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Recent Updates on the Role and Challenges of Nanotherapeutics in Diagnosis and Management of Epilepsy, Neurodegenerative Diseases

Karen DSouza[1]; Namitha Bannimath[4]; Subhankar P Mandal[1]; Deepshikha Singh[1]; Prabitha Prabhakaran[1]; Rajashree Deka[6]; Shaik Mohammed Suhail[4]; Sheshagiri R Dixit[1]; Chandan RS[1]; Vladimir N Nikolenko[2,5]; Gurupadayya Bannimath[1]; Prashant Vishwanath[7]; Mikhail Y Sinelnikov[2]; Junqi Liu[3]; Ruitai Fan[3]*; Narasimha M Beeraka[1,2,3]*

[1]Department of Pharmaceutical Chemistry, JSS Academy of Higher Education and Research (JSS AHER), JSS College of Pharmacy, Mysuru, Karnataka, India.

[2]Department of Human Anatomy, I.M. Sechenov First Moscow State Medical University of the Ministry of Health of the Russian Federation (Sechenov University), 8/2 Trubetskaya Street, Moscow, 119991, Russia.

[3]Department of Radiation oncology, Cancer Center, The First Affiliated Hospital of Zhengzhou University, #1 Jianshedong Str., zhengzhou, 450052, China.

[4]Department of Pharmacology, JSS Academy of Higher Education and Research (JSS AHER), JSS College of Pharmacy, Mysuru, Karnataka, India.

[5]M.V. Lomonosov Moscow State University, Moscow, Russian Federation.

[6]Animal Physilogy and Biochemistry Laboratory, Department of Zoology, Gauhati University, Guwahati-781014, Assam, India.

[7]Center of Excellence in Molecular Biology and Regenerative Medicine, Department of Biochemistry, JSS Medical College, JSS Academy of Higher Education and Research, Mysore, India.

***Corresponding Author(s): Narasimha M Beeraka[1] & Ruitai Fan[3]**

[1]Department of Pharmaceutical Chemistry, JSS Academy of Higher Education and Research (JSS AHER), JSS College of Pharmacy, Mysuru, Karnataka, India.

[3]Department of Radiation oncology, Cancer Center, The First Affiliated Hospital of Zhengzhou University, #1 Jianshedong Str., zhengzhou, 450052, China.

Email: bnmurthy24@gmail.com & fccfanrt@zzu.edu.cn

Abstract

Neurological diseases incidence led to the poor quality of life in several patients subsequently results in the higher mortality rate. The rapid advancement in the nanotechnology is leading to the design of nanotherapeutics in the form of nanocarrier systems to target the pathophysiology of epilepsy, and neurodegenerative diseases such as Alzheimer's Disease (AD), and Parkinson's Disease (PD). The aim of this study is to explore the efficiency of nanosystems in the diagnosis and management of epilepsy, and AD, and PD. We have searched Pubmed, Medline, relemed, national library of medicine for the published articles pertinent to nanotherapeutics, and challenges related to nanotherapeutics usage in the neurological diseases. In this review, we have discussed the targeted delivery of active therapeutics across central nervous system mainly to modulate the activity of neurons, and endothelial cells. Furthermore, the efficiency of nanobioelectronic-implantable transient electronic devices, 'pH responsive nanomaterial -based therapeutics' and

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electro-responsive nanosystems were discussed against epilepsy. In addition, the efficacy of curcumin-loaded nano-drug delivery systems, monoclonal anti-tau antibody-coated gold nanoparticles, Polyethylene Glycolpolylactide-Polyglycolide (PEG-PLGA) nanoparticle loaded with lactoferrin, Albumin/PLGA nanosystems conjugated with dopamine, curcumin-loaded onto T807/RPCNP nanoparticles were discussed against neurodegeneration. This review benefits neurologists, and clinicians to have keen knowledge pertinent to the nanotherapeutics implications and their challenges in the usage against neurological diseases.

Introduction

Over the last few years, neurodegenerative disorders have surged globally [1]. Neurodegenerative diseases could impair the normal functioning of the brain causing cognitive, sensory, and motor disabilities and thereby reducing quality of life [2]. There is a growing demand for new therapeutic options to manage these disorders, however due to 'high R&D costs, long-term research, high failure rate, unknown pathophysiology, lack of adequate diagnostic models, inefficiency in crossing physiological barriers, and Blood Brain Barrier (BBB), and failure to meet pharmacokinetic barriers' and ultimately high cost of the drug manufacturing has been making treatment accessibility very difficult among the patients diagnosed for neurological diseases like epilepsy, Alzheimer's disease, and Parkinson's disease. Several drugs which can be used to treat neurological disease require nanoformulations as part of novel drug delivery systems to enhance the drug entrapment efficiency, and drug delivery at a higher rate and in a sustained manner at the site of pathological region. Hence, nanotechnology and its advantages have been successfully utilized to develop various therapeutic and diagnostic systems by altering nanosystem properties in order to facilitate loading of drugs. This novel therapy-based approach has changed the course of treatment in the clinical sector mainly in the patient with neurodegenerative disorders by providing site specific drug delivery, lesser side effects, easily penetrating BBB and overall improving therapeutic outcome of treatments as compared to conventional drug delivery systems [1,2]. This nanotherapeutics can target microglia-mediated pathophysiology in neurodegeneration. Furthermore, stem-cell derived exosomes can be used as the nanotherpeutics to effectively mitigate the pathophysiology of neurodegenerative diseases [2].

Nanotechnology provides a wide range of engineered material systems for drug delivery, each having their own uniqueness and advantage. They include dendrimers, liposomes, hydrogels, metal nanoparticles, polymer nanoparticles, micelles, nanotubes, biodegradable nanoparticles, nanocomposites. Nano-drug delivery systems have been successfully used to treat various types of cancer, gene therapy, modulating immune system [1,2]. Multifunctionality, biocompatibility and versatility of nanotechnology can be leveraged to target brain tissue, permeate the BBB and overcome any pharmacokinetic barriers and thus make it an indispensable tool in diagnosis and treatment of various neurological disorders [2]. In this review, we have discussed the implications of nanotherapueutics in the neurological diseases and the current challenges pertinent to the usage of nanotherapeutics in the management of these diseases.

Literature search

A thorough literature survey of several databases such as Pubmed, Medline, eMedicine, National Library of Medicine (NLM), and ReleMed for the published reports, and articles including review and original types. The information pertinent to the updated novel implications of nanotechnology in neurodegenerative disorders was gathered and reported.

Implications of Nanotherapeutcs in the neurological diseases

Epilepsy

Epilepsy is a complex neurological disorder characterized by the incidence of seizures due to abnormal neuronal signalling. Millions of people are diagnosed with epilepsy around the world annually adding to the demand for safer and efficacious therapeutic options for the management of epilepsy. In recent times, various nanotechnology-based therapeutic and diagnostic agents have been developed for the management of epilepsy [2]. For instance, 'nanobioelectronic-implantable transient electronic devices' are referred to as the automated transient nanogenerators equipped with electrically charged nanomaterials which function as biomechanical sensors to monitor neuronal activity of the brain and release anticonvulsants in response to a seizure attack. The distinct, abnormal neuronal activity is successfully detected in the *in vivo* studies through signal amplifier and wireless emitter which triggered electrothermal drug (phenobarbital) release from controlled resistor heater attached to the nanogenerators. The decrease in seizure frequency and biodegradability is successfully evaluated through *in vivo* and *in vitro* studies. Such nanobioelectronic implants can be optimized for successful management of epilepsy for obtaining effective clinical outcomes in the epilepsy patients [2-4].

The 'pH responsive nanomaterial -based therapeutics' modulates pH at the diseased site to diagnose epilepsy and subsequently release drug locally without affecting normal tissue and ensuring site-specific action. In epilepsy conditions, microenvironment pH shifts from neutral to acidic or alkaline due to the pathophysiology factors such as inflammation, hypoxia, excess carbonic acid. Such pH responsive nanocarriers (modified hydrogels, liposomes and other nanoparticles) functionalized with pH sensitive agents which can effectively detect change in pH and cause physical change, subsequently triggering the drug release by weakening drug-polymer bonds. The pH-responsive macromer poly(methacrylic acid-g-ethylene glycol) can be used for pregabalin prolonged drug delivery for 5 hours with good

drug release profile in basic PH [5-8].

Electro-responsive nanosystems comprised of nanostructures made of electroresponsive polymers which undergo conformational changes in response to the fluctuating electrical environments specifically in the abnormal neuronal impulses during epilepsy and effectively release drug in response to electrical stimuli. An electroresponsive nanosystem for on-demand drug delivery comprising of phenytoin-loaded onto electroresponsive hydrogel nanoparticles linked to angiopep-2 to facilitate BBB permeation was evaluated using electrical and chemical-induced seizure models and successfully lowered phenytoin dose, lowered seizure duration and frequency. This kind of nanostrategies may generate effective clinical outcomes in the patients with epilepsy [8-11].

Alzheimers disease (AD)

Alzheimer's disease is a neurocognitive abnormality caused by the atrophy of the brain leading to dementia, subsequently induce damage to the core mental functions. Lack of proper diagnostic methods and etiology, and pathophysiology pertinent to AD are significant barriers to the efficient disease management [1].

Beta-Amyloid deposits in the brain are mostly observed in the patients diagnosed with AD. A unique fluorescent chelator (TBT) with excellent BBB permeability was developed with dual functionality due to the high affinity and selectivity towards Beta-Amyloid deposits allowing easy NIR imaging/diagnostics and inhibition of metal induced Beta-Amyloid aggregation (by chelating Zn^{2+} and Cu^{2+}) [12]. TBT binding affinity to Beta amyloid aggregates was proven by ThT fluorescence competition assay and the inhibition of beta amyloid aggregation by TBT was assessed in vitro by microBCA assay and visualized using TEM [12].

A series of novel phenothiazine compounds were developed as smart NIRF imaging probes for diagnosis of Beta Amyloid deposits and as the inhibitors of beta amyloid aggregation as potential treatment of Alzheimer's disease. They were evaluated for binding affinity to beta amyloid aggregates and showed good affinity in nanomolar scale. Aggregation inhibitory activity was assessed followed by fluorescence microscopy and showed activity in micromolar scale in addition to fluorescence staining of amyloid deposits confirming its diagnostic and therapeutic role in Alzheimer's disease [13].

Curcumin-loaded nanodrug delivery systems have been implicated in diagnosis and management of Alzheimer's disease. Curcumin based diagnostic nanosystems (micelles and nanoparticles) were developed using DSPE-PEG2000 and Pluronic 127; these nanosystem showed excellent penetration across the BBB for the detection of beta amyloid plaques at low concentrations due to its ability to it fluoresce as yellow/green under a violet/blue (436 nm) light [14,15].

Monoclonal anti-tau antibody-coated gold nanoparticles have been developed and validated as the in vitro targeting agents to detect tau protein in Cerebrospinal Fluid (CSF) and beta amyloid plaques in the brains of patient with AD [16]. Curcumin-loaded onto T807/RPCNP nanoparticles cross BBB easily and exhibit a high binding affinity to hyperphosphorylated tau in nerve cells, block multiple pathways involved in tau-associated pathogenesis of Alzheimer Disease as well as prevent neuronal death (proven by in vitro and in vivo studies)[17]. Curcumin-gold nanoparticles have been successfully developed to inhibit beta amyloid aggregation, cause its dissociation, subsequently mitigates Aβ-mediated peroxidase activity-mediated cytotoxicity thus retain spatial learning and memory in rats (*in vivo*) [18,19].

Parkinson's disease (PD)

Parkinson's disease is a neurodegenerative disorder which causes progressive loss of motor control and induces uncontrollable movements, tremors, rigidity and limits the ability of the patient to perform simple daily tasks. Degeneration of substantia nigra and subsequent deficit of dopamine across the mesolimbic system could cause a prominent pathophysiology of PD and the expression of alpha-synuclein is potentially higher across the brain during PD, and this alpha-synuclein expression is considered as the significant biomarker in PD [20].

A novel biodegradable Polyethylene Glycolpolylactide-Polyglycolide (PEG-PLGA) nanoparticle loaded with lactoferrin was developed to facilitate accumulation of lactoferrin in the brain thus facilitate CNS drug delivery in the PD models. In vivo uptake studies in mice has shown higher concentrations of lactoferrin-loaded nanoparticles in the brain models of PD and, thus demonstrating its potential as a nanotherapeutic candidate for the management of PD [20].

Albumin/PLGA nanosystems conjugated with dopamine were developed and evaluated in mice models. They have successfully penetrated the BBB, and restored the dopamine levels in substantia nigra and hence significantly improved motor control, coordination, balance and sensorimotor performance as compared to other groups [21].

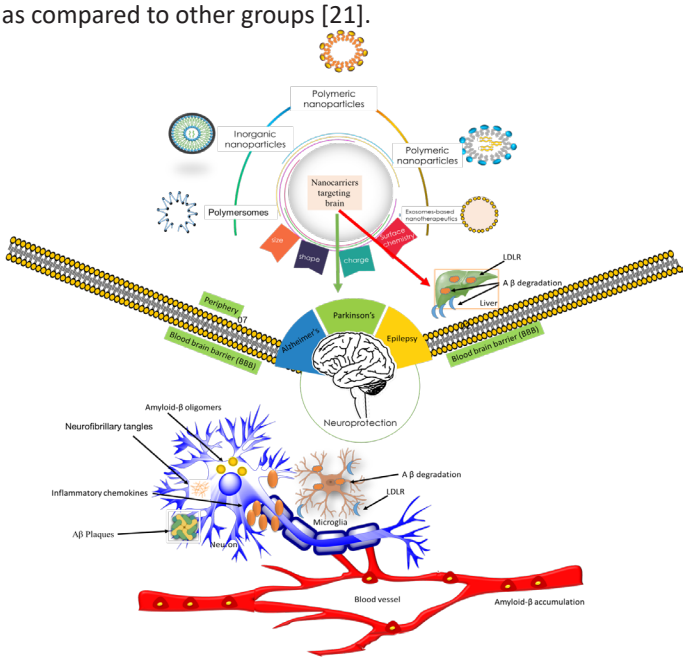

Figure 1: Implications of the polymeric/inorganic/ exosome-based nanotherapeutics in carriers [Curcumin-loaded nanodrug delivery systems Monoclonal anti-tau antibody-coated gold nanoparticles, polyethylene glycolpolylactide-polyglycolide (PEG-PLGA) nanoparticle loaded with lactoferrin, Albumin/PLGA nanosystems conjugated with dopamine, curcumin-loaded onto T807/RPCNP nanoparticles] in the diagnosis, and management of beta-amyloid peptides in Alzheimer's disease, and neurofibrillary tangles in Parkinson's diseases. LDLR: Low density lipoprotein receptor.

Challenges

Nanotherapeutics has many advantages over current conventional drug delivery. However, it comes with a few limitations and challenges which need to be understood in order to unleash its full potential as the treatment and management

options in neurodegenerative disorders. One major limitation is the genetic variation and differences in neural physiology among the patients, which makes it challenging to find a single therapeutic agent common to all. Health care practitioners may have to diagnose neurological disease conditions individually as well as to identify specific treatment for them [22]. Efficacy of Nanotherapeutics also constrained by the pharmacokinetic limitations include low absorption time, possibility of absorption into other body parts and ultimately decreased concentration of active agent at the site of action [23].

Real-time treatment monitoring for assessing efficacy is not possible and hence it becomes difficult for the health practitioners to track patient progress and significant impact on the treatment thus making it ineffective. Currently, nanotherapeutics is in an infantile stage and requires huge monetary investments for extensive research and development of therapeutic agents ultimately making the said agents very expensive to acquire and afford [24]. These challenges and limitations have to be overcome in order to enhance the applicability and scope of nanotherapeutics [25-30].

Conclusion

Neurodegenerative disorders affect millions of people worldwide and requires more extensive research to develop newer therapeutic options. The concept of reformulation of existing drugs into nanosystems has emerged due to increasing advancements in nanomedicine. Several nan-drug delivery systems and have been reported as potential candidates for diagnosis and management of neurological disorders. Although these nanosystems have been evaluated in cell and animal models, and lack substantial results which can be scaled to humans, they have demonstrated mitigative and therapeutic potential in preliminary studies and hence can be optimized and researched further. However, these novel therapeutic tools are bound by certain challenges and limitations which should be sought to expand its applications in nanomedicine.

Author contributions

Karen DSouza (KDS), Subhankar P. Mandal (SPM), Namitha Bannimath (NBM), Deepshika Singh (DS), Prabitha Prabhakaran (PPK), Sheshagiri R Dixit (SRD), Vladimir N Nikolenko (VNN), Prashant Vishwanath (PV), Rajashree Deka (RD), Gurupadayya Bannimath (GB), Junqi Liu (JL), Ruitai Fan (RF), Chandan RS (CRS), Shaik Mohammed Suhail (SMS), Mikhail Y Sinelnikov (MYS), Narasimha M. Beeraka (NMB), conceptualized and designed the study. KDS, RF, NMB performed the literature analysis, and wrote the original manuscript draft. NMB, JL, RF, GBM revised, edited, and extended the final draft. All authors have reviewed and approved the manuscript before submission.

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