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Review Article

Recent advances in nanotherapeutics for epilepsy and neurodegenerative diseases

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ABSTRACT

This review focuses on the potential of nanotherapeutics in the diagnosis and treatment of neuronal abnormal conditions particularly epilepsy, alzheimer's disease (AD), and Parkinson's disease (PD). The advancements in nanotechnology have paved the way for the development of nanocarrier systems that can target the underlying pathogenesis of these diseases. The study aimed to explore the efficacy of nanosystems in treating epilepsy, AD, and PD by analyzing relevant articles from databases such as Medline, PubMed and the national library of medicine. The review discusses the targeted delivery of active therapeutics to the central nervous system, with a focus on modulating neuronal and endothelial cell activity. It highlights various nanotherapeutic approaches, including pH-responsive nanomaterial-based therapeutics, nano-bioelectronic-implantable transient electronic devices, and electro-responsive nanosystems for the treatment of epilepsy. Additionally, the efficacy of nanodrug delivery systems loaded with curcumin, monoclonal anti-tau antibody-coated gold nanoparticles, Polyethylene Glycolpolylactide-Polyglycolide (PEG-PLGA) nanoparticles loaded with lactoferrin, dopamine-conjugated Albumin/PLGA nanosystems, and curcumin-loaded T807/RPCNP nanoparticles against neurodegeneration is discussed. The findings of this review provide valuable insights into the implications and challenges of nanotherapeutics in the field of neurological diseases. Neurologists and clinicians can benefit from this knowledge to better understand the potential applications of nanotherapeutics in the diagnosis and treatment of these conditions.

1. Introduction

Neurodegenerative disorders have become a significant global health concern in recent years. These diseases, characterized by the progressive degeneration of neurons, lead to sensory, cognitive, and motor impairments, greatly hampered the quality of life for affected individuals[1] The need for effective therapeutic approaches to manage these disorders is growing. Additionally, the development and accessibility of treatments for neurological diseases such as epilepsy, AD, and PD face numerous challenges, including high research and development costs, long-term research requirements, high failure rates, unclear pathogenesis, unavailability of diagnostic models, inefficiency in crossing physiological barriers including the Blood-Brain Barrier (BBB), and difficulties in meeting pharmacokinetic barriers. Consequently, the cost of manufacturing drugs for these disorders remains high, making treatment accessibility difficult for patients.[2]

To overcome these challenges and improve treatment outcomes, the field of nanotechnology has emerged as a promising avenue. Nanotechnology offers several

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advantages that can be harnessed to develop innovative therapeutic and diagnostic systems for neurodegenerative disorders.[3] By altering the properties of nanosystems, drugs can be efficiently loaded and delivered to specific sites within the brain, enhancing drug entrapment efficiency and ensuring sustained release at pathological regions. Compared to conventional drug delivery systems, nanotherapeutics offer benefits such as site-specific drug delivery, reduced side effects, and enhanced blood-brain barrier penetration, ultimately improving therapeutic outcomes.[4] Nanotherapeutics can specifically target microglia-mediated pathogenesis in neurodegeneration, addressing the underlying mechanisms of these diseases. Additionally, stem cell-derived exosomes have shown promise as nanotherapeutics in mitigating the pathophysiology of neurodegenerative diseases.[5] With each having its own benefits and distinctiveness, nanotechnology offers a wide variety of tailored material solutions for drug administration. Dendrimers, liposomes, hydrogels, metal and polymer nanoparticles, micelles and nanotubes, biodegradable nanoparticles, and nanocomposites are a few examples.[6] These nano-drug delivery systems have been used effectively in a number of domains, including the treatment of cancer, gene therapy, and immune system modification. Nanotechnology is an essential tool in the identification and management of numerous kinds of brain diseases due to its flexible, biocompatible and multifunctional approaches. Nanotherapeutics offer the potential to target brain tissue, permeate the blood-brain barrier, and overcome pharmacokinetic barriers, revolutionizing the management of these diseases.[7]

The present article explore the consequences of nanotherapeutics in the field of neurological disorders, particularly epilepsy, AD &PD disease. We will also discuss the present difficulties associated with t Using nanotherapeutics to treat these disorders. By examining the existing literature and research, this review seeks to shed light on the potential of nanotechnology in advancing the diagnosis and treatment of neurodegenerative disorders, providing valuable insights for researchers, clinicians, and neurologists working in this field.

2. Epilepsy

Epilepsy is a complex neurological disorder marked by abnormal neuronal signalling, leading to the occurrence of seizures. The increasing prevalence of epilepsy worldwide has created a need for safer and more effective therapeutic options for its treatment. Recently nanotechnology-based therapeutic and diagnostic agents have shown promise in addressing the challenges associated with epilepsy.[8] One example of nanotechnology application in epilepsy management is the development of nanobioelectronic-implantable transient electronic devices. These electronic devices are electrically powered nanomaterial-equipped automated transient nanogenerators. They serve as biomechanical sensors that track the brain's neuronal activity and release anticonvulsants in the event of a seizure. In in vivo studies, these nanogenerators successfully detect distinct abnormal neuronal activity and trigger the release of an anticonvulsant drug (such as phenobarbital) through controlled resistor heaters. The efficacy of these nanobioelectronic implants in reducing seizure frequency and their biodegradability has been evaluated through in vivo and in vitro studies, showing promising outcomes for epilepsy management.[9]

Another approach involves the use of pH-responsive nanomaterial-based therapeutics. In epilepsy, the microenvironment pH at the diseased site may shift from neutral to acidic or alkaline due to factors including hypoxia, inflammation, or excess carbonic acid.[10] PH-responsive nanocarriers, such as modified hydrogels, liposomes, and other nanoparticles, are functionalized with pH-sensitive agents. These nanocarriers effectively detect changes in pH and undergo physical changes, leading to the release of drugs specifically at the diseased site without affecting normal tissue. For instance, a pH-responsive macromer called poly(methacrylic acid-g-ethylene glycol) has been utilized for the prolonged delivery of pregabalin, an antiepileptic drug. This system demonstrated good drug release profiles at basic pH conditions for up to 5 hours, highlighting its potential for epilepsy treatment.[11] Electro-responsive nanosystems represent another avenue for epilepsy management. These nanosystems are composed of nanostructures made from electroresponsive polymers that undergo conformational changes in response to electrical environments, particularly the abnormal neuronal impulses observed during epilepsy. By utilizing electrical stimuli, these electroresponsive nanosystems can effectively release drugs in response to the fluctuating electrical conditions associated with seizures. In an evaluation of an electroresponsive nanosystem loaded with phenytoin and linked to angiopep-2 for enhanced blood-brain barrier permeation, it demonstrated promising outcomes in reducing phenytoin dose, lowering seizure duration and frequency in electrical and chemically induced seizure models. Such nanostrategies hold potential for generating effective clinical outcomes in epilepsy patients.[12,13] These advancements in nanotechnology-based approaches for epilepsy management offer novel ways to address the challenges associated with traditional drug delivery systems. Nanotherapeutics have the potential to improve treatment efficacy, reduce side effects, and provide site-specific drug delivery for enhanced clinical outcomes. Changes in the diagnosis and treatment of epilepsy may result from more study and development in this area.[14]

2.1. Alzheimer's disease

AD is a neurocognitive disorder characterized by brain atrophy that leads to dementia and impairs core mental functions. However, the lack of proper diagnostic methods, understanding of the etiology, and knowledge of the underlying pathophysiology pose significant challenges to effectively managing the disease.[15] In patients with AD, the presence of beta-amyloid deposits in the brain is commonly observed. To address this, researchers have developed a unique fluorescent chelator called TBT, which possesses excellent blood-brain barrier permeability and dual functionality.[16] TBT has a high affinity and selectivity for beta-amyloid deposits, enabling easy near-infrared imaging/diagnostics. Additionally, it inhibits metal-induced beta-amyloid aggregation by chelating Zn2+ and Cu2+ ions. The binding affinity of TBT to beta-amyloid aggregates has been confirmed through a Thioflavin (ThT) fluorescence competition assay. In vitro studies using a microBCA (bicinchoninic acid) assay and visualization with transmission electron microscopy (TEM) have demonstrated the inhibition of beta-amyloid aggregation by TBT.[17,18]

To aid in the diagnosis and potential treatment of AD, as clever NIRF imaging probes, a number of unique phenothiazine compounds have been synthesised. These compounds serve as diagnostic tools for detecting beta-amyloid deposits and as inhibitors of beta-amyloid aggregation. They exhibit good affinity for beta-amyloid aggregates in the nanomolar range and demonstrate aggregation inhibitory activity in the micromolar range. Fluorescence microscopy confirms their diagnostic and therapeutic potential in AD.[19] Nanoparticles loaded with curcumin systems have also shown promise in the diagnosis and treatment of AD. Nanosystems such as micelles and nanoparticles, developed using DSPE-PEG2000 and Pluronic 127, enable outstanding penetration across the blood-brain barrier. These nanosystems can detect beta-amyloid plaques at low concentrations by fluorescing as yellow/green under violet/blue light (436 nm).[20]

In the search for effective targeting agents, the capacity to identify beta-amyloid plaques in AD patients' brains and the presence of tau protein in cerebrospinal fluid has been established and confirmed using monoclonal anti-tau antibody-coated gold nanoparticles.[21] Furthermore, curcumin-loaded T807/RPCNP nanoparticles easily cross the blood-brain barrier and possess a strong affinity for the hyperphosphorylated tau seen in nerve cells. They inhibit neuronal death by suppressing many tau driven pathways implicated in the pathophysiology of AD, as confirmed by recent in-vivo & invitro investigations.[22] Curcumin-gold nanoparticles have successfully been developed to inhibit beta-amyloid aggregation, promote its dissociation, and mitigate Aβ-mediated peroxidase activity-mediated cytotoxicity. These nanoparticles have been shown for sustaining in vivo spatial learning and memory in rats. These findings hold promise for the diagnosis and management of AD by utilizing nanotechnology-based approaches.[23,24]

2.2. Parkinson's disease (PD)

PD is a progressive neurodegenerative disorder characterized by the loss of motor control, resulting in involuntary movements, tremors, rigidity, and difficulty performing day to day activities. The degeneration of the substantia nigra and the afterwards reduction in dopamine levels in the mesolimbic system play a crucial role in the pathogenesis of PD. The expression of alpha-synuclein, a protein associated with the disease, is significantly increased throughout the brain in PD and is considered a significant biomarker.[25,26]

To address the management of PD, researchers have developed a novel biodegradable nanoparticle composed of Polyethylene Glycolpolylactide-Polyglycolide (PEG-PLGA) loaded with lactoferrin. This nanoparticle formulation aims to facilitate the accumulation of lactoferrin in the brain and improve central nervous system drug delivery in PD models. In vivo uptake studies in mice have demonstrated higher concentrations of lactoferrin-loaded nanoparticles in the brain models of PD, indicating their potential as nanotherapeutic candidates for managing the disease .In addition, albumin/PLGA nanosystems conjugated with dopamine have been developed and evaluated in mice models of PD. These nanosystems have successfully crossed the blood-brain barrier, restored dopamine levels in the substantia nigra and had considerably better sensory-motor function, balance, motor control, and coordination than the rest of the group. This demonstrates the potential of these nanosystems as an effective approach for managing PD. These advancements in nanotechnology-based therapies offer promising strategies for the treatment and management of PD by specifically targeting the affected areas of the brain, enhancing drug delivery, and potentially improving the quality of life for patients.[27,28]

3. Challenges

Nanotherapeutics and nanotechnology offer numerous advantages for drug delivery in the treatment and management of central nervous system (CNS) diseases. However, they also face several limitations and challenges that must be addressed to fully harness their potential. One significant challenge is the genetic variation and differences in neural physiology among patients. Each individual may respond differently to nanotherapeutic agents, making it challenging to find a single treatment that is effective for all. Health care practitioners may need to diagnose neurological conditions individually and identify specific treatments tailored to each patient's needs. The efficacy

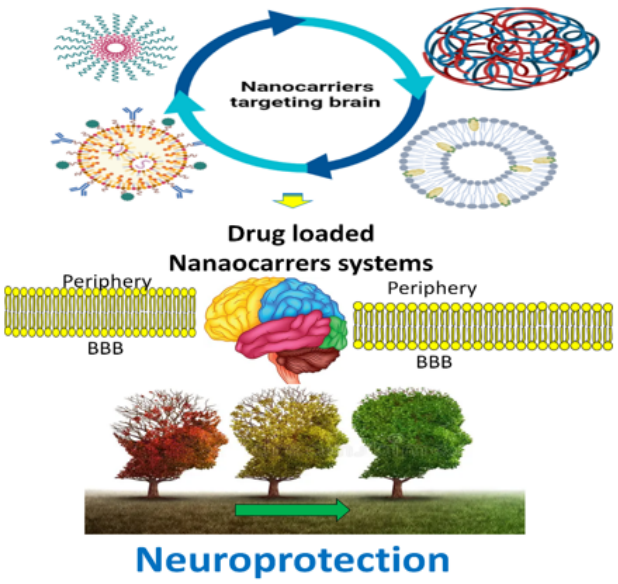

Fig. 1: Nano carrier system as a drug delivery in brain diseases

of nanotherapeutics is also constrained by pharmacokinetic limitations. Factors such as low absorption time and the possibility of absorption into other parts of the body can result in decreased concentrations of the active agent at the target site. This can impact the effectiveness of the treatment.[29,30]

Another challenge is the lack of real-time treatment monitoring to assess efficacy. Without the ability to monitor the response and progress of patients receiving nanotherapeutics, healthcare practitioners face difficulties in tracking the impact of the treatment and making necessary adjustments. This limitation hinders the optimization of treatment outcomes .Furthermore, nanotherapeutics is still in its early stages of development, requiring significant financial investments for extensive research and the development of therapeutic agents. The high costs associated with research and development contribute to the expensive nature of acquiring and affording these agents. This poses a barrier to their widespread application and accessibility.[31]

Overcoming these challenges and limitations is crucial to enhance the applicability and scope of nanotherapeutics in the management of CNS diseases. Further research, innovation, and investment are needed to improve the understanding of individual patient responses, optimize pharmacokinetic properties, establish effective monitoring methods, and make nanotherapeutics more cost-effective and accessible.[32,33] In summary, while nanotherapeutics offer promising possibilities for the treatment and management of CNS diseases, challenges such as individual variability, pharmacokinetic limitations, lack of real-time monitoring, and high costs need to be addressed. Overcoming these challenges will pave the way for the wider utilization and effectiveness of nanotherapeutics in improving patient outcomes and quality of life.

4. Conclusion

Neurodegenerative disorders have a significant global impact, affecting a large number of individuals. To address the need for more effective treatments, extensive research is necessary to develop new therapeutic options. In this context, the field of nanomedicine has emerged, offering the potential for reformulating existing drugs into nanosystems. Numerous nanodrug delivery systems have been explored as potential candidates for the diagnosis and management of neurological disorders. While these nanosystems have shown promise in cell and animal models, their efficacy and safety in humans have yet to be fully established. Nevertheless, early studies have demonstrated their potential for mitigating symptoms and providing therapeutic benefits, warranting further optimization and research. Despite the promising nature of these novel therapeutic tools, they face certain challenges and limitations that need to be addressed to expand their applications in nanomedicine. These challenges may include issues related to scalability, efficacy in human subjects, and safety concerns. While initial studies have shown positive results, it is crucial to conduct more comprehensive investigations to determine the feasibility and practicality of these nanosystems for clinical use. Moreover, regulatory considerations, manufacturing scalability, and cost-effectiveness are important factors that need to be addressed to ensure the wider implementation and accessibility of nanomedicine approaches.

In summary, the development of nanosystems for the diagnosis and management of neurodegenerative disorders represents a promising avenue for research and innovation. While early studies have shown encouraging results, further investigation and optimization are required to establish their safety, efficacy, and scalability for human use. Overcoming the challenges and limitations associated with these nanosystems will pave the way for their expanded applications in nanomedicine, ultimately benefiting individuals affected by neurological disorders.

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None.

6. Conflict of Interest

None.

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