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Advances in Nanomedicine for Treatment of Neurological Disorders

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ABSTRACT

Nanomedicine has become a revolutionary approach to the management of neurological conditions, providing the innovative means of addressing the flaws of the traditional treatment methods. The review concentrates on preclinical animal research, emphasizing on the progress of nanoparticles-based delivery systems, liposomes, micelles, dendrimers and nanogels, which have the potential to increase the drug transport across the blood-brain barrier, specific brain targeting, and controlled, sustained delivery of therapeutic agents. The main results indicate that functionalized nanoparticles are able to suppress neuroinflammatory signals, eliminate reactive oxygen species, and prevent neuroprotection and neuroregeneration, and thus enhance the cognitive and motor outcomes in models of Alzheimer disease, Parkinson disease, stroke, and traumatic brain injury. Although these are encouraging findings, there are still issues to deal with, including long-term safety, biocompatibility, scalability of synthesis, and translational feasibility, which means that further studies must be performed to maximize the effectiveness and enable a clinical implementation. Although, comprehensive, preclinical data highlights the potential of nanomedicine as a means of transforming treatment approaches to central nervous system disease so that more specific, effective, and safer treatment approaches can be provided in the future.

Key Words:

Nanomedicine, Neurological Disorders, Blood-Brain Barrier, Nanoparticles, Liposomes, Micelles, Dendrimers, Nanogels.

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1. INTRODUCTION

Neurological illnesses such as Alzheimer's disease, Parkinson disease, stroke, and traumatic brain injury are significant problems that are seen in millions of people in the world and are extremely difficult to treat[1]. The intricacy of the central nervous system (CNS) and the existence of blood-brain barrier (BBB) inhibit the capacity of typical medicines to attain treatment levels in the brain, commonly causing under-optimal results and side effects in the body. These challenges have been challenged with the recent finding in nanomedicine, which provides the avenue through which therapeutic agents can be delivered in a targeted, controlled and sustained manner[2]. It has been demonstrated in preclinical studies that nanoparticle-based systems can improve drug bioavailability, neuroinflammation, scavenge reactive oxygen species, and neuroprotection and regeneration, providing new promise of successfully treating CNS disorders[3].

1.1. Background

Neurological diseases such as Alzheimer disease, Parkinson disease, stroke, and traumatic brain injury are some of the most complicated diseases in the field of modern medicine with little or no treatment methods. The blood-brain barrier (BBB) is a highly protective barrier of the central nervous system (CNS), which is selective both in terms of substances that are permitted entry into the brain[4]. Although the BBB maintains neural homeostasis, it also severely limits the intake of therapeutic agents, which makes the traditional administration of drugs ineffective in most cases. Besides, other factors that also reduce the efficacy of traditional therapies are systemic metabolism, poor solubility of drugs and off-target effects.

Nanomedicine has been identified as a revolutionary solution to such problems through the use of nanoscale drug delivery vehicles. Such systems as liposomes, micelles, dendrimers and nanogels may be designed to cross the BBB, deliver to particular brain areas or cell types and deliver controlled and sustained release of neuroprotective or regenerative factors[5]. The preclinical trials on animal models have shown that these nanotherapeutics have the potential to enhance neuronal survival, decrease oxidative stress and inflammation and induce functional recovery in CNS disorders[6].

1.2. Objectives of the Review

This review aims to:

- To summarize recent advancements in nanoparticle-based therapies for neurological disorders using preclinical animal studies.
- To examine nanoparticle types, functionalization strategies, and targeted delivery mechanisms.
- To assess the efficacy of nanomedicine in reducing neuroinflammation, oxidative stress, and promoting neuroprotection and regeneration.
- To identify research gaps, challenges, and propose directions for future clinical translation.

1.3. Importance of the Study

It is important to learn the progress made in nanomedicine concerning CNS disorders to come up with better and safer treatment methods[7]. The actual preclinical studies can be used to understand the mechanism, safety, and therapeutic potential of nanotherapeutics which can be used to design future clinical research[8]. Overcoming the difficulties of the BBB and traditional methods of drug delivery, nanomedicine promises a lot to change the results of patients with debilitating neurological diseases.

1. NANOPARTICLE-BASED DRUG DELIVERY SYSTEMS

Nanoparticles have transformed the delivery of therapeutic agents to the central nervous system (CNS) to overcome the blood-brain barrier (BBB) drawback. Most of the conventional drugs are restricted by the BBB and this means that it is hard to get therapeutic levels in the brain[9]. Drug delivery systems grounded on nanoparticles offer novel approaches to deliver drugs, genes, and neuroprotective agents directly to the target locations in the CNS. Such systems can be designed in such a way that they enhance drug solubility, stability, bioavailability, and controlled release, in addition to reducing side effects in the system[10]. Various types of

nanoparticles, such as liposomes, micelles, dendrimers and nanogels have demonstrated good results in preclinical animal studies.

2.1.Liposomes and Micelles

Liposomes are vesicles that are spherical in nature, consist of phospholipid bi-layers enclosing an aqueous core. They are able to entrap hydrophilic and hydrophobic drugs thus are very versatile carriers. Smaller amphiphilic molecules, which are the products of the self-assembling of surfactants in the aqueous solution, are called micelles[11]. Their hydrophobic core enables them to encapsulate poorly water-soluble drugs and the hydrophilic shell increases the circulation period in the bloodstream.

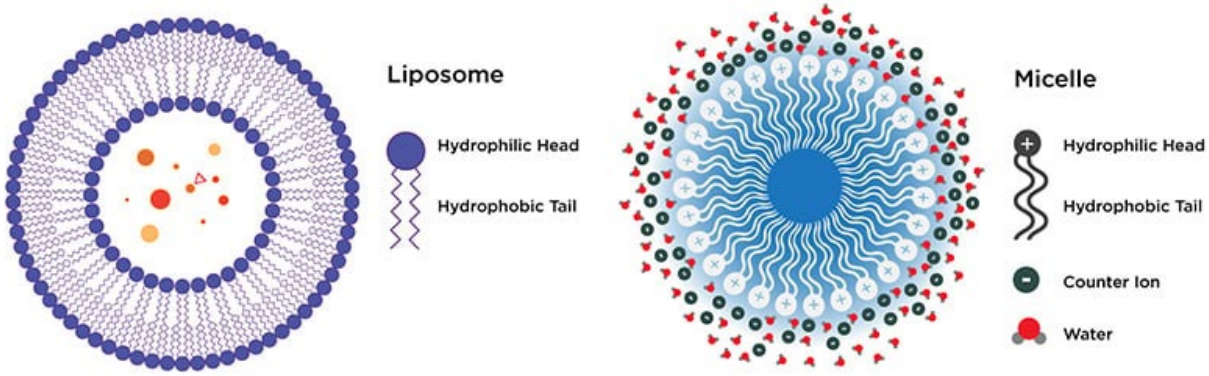

Figure 1: Liposomes and Micelles[12]

Liposomes and micelles have shown great possibilities in crossing the BBB in preclinical studies. Their delivery to the brain has been increased by functionalization with ligands (e.g. transferrin or endothelial receptor-targeting peptides).

Table 1: Preclinical Applications of Liposomes and Micelles[13]

Disease Model	Nanoparticle Type	Therapeutic Agent	Key Outcomes	Animal Model
Stroke	Liposomes	Neuroprotective agents	Reduced infarct volume, improved neuronal survival	Rodents
Alzheimer's Disease	Micelles	Antioxidants, anti-inflammatory drugs	Reduced amyloid-beta, improved cognition	Rodents
Parkinson's Disease	Micelles	Neuroprotective drugs	Attenuated neuronal death, improved motor function	Rodents

Advantages:

- Good encapsulation capacity towards hydrophilic and hydrophobic drugs.
- Capability to access particular parts of the brain through superficial modification.
- Local delivery causes a reduced systemic toxicity.

Limitations:

- Rapid elimination by the reticuloendothelial system (RES).

- Physiological conditions instability.

2.2.Dendrimers

Dendrimers are macromolecules with several functional groups on the surface that have a highly branched and tree-like structure[14]. Their design enables them to be controlled in size, shape and surface chemistry with great precision and are therefore suitable in targeted drug delivery/gene therapy. The core in the middle is able to entrap small molecules and the outer branches may be functionalized with targeting ligand, imaging or therapeutic moieties.

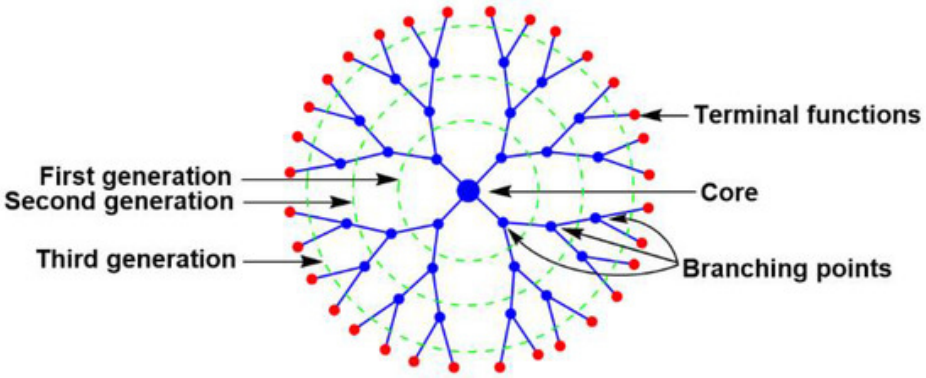

Figure 2: Structural Illustration of a Third-Generation Dendrimer Highlighting Core, Branches, and Surface Functional Groups[15]

CNS Animal models have had success with the dendrimers to deliver anti-inflammatory drugs, gene silencing molecules, and neurotrophic factors. Incidences in rodent models of Alzheimer disease, dendrimer-conjugated therapeutic agents inhibited the deposition of amyloid-beta plaques and neuroinflammation. In the same way, in models of the disease Parkinson, the dendrimer-based systems helped in the delivery of neuroprotective compounds into dopaminergic neurons to enhance motor activities and minimize neuronal loss.

Table 2: Preclinical Applications of Dendrimers[16]

Disease Model	Nanoparticle Type	Therapeutic Agent	Key Outcomes	Animal Model
Alzheimer's Disease	Dendrimers	Anti-inflammatory, anti-amyloid agents	Reduced plaques, improved cognition	Rodents
Parkinson's Disease	Dendrimers	Neuroprotective drugs	Enhanced neuron survival, improved motor function	Rodents

Advantages:

- Branched structure has a high drug-loading capacity.
- Targeted delivery is made possible by functionalize surface.
- Has the capability of transporting small molecules, genes and proteins.

Limitations:

- Cytotoxicity may develop when not adapted appropriately.
- Complicated and expensive production.

2.3.Nanogels

Nanogels are cross-linked polymer networks, which are hydrophilic and three-dimensional and can be swollen in aqueous environment and still maintain their structure[17]. They have the ability to entrap a large number of therapeutic drug options, such as small drugs, proteins, or nucleic acids, and liberate them in a directed or stimuli-responsive fashion.

Nanogels have demonstrated a potential to reduce neuroinflammation, oxidative stress and neuronal death in animal stroke, TBI and neurodegenerative diseases models, as demonstrated in preclinical studies. Their tiny size enables them to penetrate the BBB effectively and surface functionalization to targeting ligands only improves site-specific delivery. Nanogel delivery of anti-amyloid and antioxidant agents in rodent models of Alzheimer diseases also showed significant enhancement of cognitive ability and decrease in neuron damage.

Table 3: Preclinical Applications of Nanogels[18]

Disease Model	Nanoparticle Type	Therapeutic Agent	Key Outcomes	Animal Model
Stroke	Nanogels	Anti-inflammatory agents	Reduced neuronal death, improved recovery	Rodents
Alzheimer's Disease	Nanogels	Antioxidants, anti-amyloid agents	Improved cognition, reduced plaque load	Rodents
Traumatic Brain Injury	Nanogels	Neuroprotective drugs	Reduced inflammation, enhanced neuronal survival	Rodents

Advantages:

- High water content- biomimetic of the biological tissues, increasing biocompatibility.
- Sustained and controlled drug delivery.
- Capable of the provision of extensive variety of therapeutics, such as proteins and nucleic acids.

Limitations:

- Hypothetical issues with mass production.
- Kinetics of stability and release should be optimized.

Drug delivery systems made using nanoparticles are liposomes, micelles, dendrimers, and nanogels; and they have displayed impressive preclinical effectiveness in the treatment of neurological illnesses[19]. These nanoparticles have a big potential of increasing the rate of therapeutic success and reducing systemic side effects by increasing BBB penetration, delivering specificity, and controlling release. Nevertheless, biocompatibility, stability, and scalability need to be optimized in the future in progression of translational studies.

3. TARGETED DELIVERY STRATEGIES

The most significant issue in the treatment of the neurological disorders is the accurate delivery of therapeutics to the affected areas of the brain with minimum side effects on the rest of the body[20]. The increasing drug levels at the target site and place are commonly achieved with conventional drug delivery as the blood-brain barrier (BBB) is restrictive and the drug is widely distributed throughout the body. To overcome these limitations, the use of specific nanoparticle

delivery plans has become a more progressive solution to improve the efficacy and safety of neurotherapeutics.

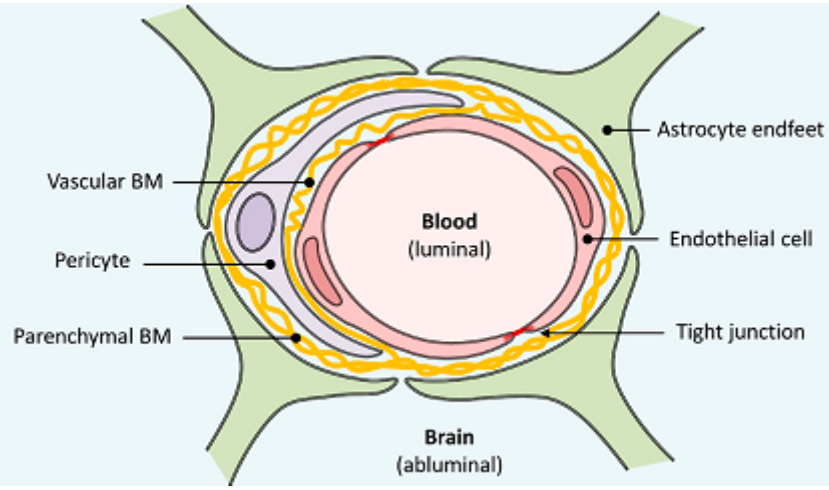

Figure 3: Blood-Brain Barrier (BBB)[21]

3.1.Functionalization with Targeting Ligands

A variety of targeting ligands can be functionalized onto nanoparticles as a way of enhancing specificity to neuronal cells, glial cells or specific brain regions[22]. Common ligands include:

- **Antibodies:** Nanoparticles can have monoclonal antibodies bound on them to identify particular receptors on neurons or pathological tissues. As an illustration, antibodies against the amyloid-beta plaques in Alzheimer can be used to target nanoparticles to the target site to amplify concentration of the drug at the site and reduce off-target interactions.
- **Peptides:** Short peptides, which mimic natural ligands or interact with transporters on the BBB (e.g., transferrin receptor, insulin receptor) promote receptor-mediated transcytosis across the BBB[23]. Functionalized nanoparticles functionalized with peptides have demonstrated increased brain absorption in stroke and Parkinson rodent models.
- **Aptamers:** These are nucleic acid-based ligands, aptamers, that have the ability to selectively bind cellular markers. Aptamer-functionalized nanoparticles have the potential to provide a highly specific targeted therapy of neurons or glial cells undergoing a neurodegradative process.

These surface modifications enable nanoparticles to bypass the BBB more effectively and also to target particular population of neurons or pathological structures including amyloid plaques, Lewy bodies or ischemic areas[24].

3.2.Mechanisms of Targeted Delivery

The common mechanisms used in targeted delivery strategies include one or more of the following:

1. **Receptor-Mediated Transcytosis:** Nanoparticles attach to receptors of the endothelial cells of the BBB and are actively delivered into the brain[25].
2. **Cell-Penetrating Peptides (CPPs):** CPPs help nanoparticles to be internalized into glial cells or neurons.

3. **Pathology-Specific Targeting:** Pathological markers, e.g. overexpressed protein or inflammatory marker can be used to target functionalized nanoparticles to accumulate preferentially in diseased brain regions[26].

3.3.Preclinical Evidence

The effectiveness of animal models in preclinical studies has been demonstrated with regard to targeted delivery of nanoparticles:

Table 4: Preclinical Evidence of Targeted Nanoparticle Delivery in Neurological Disorders

Author's Name	Disorder	Nanoparticle Type	Targeting Ligand	Animal Model	Method	Key Outcomes
Arora & Baldi, 2024[27]	Alzheimer's Disease	Liposomes / Dendrimers	Anti-amyloid-beta antibody	Transgenic mice	Intravenous nanoparticle administration	Selective accumulation in amyloid plaques, reduced plaque burden, improved cognition
Nemeth et al., 2019[28]	Parkinson's Disease	Polymeric nanoparticles	Dopaminergic neuron-targeting peptide	Rodents	Systemic administration via tail vein	Enhanced dopaminergic neuron survival, improved motor function
Gupta et al., 2024[29]	Stroke	Liposomes / Micelles	Transferrin or RGD peptide	Rodents	Intravenous administration with targeting ligands	Accumulation in ischemic regions, reduced neuronal damage, improved functional recovery
Gholami et al., 2024[30]	Traumatic Brain Injury	Liposomes	Anti-inflammatory aptamer	Rodents	Tail vein injection of functionalized nanoparticles	Targeted delivery to injured regions, attenuated microglial activation, reduced cytokine levels

Specific methods of delivery will increase the accuracy of nanoparticle-based treatment of neurological diseases. Researchers can further increase penetration by the BBB using ligands, e.g. antibodies, peptides or aptamers to control the nanoparticles, subsequently delivering therapeutic agents in diseased neurons selectively and also, attain better treatment results in

animal models. These strategies need to be optimized further to ensure maximization of effectiveness, minimization of unwanted outcomes, and translation to clinical practice.

4. NEUROPROTECTIVE AND REGENERATIVE APPROACHES

Several neurological diseases such as stroke, Alzheimer disease, Parkinson disease and traumatic brain injury include neuronal damage, which is triggered by oxidative stress, inflammation and inhibited neurogenesis[31]. Conventional pharmacological treatments often have no therapeutic effect on the brain because of the blood-brain barrier (BBB) and generally the metabolism in the body restricting their neuroprotective capacity. The challenge presented by nanoparticle-based delivery systems is that it offers a potential solution to the delivery of neuroprotective and regenerative factors straight to the brain by providing a targeted, controlled and sustained method of delivering these factors to the CNS[32].

➢ Modulation of Neuroinflammatory Pathways

Neuroinflammation is an apparent feature of numerous CNS diseases and leads to the loss of neurons and disease progression. To counter inflammation, nanoparticles have been developed to give anti-inflammatory agents, cytokine suppressors and gene-silencing aptamers[33]. For example:

- Polymeric nanoparticles of anti-inflammatory agents like dexamethasone or minocycline have demonstrated a significant decrease in the microglial activation and pro-inflammatory cytokines in rodent models of ischemic stroke.
- Like nanoparticles, dendrimer-based nanoparticles conjugated with anti-inflammatory agents are selectively accumulated in activated microglia, and thus reduce neuroinflammation without targeting healthy brain cells.

These methods not only minimize the damage to the neurons, but also provide a more good environment to repair and regenerate.

➢ Scavenging Reactive Oxygen Species (ROS)

One significant cause of neuronal injury in neurodegenerative conditions is oxidative stress which is excessive generation of reactive oxygen species (ROS)[34]. Nanoparticles may be utilized as antioxidant carriers or may be ROS scavengers:

- Oxide nanoparticles (nanoceria) are ROS-scavengers by their nature and have been demonstrated to protect neurons against oxidative injury in rodents with Parkinson and stroke diseases.
- Polymeric or liposomal nanoparticles containing antioxidants, such as curcumin, resveratrol, or N-acetylcysteine, are effective in reducing the levels of ROS and other lipid peroxidation, as well as preserving neuronal health in preclinical models.

Nanoparticles have the capacity to reduce the development of neurodegenerative diseases and advance neuronal survival by mitigating oxidative stress.

➢ Promotion of Neurogenesis and Neural Regeneration

Along with preserving the activity of the already existing neurons, nanoparticles can aid regeneration through the delivery of growth factors[35], genes, or small molecules to promote neurogenesis:

- **Neurotrophic factor loaded nanoparticles:** Brain-derived neurotrophic factor (BDNF), glial cell-derived neurotrophic factor (GDNF), and nerve growth factor (NGF) in nanoparticles have improved neuronal progenitor cell survival, differentiation, and migration in stroke and neurodegeneration animal models.
- **Nanoparticles:** Nanoparticles containing gene therapy in the form of small interfering RNA (siRNA) or plasmid DNA can be used to regulate gene expression in order to enhance neuronal repair and suppress cell death.
- **Combination strategies:** Nanoparticles containing antioxidants with neurotrophic factors have synergistic effects, enhancing neuronal survival, as well as neuronal functional recovery in rodent brain tissue.

The advantages of these regenerative approaches are two-fold; they block additional neuronal damage and also promote the repair processes in the CNS.

➢ **Preclinical Evidence**

The use of nanoparticle-based neuroprotective and regenerative therapies has always been proven to be effective in preclinical studies in animal models:

Table 5: Preclinical Nanoparticle Therapies for Neurological Disorders[36]

Disorder	Nanoparticle Type	Therapeutic Agent	Animal Model	Key Outcomes
Stroke	Liposomes	Antioxidants (curcumin, resveratrol)	Rodents	Reduced infarct volume, improved motor coordination, decreased neuronal apoptosis
Alzheimer's Disease	Dendrimers	Anti-inflammatory + anti-amyloid agents	Transgenic mice	Reduced amyloid-beta plaques, decreased neuroinflammation, improved cognitive performance
Parkinson's Disease	Nanoceria & GDNF-loaded nanoparticles	ROS scavengers & neurotrophic factor	Rodents	Protected dopaminergic neurons, improved motor function, reduced oxidative stress
Traumatic Brain Injury	Polymeric nanoparticles	Anti-inflammatory agents	Rodents	Attenuated microglial activation, reduced cytokine levels, enhanced neuronal survival

Neuroprotective and regenerative NPs based on nanoparticles are the innovative solution to CNS disorders. Nanoparticles are capable of alleviating neuronal damage and promoting functional recovery by modulation of neuroinflammatory pathways, scavenging prohibited oxygen species, and neurogenesis in preclinical models. Further development needs to be done on these systems to make them safer, more effective, and ultimately translate able to clinical practice.

5. CHALLENGES AND LIMITATIONS

Although the use of nanoparticles in drug delivery provides revolutionary opportunities in neurological disorders treatment, various key issues have to be tackled to make sure their

successful and safe implementation in preclinical models to clinical practice[37]. These obstacles mainly relate to the biological obstacles, safety issues and production restrictions.

5.1.Blood-Brain Barrier Penetration

The blood-brain barrier (BBB) is a highly selective and protective barrier that is made up of very closely interlaced endothelial cells, pericytes and astrocytic end-feet. It serves majorly in maintaining the CNS homeostasis by limiting the intake of substances which may harm the body through the blood. But this protective system has a terrible consequence as well in the sense that it impairs the passage of therapeutic agents to the brain.

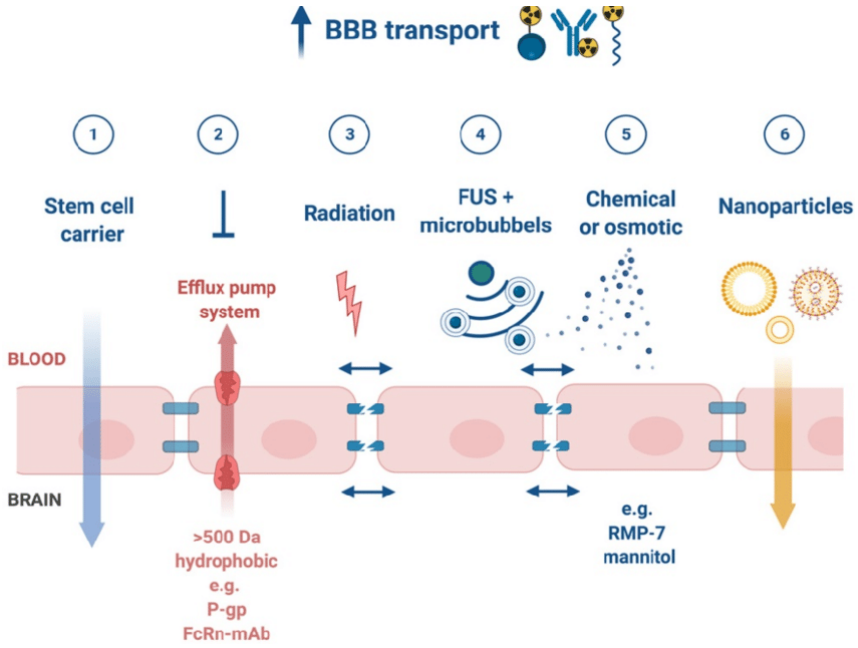

Figure 4: Approaches to Enhance Blood-Brain Barrier (BBB) Penetration for Targeted Drug Delivery[38]

The figure demonstrates the important measures to increase drug delivery across the blood-brain barrier (BBB) which is one of the most significant issues in treatment of neurological diseases. Some of the approaches are harnessing stem cell homing, regulating efflux pumps, targeted irradiation, focused ultrasound with microbubbles, infusion of hypertonic solution or vasodilator and nanoparticle mediated delivery. The purpose of these strategies is to temporarily or selectively open the BBB so that specific therapeutic agents can be delivered into the brain in a controlled, selective, efficient, and minimally side effects systemically.

5.2.Biocompatibility and Toxicity

Long-term safety of nanoparticles is of utmost importance since the specific physicochemical characteristics of such nanoparticles, including size, surface charge, and chemical composition, may affect biocompatibility and cause cytotoxic effects[39].

- **Potential Toxic Effects:** It has a potential to cause oxidative stress, inflammation, or unwanted immune response in the CNS or peripheral organs due to the nanoparticles. Some of these materials, particularly inorganic nanoparticles such as gold, silver, or cerium oxide can build over the long-run, creating the issue of chronic toxicity.
- **Necessity of Comprehensive Assessment:** Systematic evaluation of acute and long-term toxicity, immunogenicity, and biodegradation is necessary. The preliminary

understanding of animal studies should not be extrapolated because of the variations in the metabolism and immunity of animals and humans.

- **Improvement Strategies:** The cytotoxicity can be lowered by surface modification with biocompatible polymers (e.g. PEGylation) and by using biodegradable materials.

5.3.Scalability and Reproducibility

To be clinically translated nanoparticles need to be generated in large scale and in a consistent quality, size distribution, and surface properties[40]. Nevertheless, the realization of this is extremely difficult:

- **Complex Synthesis:** Multipass Synthesis of many nanoparticles needs to be carefully done and functionalized with targeting ligands, and this is not always readily standardized.
- **Three-to-Three Batch Variability:** Therapeutic performance and safety can be variably affected by the changes in the particle size, drug loading efficiency and surface chemistry that does not result in consistent outcomes.
- **Regulatory Considerations:** To gain regulatory approval standardization is required and insensitivity to reproducibility may slow down or inhibit clinical uptake. To increase production and simultaneously maintain quality high levels, it is necessary to have high-technological production resources and a high level of quality control measures.

5.4.Additional Considerations

- **Immune Clearance**: The reticuloendothelial system (RES) tends to recognize nanoparticles which leads to immediate elimination out of circulation and decreased brain therapeutic availability[41].
- **Cost and Complexity:** Nanoparticles with a high level of functionalization or targeting can be costly and this may not be accessible to everyone or be used widely.
- **Differences in Species:** BBB differences, immune responses and metabolism BBB differences between animals and humans: Preclinical efficacy in animal species may not be fully retained in humans.

Although the nanoparticle-based therapies have enormous potential in the treatment of the neurological disorders, their clinical application is hampered because of the difficulty in remarkable penetration of the blood brain barrier, the long-term biocompatibility, toxicity, and scalable production. The only way to maximize the therapeutic potential of nanomedicine in the CNS is to deal with these limitations by ensuring that nanomedicine is carefully designed, optimized in materials, possessing specific delivery strategies, and rigorously tested in preclinical trials[42].

6. DISCUSSION

Nanomedicine is an emerging discipline that has been developing quickly as an alternative approach to overcome the shortcomings of current treatments to treat the neurological illnesses. Animal studies Preclinical animal studies have shown that nanoparticles have the potential to deliver drugs across the blood-brain barrier, specifically target therapies to diseased areas, and deliver controlled and sustained release of therapeutic agents. Nanoparticle based strategies have neuroprotective and regenerative advantages, including modulation of neuroinflammatory processes, scavenging of reactive oxygen species and stimulation of

neurogenesis. These results demonstrate the promise of nanomedicine to enhance functional outcomes in diseases like Alzheimer's disease, Parkinson's disease, stroke, and traumatic brain injury and, at the same time, reduce the systemic toxicity and off-target effects[43].

6.1.Interpretation and Analysis of Findings

The reviewed preclinical studies indicate that nanomedicine provides a revolutionary model of treatment of neurological disorders. Drug delivery systems based on nanoparticles such as liposomes, micelles, dendrimers, and nanogels can be used to overcome the limiting properties of the blood-brain barrier (BBB) and increase the level of therapeutic concentration at target locations. Specific accumulation of targeted therapy in diseased areas reduces off-target effects and increases the potential therapeutic efficacy by selecting the site of action of the target (e.g. by functionalizing with antibodies, peptides or aptamers)[44].

Nanoparticle-based neuroprotective/regenerative therapies have great potential in reducing neuronal injury. The administration of nanoparticles that contained antioxidants or a reactive oxygen species (ROS) scavenger, neurotrophic factor, or gene-silencing molecule was effective in reducing oxidative stress and neuroinflammation, as well as, apoptotic pathways in animal models. Besides, the strategies based on the combination of antioxidants and neurotrophic factors were used in a combinatorial manner, and they were found to have a synergistic effect, enhancing the survival of neurons and functional recovery.

Continued preclinical evidence indicates better motor and cognitive outcomes of animal models of stroke, Alzheimer disease, Parkinson disease and traumatic brain injury, which points to the fact that nanoparticles can be effectively used to regulate pathological processes in these diseases. These results support the possibility of nanomedicine to circumvent the drawbacks of traditional pharmacological treatments especially in the implementation of controlled, sustained and targeted delivery into the CNS[45].

6.2. Implications and Significance

The considered evidence indicates a great possibility of nanomedicine to revolutionize the treatment of neurological disorders:

- **Improved Liquidity:** When compared to unfunctionalized nanoparticles, functionalized nanoparticles increase BBB penetration in the body and allow the space to be targeted to the pathological location to reduce systemic exposure and side effects[46].
- **Neuroprotection and Regeneration:** Nanoparticles have an ability to prevent neuronal loss as well as stimulate repair pathways to have a dual therapeutic effect.
- **Platform Versatility:** Due to the versatility of different nanoparticle systems, it is possible to deliver small molecules, proteins, nucleic acids and combination therapy[47].

These results have significant implications on therapeutics development of CNS disorders in the next generation and they form a basis of clinical translation in the future. Nanomedicine has the potential to decrease drug toxicity, enhance patient outcomes and possibly reduce recovery times in neurological conditions because it has been shown to have better efficacy at lower doses.

6.3. Gaps in Current Research

Even though these results have shown promising preclinical results, several research gaps restrict the use of the findings into clinical uses:

1. **Long-Term Safety:** There are few studies of toxicity and immunogenicity. The vast majority of research is done in short-term effects of rodents, and it remains unclear how chronic exposure and accumulation might be in humans.
2. **Species-Specific differences:** BBB permeability, immune reactions, and nanoparticle metabolism vary among different species and this poses a problem in extrapolation of the animal model findings in humans.
3. **Scalability and Reproducibility:** Most nanoparticle preparations involve complicated synthesis in terms of accurate size, surface chemistry and ligand functionalization. There are no standardized and reproducible manufacturing processes that can be used in large scale production.
4. **Poor Mechanistic Insight:** Therapeutic efficacy has been proven however the exact molecular dynamics and pathways that the nanoparticles alter is poorly comprehended, especially with respect to neurogenesis and lasting neuronal healing[48].
5. **Comparative Studies:** There are very few direct comparative studies of the different nanoparticle platforms, targeting strategies and therapeutic agents, which hinders optimization and clinical prioritization.

6.4.Future Research Directions

In order to fill these gaps and improve the potential of translational research, the studies in the future must be aimed at the following points:

- **Advanced Targeting Strategies:** Construct versatile nanoparticles that are able to cross the BBB efficiently and homing to pathological areas, release drugs in a stimulus regulated fashion.
- **Long-Term Toxicity and Biocompatibility Studies:** Larger animal models such as non-human primates should be used to conduct chronic exposure studies, which determine safety, accumulation and immunogenicity[49].
- **Comparison and Combination Therapies:** Compare the various nanoparticle systems and different strategies to combine them to come up with the best formulations to be translated into clinical applications.

Overall, although the same research (preclinical studies) demonstrate a strong promise of nanomedicine in treating neurological disorders, future directions should be dedicated to the issues of safety, mechanistic insights, reproducibility, and translational viability to achieve clinical effects.

7. CONCLUSION

In this review, it is emphasized that nanomedicine has shown great advancements in the development of therapeutic approaches on neurological conditions using preclinical animals. Systems involving nanoparticles, such as liposomes, micelles, dendrimers, and nanogels have shown themselves capable of overcoming the limiting blood-brain barrier, including delivery of drugs with precision and controlled release to improve therapeutic effects and reduce side effects of systems. Their role in the amelioration of neuroinflammatory, reactive oxygen species scavenging activity, and the promotion of neuroprotection and neuroregeneration is highlighted by evidence obtained in animal models of Alzheimer disease, Parkinson disease, stroke, and traumatic brain injury. The results confirm the significance of nanotechnology as a

new platform of neurotherapeutics in the future. Nonetheless, issues on safety in the long term, scale reproducibility, and translational use, should be overcome with strict preclinical trials, better targeting mechanisms, and standardized manufacturing guidelines. Nanomedicine has great potential to transform the treatment of the neurological diseases with further research and development and seal the gap between clinical application and management.

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