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NANOMEDICINE DRUG DELIVERY SYSTEM FOR BRAIN DISEASES

THOTA NEELIMA

Department of Biochemical Engineering and Biotechnology,
Osmania University College of Technology, OU, Hyderabad, India.

ABSTRACT

Brain is the control center of the body. It controls each and every stimulus in the body. Disease is an impairment of health or a condition of abnormal functioning of our body. The cause of disease is either external like infectious diseases may be an internal disease such as auto immune diseases. Some of these are fatal. There are many deadliest diseases in human one among them is Brain diseases, with this whole body control system gets affected. There are many therapies in practice, but they control the progress of the disease rather than cure. A new technique in nanotechnology in the field of medicine is Nanomedicine. Nanomedicine therapy showed immense results in curing as well as imaging various diseases along with Brain diseases. The main aim of this review article is to provide the information to the researchers about the scientific works done on some of the brain diseases like Alzheimer's disease, Cerebral palsy, epilepsy, multiple sclerosis, Parkinson's using nanomedicine technique in a concise manner and to develop other potent drug delivery systems for imaging and curing of brain diseases as well as to include new tests and testing guidelines.

Key words: **Nanoparticles,, Alzheimer's disease, Cerebral palsy, epilepsy, multiple sclerosis, Parkinson's disease, Blood Brain Barrier (BBB).**

THOTA NEELIMA
Department of Biochemical Engineering and Biotechnology,
Osmania University College of Technology, OU, Hyderabad, India.

***Corresponding author**

INTRODUCTION

Nanotechnology is the science and technology of miniature things in particular, things that are less than 100nm in size. One nanometer is 10-9 meters or about 3 atoms long. For comparison, a human hair is about 60-80,000 nanometers wide. Scientists have discovered that materials at small dimensions small particles, thin films, etc., can have significantly different properties than the same materials at mega size. There are thus endless possibilities for improved devices, structures, and materials if we can understand these differences, and learn how to control the assembly of small structures [(1)]. Various technical divisions in nanotechnology are nanobiotechnology, nanocomposites, nanoelectronics, nanoengineering, nanofabrication, nonmaterial, nanomedicine, and nanorobotics. The method of applying nanoparticles for transporting drug molecules across the blood brain barrier is nanoparticle drug delivery system. These drugs cross the BBB and deliver pharmaceuticals to the brain for therapeutic treatment of neurological or central nervous system disorders. Nanomedicine which is named by American National Institute of Health (NIH). This is the innovation of nanotechnology in the field of medicine. One of the most important applications of nanotechnology is in medicine. This new field of science has become increasingly popular for diagnosis, treatment, prevention and follow ups of diseases[(2,3)]. Diseases like cancer, diabetes, chronic pulmonary diseases, cardiovascular diseases, chronic inflammatory diseases (autoimmune and others), neurologic disorders, renal diseases and infection are big challenge that are faced by medical scientists. Nanomedicine that link material science specialists to medical scientists may help in findings efficient diagnostic and therapeutic intervention[(4)].

NANOMEDICINE FOR CENTAL NERVOUS SYSTEM DISEASES

Targeting of the central nervous system (CNS) in order to treat disorders is actually challenging due to the necessity to cross the blood brain barrier (BBB). Several current methods for drug delivery to the brain include the use of liposomes, prodrugs, and carrier-mediated transporters. Many different delivery methods exist to transport these drugs into the body, such as per oral delivery, intranasal delivery, intravenous injections, and intracranial delivery. For nanoparticles the majority of studies have shown increasing progression with intravenous delivery specifically. In addition to delivery and transport methods, there are several means of functionalizing, or activating, the nanoparticle carriers. These means include dissolving or absorbing the drug throughout the nanoparticle, encapsulating the drug inside the particle, and attaching the drug on the surface of the particle[(28)]. This review aims to show how nanomedicine can propose new approach for the treatment and the diagnosis of CNS diseases[(5)].The use of targeted nanotherapies to cross the BBB and to bind and act only on the target, has made a great deal of difference in many CNS diseases where the flexibility of nanomaterials shows the greatest promise. Getting therapeutics to cross the BBB used to be an insurmountable barrier. Agents that were originally intended for the brain, based on their success in treating other diseases, ran into a major stumbling block when administered in the brain. This appears to be changing: by using a combination of therapeutics with increased circulation times in the blood and adding a transit ligand allows the nanoparticle to pass the endothelial tissue in the brain [(6)]. Then, adding the secondary targeting moiety allows the nanocarrier to bind or internalize into the diseased cell [(7)]. These new delivery vehicles for not only therapeutics, but also DNA and RNA, will start to make inroads in curing many of the diseases that were once thought to be incurable [(8,9)]. Nanosized constructs allow for the controlled release of much nanotherapeutics and can create a reservoir to deliver drugs over months or, in some cases, years. This may be an area that

can be employed to fundamentally change the hormone replacement therapy (HRT) problem, enabling many to retain more mental function without the side effects caused by hormones in the wrong place[10-12].

ALZHEIMER'S DISEASE (AD)

Alzheimer's is an auto immune disorder and cognitive dysfunction, due to an irreversible degeneration of neurons that leads to total loss of autonomy and leads to death. The treatments that are available only provide symptomatic relief, temporarily improving cognitive function, but are unable to slow the long-term progression of the disorder. Scientists, in present days have mainly focused on the protein fragment Aß for the treatment of AD. Scientists detected two abnormal structures in the brain of AD patients, senile plaques and neurofibrillary tangles are intrinsically tied to Aß. Senile plaques former are deposits of the protein, while neurofibrillary tangles are considered a consequence of neuron exposure to it [13].Because of improper knowledge on Alzheimer physiopathology and lack of early diagnosis there is no effective therapeutic approach. Many drawbacks such as poor bioavailability or limited BBB arising of tested molecules in the current or new therapeutic strategies explain their failure but can be resolved by the use of nanotechnology. Ideal nanocarriers for this aim must be able to pass through the BBB and to interact with an AD marker as soluble extracellular Aβ forms which are known as the most toxic ones [14]. Advancements in AD treatment are being made in drug delivery with the development of huperzine- packaged poly(lactic-co-glycolytic acid) NPs and in diagnosis with the development of gold NPs complexes with fragments of Aβ antibody[15].

CEREBRAL PALSY

Cerebral palsy is a chronic childhood disorder that can have diverse etiologies. Injury to the developing brain that occurs either in uterus or soon after birth can result in the motor, sensory, and cognitive deficits seen in cerebral palsy. There is no effective cure for cerebral palsy in present days. Nanomedicine offers a new frontier in the development of therapies for prevention and treatment of brain injury resulting in cerebral palsy. Multiple drugs can be delivered to mitigate various pathways that are involved in injury and these drugs can be delivered to the cells that are responsible for neuron inflammation as well as injury by means of Nanomaterials such as Dendrimers. These nanomaterials drug delivery system promote repair and regeneration in the brain, resulting not only in attenuation of injury, but also enabling normal growth [16].Bindu Balakrishnan et al used G4OH-PAMAM (Polyamidoamine) dendrimers they were administered intravenously to newborn rabbits with CP, the dendrimers crossed the BBB and selectively localized in cells associated with neuroinflammation. This selective localization into activated microglia and astrocytes was seen in CP kits, with minimal brain uptake and localization shown in healthy kits. To take advantage of this selective localization, coupling of N-acetyl cysteine (NAC) to these dendrimers, and engineered them for tailored intracellular release. NAC has both antioxidant and anti-inflammatory properties, and is widely used clinically in children and adults it is being evaluated in several clinical trials Improved delivery and efficacy with a safe drug [16].

EPILEPSY

Epilepsy is a neurological disorder leads to loss of consciousness, or convulsions, associated with abnormal electrical activity in the brain. The aim in treating epilepsy with drugs is, to decrease seizure frequency and severity while minimizing toxicity to the brain and other tissues. Antiepileptic drugs (AEDs) are not always effective they are usually administered by oral and intravenous routes. Drug access to the brain is severely limited by a number of biological factors, particularly the blood-brain barrier, which impedes the ability of AEDs to enter and remain in the brain. To improve the efficacy of AEDs, new drug delivery strategies are being developed; these methods fall into the three main categories: drug modification, blood-brain barrier modification, and direct drug delivery. Recently, all three methods have been

improved through the use of drug-loaded nanoparticles[17]. Władysław Lasoń *et al* found that Pharmacodynamic activity of antiepileptic drugs delivered in nanosystems may be significantly enhanced. To this end, phenytoin-loaded liposomes given locally inhibited the cAMP/EDTA-induced seizures in rats. Furthermore, intravenous administration of an antagonist of NMDA receptor, MRZ 2/576 incorporated into nanoparticles prolonged its anticonvulsant activity more than 10 times compared to free compound. It was also found that the intranasal delivery of TRH-PLA (thyrotropin-releasing hormone-polylactide) nanoparticles retarded experimental epileptogenesis and reduced clonic seizure intensity in mice. Regarding a potential application of nanotechnology in diagnosis, it has been found that non-radioactive alpha methyl tryptophan bound to magnetonano particles, readily crosses the blood-brain barrier, accumulates in the epileptic focus and can be detected by MRI [18].

MULTIPLE SCLEROSIS

Multiple Sclerosis is a typically progressive disease with several pathogenic mechanisms and pathways. Successful MS management and medical care requires early, accurate diagnosis along with specific treatment protocols based upon multifunctional nanotechnology approach .The current nanotheranostics utilize tamed drug vehicles and contain cargo, targeting ligands, and imaging labels for delivery to specific tissues, cells, or subcellular components. Considering the potential inflammatory triggers in MS pathogenesis, a multifunctional nanotechnology approach will be needed for the prognosis[19].Cell signaling pathways for tumor cell surfaces are deactivated by direct targeting of antibodies and peptides which are conjugated with magnetic nanomaterials [20],that are targeting the sclerotic lesion with growth factor to treat the lesions patients with multiple sclerosis. The active targeting strategy with site-specific ligands binding increases penetration and surface nanoengineering of NPs, which provided new ways to control pharmacokinetics and bioavailability of CNS-related drugs across BBB and RES[21]. Pegylation of liposome with particle diameter at <100□nm help in combating problem associated with conventional liposomes (aggregation, short half-lives, modest transport capacity across the blood-brain barrier, and rapid RES clearance) by receptor or absorptive-mediated transcytosis [22]. Coating the liposome surface with monoclonal antibodies to glial fibrillary acidic proteins, transferrin receptors or human insulin receptors (nanoliposome) further help in escaping RES and BBB and delivering therapeutic genes[19,23]. S.S.Ali, L.L.Dugan, et al works proven Glutamate receptors, which mitigate neuronal toxicity via intracellular calcium influx and limiting excitotoxicity, were shown by fullerenol [polyhydroxylated C60] and carboxyfullerene [malonic acid C60 derivative], respectively, in an in vivo mouse model of familial amyotrophic lateral sclerosis, an animal model for multiple sclerosis[19,24,25] .

PARKINSON'S DISEASE

Parkinson's disease is a common progressive neurodegenerative disorder with marked by tremor, muscular rigidity, and slow, imprecise movement, chiefly affecting middle-aged and elderly people. It is associated with degeneration of the basal ganglia of the brain. To attenuate this disease, no proper treatment is available in current days. To this end, a cell-based nanoformulation delivery system was developed using the antioxidant enzyme catalase to attenuate neuroinflammatory processes linked to neuronal death, Anna M Brynskikh et al used Nanoformulated catalase and it was obtained by coupling catalase to a synthetic polyelectrolyte of opposite charge, leading to the formation of a polyion complex micelle. The nanozyme was loaded into bone marrow macrophages and its transport to the substantia nigra, pars compacta was evaluated in1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-intoxicated mice.Therapeutic efficacy of bone marrow macrophages loaded with nanozyme was confirmed by twofold reductions in microgliosis as measured by CD11b expression. A twofold increase in tyrosine hydroxylase-expressing dopaminergic

neurons was detected in nanozyme-treated compared with untreated MPTP-intoxicated mice. Neuronal survival was confirmed by magnetic resonance spectroscopic imaging. Bone marrow macrophage-loaded catalase showed sustained release of the enzyme in plasma[26]. Ari Nowacek et al used C_{60} fullerenes in the treatment of PD. C_{60} fullerenes have unique physical and chemical properties and have been researched for their potential biomedical applications. C_{60}shows potent antioxidant capabilities and could offer therapeutic benefit through the reduction of free radicals. Cyprinus carpio brain homogenates with added C_{60} produced significantly more lipid hydroperoxides when exposed to light, thus raising concerns that in vivo C_{60} could cause damage when present in photic regions of the brain. Such approaches remain in development. C_{60} fullerenes have unique properties and offer many potential uses for the treatment of neurodegenerative disorders [27].

CONCLUSION

Nanomedicine till now has brought a tremendous change in the medical field. The above research works as well as other works by the eminent research scholars has proven that nanomedicine technology has an opportunity in alleviating various brain diseases, thus nanomedicine promises to bring a great future to the individuals with functional central nervous system disorders. Still, it is in commencement stage. In future there is expectancy that this technology brings a revolution in the field of medicine which progresses the health of the individuals by curing pathogenic diseases which are difficult with existing therapies. Further research works should focus on nanotoxicological risk assessments, cost effective assements as well as development of biodegradable nanoparticles.

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