneration Research, 18(1), 57. 10.4103/1673-5374.343897
35. Koutsodendris, N., Nelson, M. R., Rao, A., & Huang, Y. (2022). Apolipoprotein e and alzheimer's disease: Findings, hypotheses, and potential mechanisms. Annual Review of Pathology: Mechanisms of Disease, 17, 73-99. https://doi.org/10.1146/annurev-pathmechdis-030421-112756
36. Bagheri, S., Squitti, R., Haertlé, T., Siotto, M., & Saboury, A. A. (2018). Role of copper in the onset of Alzheimer's disease compared to other metals. Frontiers in aging neuroscience, 9, 446. https://doi.org/10.3389/fnagi.2017.00446
37. Pickett, E. K., Herrmann, A. G., McQueen, J., Abt, K., Dando, O., Tulloch, J., ... & Spires-Jones, T. L. (2019). Amyloid beta and tau cooperate to cause reversible behavioral and transcriptional deficits in a model of Alzheimer's disease. Cell reports, 29(11), 3592-3604. https://doi.org/10.1016/j.celrep.2019.11.044
38. Ghaffari, M., Sanadgol, N., & Abdollahi, M. (2020). A systematic review of current progresses in the nucleic acid-based therapies for neurodegeneration with implications for Alzheimer's disease. Mini Reviews in Medicinal Chemistry, 20(15), 1499-1517. https://doi.org/10.2174/1389557520666200513122357
39. Maher, B. A. (2019). Airborne magnetite-and iron-rich pollution nanoparticles: potential neurotoxicants and environmental risk factors for neurodegenerative disease, including Alzheimer's disease. Journal of Alzheimer's Disease, 71(2), 361-375. 10.3233/JAD-190204
40. Spires-Jones, T. L., & Hyman, B. T. (2014). The intersection of amyloid beta and tau at synapses in Alzheimer's disease. Neuron, 82(4), 756-771. https://doi.org/10.1016/j.neuron.2014.05.004
41. Pecic, S., McAnuff, M. A., & Harding, W. W. (2011). Nantenine as an acetylcholinesterase inhibitor: SAR, enzyme kinetics and molecular modelling investigations. Journal of enzyme inhibition and medicinal chemistry, 26(1), 46-55. https://doi.org/10.3109/14756361003671078
42. Cunha, A., Gaubert, A., Latxague, L., & Dehay, B. (2021). PLGA-based nanoparticles for neuroprotective drug delivery in neurodegenerative diseases. Pharmaceutics, 13(7), 1042. https://doi.org/ 10.3390/ pharmaceutics13071042
43. Kouli, A., Torsney, K. M., & Kuan, W. L. (2018). Parkinson's disease: etiology, neuropathology, and pathogenesis. Exon Publications, 3-26. https://doi.org/10.15586/codon publications. Parkinsons disease.2018.ch1
44. Spires-Jones, T. L., Attems, J., & Thal, D. R. (2017). Interactions of pathological proteins in neurodegenerative diseases. Acta neuropathologica, 134(2), 187-205. https://doi.org/10.1007/s00401-017-1709-7
45. Marras, C., Canning, C. G., & Goldman, S. M. (2019). Environment, lifestyle, and Parkinson's disease: implications for prevention in the next decade. Movement Disorders, 34(6), 801-811. https://doi.org/10.1002/mds.27720
46. Priyadarshi, A., Khuder, S. A., Schaub, E. A., & Priyadarshi, S. S. (2001). Environmental risk factors and Parkinson's disease: a meta analysis. Environmental research, 86(2), 122-127. https://doi.org/ 10.1006/enrs.2001.4264
47. Emamzadeh, F. N., & Surguchov, A. (2018). Parkinson's disease: biomarkers, treatment, and risk factors. Frontiers in neuroscience, 12, 612. https://doi.org/10.3389/fnins.2018.00612
48. Ben-Shlomo, Y. (2004). The role of well water and other factors in the aetiology of Parkinson's disease. University of London, University College London (United Kingdom). https://doi.org/10.1002/1531-8257(199911)14:6<928::AID-MDS1004>3.0.CO;2-Z
49. Bartels, A. L., & Leenders, K. L. (2009). Parkinson's disease: the syndrome, the pathogenesis and pathophysiology. Cortex, 45(8), 915-921. https://doi.org/10.1016/j.cortex.2008.11.010
50. Chaudhuri, K. R., & Schapira, A. H. (2009). Non-motor symptoms of Parkinson's disease: dopaminergic pathophysiology and treatment. The Lancet Neurology, 8(5), 464-474. https://doi.org/10.1016/S1474-4422(09)70068-7
51. Moore, D. J., West, A. B., Dawson, V. L., & Dawson, T. M. (2005). Molecular pathophysiology of Parkinson's disease. Annu. Rev. Neurosci., 28, 57-87. https://doi.org/10.1146/annurev.neuro.28.061604.135718
52. Schulz-Schaeffer, W. J. (2010). The synaptic pathology of α-synuclein aggregation in dementia with Lewy bodies, Parkinson's disease and Parkinson's disease dementia. Acta neuropathologica, 120(2), 131-143. https://doi.org/10.1007/s00401-010-0711-0
53. Prudencio, M., Humphrey, J., Pickles, S., Brown, A. L., Hill, S. E., Kachergus, J. M., ... & Petrucelli, L. (2020). Truncated stathmin-2 is a marker of TDP-43 pathology in frontotemporal dementia. The Journal of clinical investigation, 130(11). https://doi.org/10.1172/JCI139741.
54. Morris, J. (2015). Amyotrophic lateral sclerosis (ALS) and related motor neuron diseases: an overview. The Neurodiagnostic Journal, 55(3), 180-194. https://doi.org/10.1080/21646821.2015.1075181
55. Wang, G. Y., Rayner, S. L., Chung, R., Shi, B. Y., & Liang, X. J. (2020). Advances in nanotechnology-based strategies for the treatments of amyotrophic lateral sclerosis. Materials Today Bio, 6, 100055. https://doi.org/10.1016/j.mtbio.2020.100055

56. Hardiman, O., Al-Chalabi, A., Chio, A., Corr, E. M., Logroscino, G., Robberecht, W., ... & Van Den Berg, L. H. (2017). Amyotrophic lateral sclerosis. Nature reviews Disease primers, 3(1), 1-19. https://doi.org /10.1038/nrdp.2017.71
57. Motataianu, A., Serban, G., Barcutean, L., & Balasa, R. (2022). Oxidative Stress in Amyotrophic Lateral Sclerosis: Synergy of Genetic and Environmental Factors. International Journal of Molecular Sciences, 23(16), 9339. https://doi.org/10.3390/ijms23169339
58. Webster, C. P., Smith, E. F., Bauer, C. S., Moller, A., Hautbergue, G. M., Ferraiuolo, L., ... & De Vos, K. J. (2016). The C9orf72 protein interacts with Rab1a and the ULK 1 complex to regulate initiation of autophagy. The EMBO journal, 35(15), 1656-1676. https://doi.org/10.15252/embj.201694401
59. Petracca, M., Di Tella, S., Solito, M., Zinzi, P., Lo Monaco, M. R., Di Lazzaro, G., ... & Bentivoglio, A. R. (2022). Clinical and genetic characteristics of late-onset Huntington's disease in a large European cohort. European Journal of Neurology. https://doi.org/10.1111/ene.15340
60. Stamelou, M., & Bhatia, K. P. (2015). Genetics of Atypical Parkinsonism. In Movement Disorder Genetics (pp. 35-64). Springer, Cham. 10.1007/978-3-319-17223-1_3
61. Ferrante, R. J., Kowall, N. W., Beal, M. F., Richardson Jr, E. P., Bird, E. D., & Martin, J. B. (1985). Selective sparing of a class of striatal neurons in Huntington's disease. Science, 230(4725), 561-563. 10.1126/science.2931802
62. Valadão, K. M. G., Luizeti, B. O., Yamaguchi, M. U., Issy, A. C., & Bernuci, M. P. (2022). Nanotechnology in Improving the Treatment of Huntington's Disease: a Systematic Review. Neurotoxicity Research, 1-10. https://doi.org/10.1007/s12640-021-00468-1
63. Dobson, R., & Giovannoni, G. (2019). Multiple sclerosis–a review. European journal of neurology, 26(1), 27-40. https://doi.org/10.1111/ene.13819
64. Chountoulesi, M., & Demetzos, C. (2020). Promising nanotechnology approaches in treatment of autoimmune diseases of central nervous system. Brain Sciences, 10(6), 338. https://doi.org/10.3390/brainsci10060338
65. Kumar, R., Aadil, K. R., Mondal, K., Mishra, Y. K., Oupicky, D., Ramakrishna, S., & Kaushik, A. (2021). Neurodegenerative disorders management: state-of-art and prospects of nano-biotechnology. Critical Reviews in Biotechnology, 1-33. https://doi.org/10.1080/07388551.2021.1993126
66. Isogai, R., Morio, H., Okamoto, A., Kitamura, K., & Furihata, T. (2022). Generation of a Human Conditionally Immortalized Cell-based Multicellular Spheroidal Blood-Brain Barrier Model for Permeability Evaluation of Macromolecules. Bio-protocol, 12(15), e4465-e4465. https://doi.org/10.21769/BioProtoc.4465
67. Daneman, R., & Prat, A. (2015). The blood–brain barrier. Cold Spring Harbor perspectives in biology, 7(1), a020412. 10.1101/cshperspect.a020412
68. Felgenhauer, K. (1974). Protein size and cerebrospinal fluid composition. Klinische Wochenschrift, 52(24), 1158-1164. https://doi.org/10.1007/BF01466734
69. Greene, C., & Campbell, M. (2016). Tight junction modulation of the blood brain barrier: CNS delivery of small molecules. Tissue barriers, 4(1), e1138017. https://doi.org/10.1080/21688370.2015.1138017
70. Hawkins, B. T., & Davis, T. P. (2005). The blood-brain barrier/neurovascular unit in health and disease. Pharmacological reviews, 57(2), 173-185. https://doi.org/10.1124/pr.57.2.4
71. Fujimoto, T., Morofuji, Y., Kovac, A., Erickson, M. A., Deli, M. A., Niwa, M., & Banks, W. A. (2021). Pitavastatin ameliorates lipopolysaccharide-induced blood-brain barrier dysfunction. Biomedicines, 9(7), 837. https://doi.org/10.3390/biomedicines9070837
72. Serlin, Y., Shelef, I., Knyazer, B., & Friedman, A. (2015, February). Anatomy and physiology of the blood–brain barrier. In Seminars in cell & developmental biology (Vol. 38, pp. 2-6). Academic Press. https://doi.org/10.1016/j.semcdb.2015.01.002
73. Bouhrira, N., DeOre, B. J., Tran, K. A., & Galie, P. A. (2022). Transcriptomic analysis of a 3D blood–brain barrier model exposed to disturbed fluid flow. Fluids and Barriers of the CNS, 19(1), 1-15. https://doi.org/10.1186/s12987-022-00389-x
74. Hladky, S. B., & Barrand, M. A. (2018). Elimination of substances from the brain parenchyma: efflux via perivascular pathways and via the blood–brain barrier. Fluids and Barriers of the CNS, 15(1), 1-73. https://doi.org/10.1186/s12987-018-0113-6
75. Egbert, J., Geldenhuys, W., Thomas, F., Lockman, P. R., Mumper, R. J., & Allen, D. D. (2007). Nanoparticle Targeting for Drug Delivery Across the Blood–Brain Barrier. Role of lipid excipients in modifying oral and parenteral drug delivery. 1st ed. Hoboken, NJ: John Wiley & Sons, Inc, 160-169. 10.1002/0470097981
76. van de Waterbeemd, H., Camenisch, G., Folkers, G., Chretien, J. R., & Raevsky, O. A. (1998). Estimation of blood-brain barrier crossing of drugs using molecular size and shape, and H-bonding descriptors. Journal of drug targeting, 6(2), 151-165. https://doi.org/10.3109/10611869808997889
77. Di, L., Artursson, P., Avdeef, A., Ecker, G. F., Faller, B., Fischer, H., ... & Sugano, K. (2012). Evidence-based approach to assess passive diffusion and carrier-mediated drug transport. Drug discovery today, 17(15-16), 905-912. https://doi.org/10.1016/j.drudis.2012.03.015
78. Fischer, H., Gottschlich, R., & Seelig, A. (1998). Blood-brain barrier permeation: molecular parameters governing passive diffusion. The Journal of membrane biology, 165(3), 201-211. https://doi.org/10.1007/s002329900434
79. Arora, S., Sharma, D., & Singh, J. (2020). GLUT-1: an effective target to deliver brain-derived neurotrophic factor gene across the blood brain barrier. ACS Chemical Neuroscience, 11(11), 1620-1633. https://doi.org/10.1021 /acschemneuro.0c00076

80. Hammarlund-Udenaes, M. (2022). Pharmacokinetic concepts in brain drug delivery. In Drug delivery to the brain (pp. 173-209). Springer, Cham. https://doi.org/10.1007/978-3-030-88773-5_7
81. Ayub, A., & Wettig, S. (2022). An Overview of Nanotechnologies for Drug Delivery to the Brain. Pharmaceutics, 14(2), 224. https://doi.org/10.3390/pharmaceutics14020224
82. Gallardo-Toledo, E., Velasco-Aguirre, C., & Kogan, M. J. (2021). Inorganic Nanoparticles and Their Strategies to Enhance Brain Drug Delivery. In Nanomedicines for Brain Drug Delivery (pp. 149-172). Humana, New York, NY. https://doi.org/10.1007/978-1-0716-0838-8_6
83. Wang, F., Li, C., Cheng, J., & Yuan, Z. (2016). Recent advances on inorganic nanoparticle-based cancer therapeutic agents. International journal of environmental research and public health, 13(12), 1182. https://doi.org/10.3390/ijerph13121182
84. Bhattacharya, T., Soares, G. A. B. E., Chopra, H., Rahman, M. M., Hasan, Z., Swain, S. S., & Cavalu, S. (2022). Applications of phyto-nanotechnology for the treatment of neurodegenerative disorders. Materials, 15(3), 804.https://doi.org/10.3390/ma15030804
85. Vignes, S. (2022). Safety Evaluation of Cerium Oxide Nanoparticles Using Wild-Type and Transgenic Drosophila Melanogaster Model of Alzheimer's Disease (Doctoral dissertation, SRM institue of Scienece and Technology). http://hdl.handle.net/123456789/45566
86. Parsaei, M., & Akhbari, K. (2022). Smart Multifunctional UiO-66 Metal–Organic Framework Nanoparticles with Outstanding Drug-Loading/Release Potential for the Targeted Delivery of Quercetin. Inorganic Chemistry, 61(37), 14528-14543. https://doi.org/10.1021/acs.inorgchem.2c00743
87. Hernandez, C., & Shukla, S. (2022). Liposome based drug delivery as a potential treatment option for Alzheimer's disease. Neural regeneration research, 17(6), 1190. 10.4103/1673-5374.327328
88. Pathak, N., Vimal, S. K., Hongyi, C., & Bhattacharya, S. (2022). Drug Delivery to the Brain: Targeting Technologies to Deliver Therapeutics to Brain Lesions. Targeted Drug Delivery, 389-424. https://doi.org/10.1002/9783527827855.ch15
89. Ebrahimi, H., Nezhad, S. K., Farmoudeh, A., Babaei, A., Ebrahimnejad, P., Akbari, E., & Siahposht-Khachaki, A. (2022). Design and optimization of metformin-loaded solid lipid nanoparticles for neuroprotective effects in a rat model of diffuse traumatic brain injury: A biochemical, behavioral, and histological study. European Journal of Pharmaceutics and Biopharmaceutics, 181, 122-135. https://doi.org/10.1016/j.ejpb.2022.10.018
90. Yang, X., Zou, L. H., Ding, W. Y., Zhang, Z. B., Chen, J. Q., Li, J. L., ... & Feng, J. F. (2022). Research progress on liposome and nanomicelle targeted drug delivery system across blood-brain barrier. Zhongguo Zhong yao za zhi= Zhongguo Zhongyao Zazhi= China Journal of Chinese Materia Medica, 47(22), 5965-5977. 10.19540/j.cnki.cjcmm.20220726.602
91. Kasina, V., Mownn, R. J., Bahal, R., & Sartor, G. C. (2022). Nanoparticle delivery systems for substance use disorder. Neuropsychopharmacology, 1-9. https://doi.org/10.1038/s41386-022-01311-7
92. Weller, J., & Budson, A. (2018). Current understanding of Alzheimer's disease diagnosis and treatment. F1000Research, 7. 10.12688/f1000research.14506.1
93. Stoker, T. B., & Barker, R. A. (2020). Recent developments in the treatment of Parkinson's Disease. F1000Research, 9. 10.12688/f1000research.25634.1
94. Bhat, S., Acharya, U. R., Hagiwara, Y., Dadmehr, N., & Adeli, H. (2018). Parkinson's disease: Cause factors, measurable indicators, and early diagnosis. Computers in biology and medicine, 102, 234-241. https://doi.org/10.1016/j.compbiomed.2018.09.008
95. Carrera-Juliá, S., Moreno, M. L., Barrios, C., de la Rubia Ortí, J. E., & Drehmer, E. (2020). Antioxidant alternatives in the treatment of amyotrophic lateral sclerosis: a comprehensive review. Frontiers in physiology, 11, 63. https://doi.org/10.3389/fphys.2020.00063
96. van den Bos, M. A., Geevasinga, N., Higashihara, M., Menon, P., & Vucic, S. (2019). Pathophysiology and diagnosis of ALS: insights from advances in neurophysiological techniques. International Journal of Molecular Sciences, 20(11), 2818. https://doi.org/10.3390/ijms20112818
97. Riccardi, C., Napolitano, F., Montesarchio, D., Sampaolo, S., & Melone, M. A. B. (2021). Nanoparticle-guided brain drug delivery: Expanding the therapeutic approach to neurodegenerative diseases. Pharmaceutics, 13(11), 1897. https://doi.org/10.3390/pharmaceutics13111897
98. Muntimadugu, E., Dhommati, R., Jain, A., Challa, V. G. S., Shaheen, M., & Khan, W. (2016). Intranasal delivery of nanoparticle encapsulated tarenflurbil: a potential brain targeting strategy for Alzheimer's disease. European journal of pharmaceutical sciences, 92, 224-234. https://doi.org/10.1016/j.ejps.2016.05.012
99. de Oliveira Junior, E. R., Truzzi, E., Ferraro, L., Fogagnolo, M., Pavan, B., Beggiato, S., ... & Dalpiaz, A. (2020). Nasal administration of nanoencapsulated geraniol/ursodeoxycholic acid conjugate: towards a new approach for the management of Parkinson's disease. Journal of Controlled Release, 321, 540-552. https://doi.org/10.1016/j.jconrel.2020.02.033
100. Mandal, S., Debnath, K., Jana, N. R., & Jana, N. R. (2020). Trehalose-conjugated, catechin-loaded polylactide nanoparticles for improved neuroprotection against intracellular polyglutamine aggregates. Biomacromolecules, 21(4), 1578-1586. https://doi.org/10.1021/acs.biomac.0c00143