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Review Article

Nanomedicine in Central Nervous System (CNS) Disorders: A Present and Future Prospective

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Abstract

Purpose: For the past few decades central nervous system disorders were considered as a major strike on human health and social system of developing countries. The natural therapeutic methods for CNS disorders limited for many patients. Moreover, nanotechnology-based drug delivery to the brain may an exciting and promising platform to overcome the problem of BBB crossing. In this review, first we focused on the role of the blood-brain barrier in drug delivery; and second, we summarized synthesis methods of nanomedicine and their role in different CNS disorder.

Method: We reviewed the PubMed databases and extracted several kinds of literature on neuro nanomedicines using keywords, CNS disorders, nanomedicine, and nanotechnology. The inclusion criteria included chemical and green synthesis methods for synthesis of nanoparticles encapsulated drugs and, their *in-vivo* and *in-vitro* studies. We excluded nanomedicine gene therapy and nanomaterial in brain imaging.

Results: In this review, we tried to identify a highly efficient method for nanomedicine synthesis and their efficacy in neuronal disorders. SLN and PNP encapsulated drugs reported highly efficient by easily crossing BBB. Although, these neuro-nanomedicine play significant role in therapeutics but some metallic nanoparticles reported the adverse effect on developing the brain.

Conclusion: Although impressive advancement has made via innovative potential drug development, but their efficacy is still moderate due to limited brain permeability. To overcome this constraint,powerful tool in CNS therapeutic intervention provided by nanotechnology-based drug delivery methods. Due to its small and biofunctionalization characteristics, nanomedicine can easily penetrate and facilitate the drug through the barrier. But still, understanding of their toxicity level, optimization and standardization are a long way to go.

Introduction

At present, the large spectrum of brain disorders classified as deficits in bot neurological and psychiatric chapters with short and long-term disabilities.[1] These deficits are the results of intrinsic brain dysfunction or environmental interaction with brain.[2] CNS disorders affect 1.5 million people worldwide and responsible for 1% deaths.[3] Out of any other disease, 11% brain disorder burden is reported[3] which might be increased to 14.7% by 2020.[4]

A variety of potential drugs has discovered to treat several neuronal disorders.[5-8] But, the therapeutic success of these pharmaceuticals is still limited due to the presence of (i) Blood-brain barrier (BBB), and (ii) Blood-cerebrospinal fluid barrier (BCSFB). It acts as anatomical and biochemical dynamic barriers in the brain.[9-11] BBB has made up by specific vascular endothelial cells that tightly bound with neurons, pericytes, and astrocytes.[12-14] Less than 1% of the traditional drug can cross this barrier,[15] therefore, BBB protects the brain from systematic circulatory molecules as well as externally injected molecules and poses a key challenge for drug delivery.[9,16] Although, there are several endogenous transporters are present in the nervous system, BBB makes treatment ineffective by interacting with enzymes and restricts the entry of neuropharmaceutical agents.[17] Hence, large dose of the drug requires to treat CNS disorders and neurotoxic effects observed in the form of physical or mental deformations.[11]

Several researchers are working on a multidisciplinary approach to nanotechnology to overcome these major obstacles in CNS therapeutics. Nanoparticles and combination with therapeutic agents may consider as an effective tool in brain drug targeting for safer therapies in future.[9,18]

In first decades PNPs, SLNS, liposomes, and micelles have used as nanocarriers in the medical field. But, now this nanotechnology approach has shifted towards newer and more advance nano-system e.g. dendrimers, nanoemulsions, nano gels and nanosuspensions.[10]

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Traditional therapies have very little capacity to penetrate the BBB as well as null capacity for neuronal repair and neuronal regeneration.[19] Hence, functionalized nanomaterial may serve as a potential drug delivery vehicle. It can use as both *in-vivo* and *in-vitro* viz, polysorbate coated poly (butyl cyanoacrylate) (PBCA) nanomaterial interact with endothelial cells of cerebral vessels and stimulate drug delivery via endocytosis.[20] Nanotechnology combined with stem cell therapy is being increasingly used to rebuild the neural circuit and to induce specific cellular response.[18,20-22]

Recently, biofunctionalized carbon nanotubes (CNTs) have become a promising tool due to its cell-penetrating ability, surface chemistry diversity, structural, and mechanical properties.[23] In contrast, instead of having larger structure than CNT, functionalized fullerenes have identified as more efficient in CNS drug delivery[24,25] due to its higher permeability and less excitotoxity.[26]

Normal drug delivery to CNS and their challenges

For effective traditional therapy, the drug should lipid soluble with small molecular weight (400-600 Dalton's).[27] This transport can perform by invasive, non-invasive and miscellaneous techniques,[3,28] but, BBB allows restricted entry of potential drugs.[9,15,16,29] Major reasons for therapeutic failures in the brain are slow drug action, association or conversion of the drug into non-transporting legends and less neuronal absorption.[13] Some catalytic mechanisms in the nervous system also degrade the drug which performs a non-specific action or stay in inactive form in the brain.[29]

Strategies of drug delivery in brain

BBB acts as a capillary endothelial interface, that facilitates transport of essential chemical and ion to the brain.[30] Crossing BBB is always a key obstacle for drug delivery system. Hydrophilic molecules reported transferring via specific carrier-mediated endocytosis, transporter, and paracellular pathway. Lipophilic molecules have transported by diffusion and P-glycoprotein.[31] Routes of drug delivery include:

Invasive approach

This physically breached technique penetrates BBB and directly injects the drug into the brain. It requires craniotomy for intracerebroventricular (ICV) infusion and intracerebral drug administration.[31,32] BBB disruption for drug delivery performs via breaking down the tight junction of endothelial cells.[31,33] This can administer through osmotic disruption[30,34,35] or disruptive plasma solutes.[36,37] ICV drug delivery considered as a very poor approach, because the drug transported in the peripheral blood stream, less to the targeted tissues.[38] Instead of having the advancement of high molecular drug transport, ICV also restricted to limited drug distribution and loss of desired CNS action due to high intracranial pressure during direct drug administration.[39]

Pharmacological approach

This observational approach based on the free passive movement of drugs through BBB.[31,32] These molecules can cross BBB unassisted due to their small molecular size, low hydrogen bonding capacity and lipophilicity.[40] This approach also consists chemical change, e.g. reduction in number of polar groups, which increases drug transfer across the BBB.[41] But, the modified molecule may act as P-glycoprotein efflux pump, if lipophilicity increases by many folds.[31]

Physiological approach

Receptor-mediated and carrier-mediated drug delivery to the brain considered as a most advanced technique in pharmacology.[30,31] Transferrin and insulin receptors are commonly found on the BBB.32 Hence, the drug adjoins with the ligand of these receptors might transport drugs to the targeted brain area. In the case of transporter mediated delivery, the drug needs to mimic to the endogenous carrier substrate.[42] But kinetics and binding capacity of transporter molecule limit the CNS drug delivery through physiological approach.

Nano-formulated drug delivery in CNS

Conventional drug delivery strategies are unable to restore cytoarchitecture and connection pattern in CNS disorders.[43] Nanotechnologies overcome these problems due to its nanoscale quantum effect, small and high surface area to volume ratio.[44,45] Basically, nanotechnology is a convergence of science and engineering, which needs one-dimensional designing and characterization at the nanometric scale.[21] Nanoparticles used in CNS drug delivery should have following promising features:

i. They should biodegradable, non-toxic and biocompatible.[46,47]
ii. Their physical properties should easily manipulate according to mode of delivery.[48]
iii. Different nanoparticles with modified chemical properties should achieve organ- or cell- specific drug delivery.[49]
iv. The formulation should cost-effective.

In summary, all these beneficial considerations enhance CNS drug delivery.

Nano-formulation strategies

For an affecting drug delivery system in CNS treatment, nanoparticle alters the pharmacokinetics of drug48 and enhances drug loading capacity.[50] Drugs need to chemically modify and transported to the brain via loading with different nanomaterial-based vehicles.[45] It also received in the brain via transcytosis through the BBB.[31] Nanobiotechnology has made a revolutionary progress in drug delivery system. We have mentioned the properties, nanotechnology-based drug delivery, and drug release mechanism with few example of patent nanomedicine in Table 1.[51]

Table 1. Properties of different nanocarriers, drug delivery and drug release mechanism with example of patents (partially adapted from reference 51).

Type	Size (nm)	Synthesis technique	Mode of administration	Mechanism for delivery	Drug release mechanism	Example		
						Drug	disease	Patent
PNP	10-1000	• Solvent evaporation • Nanoprecipitation • Dialysis • Supercritical fluid technology • Emulsification/solvent diffusion	Subcutaneous, intravenous and oral	• Receptor-mediated endocytosis • Transcytosis	• Swelling of PNPs via diffusion • Degradation of polymer through enzymatic reaction	Chitosan-coated erythropoietin (HMG-Co-A reductase inhibitors)	Brain targeting	US20070237827
						PLGA encapsulated NMDA-NR1 vaccine	Alzheimer's disease	US20100173004
SLN	50-1000	• High-pressure homogenization • Ultrasonication • Microemulsification • Supercritical fluid technique • Spray drying technique	Nasal, oral, parenteral, rectal and respiratory	• Absorption	• High-pressure homogenization causes dispersed molecular drug in solid solution • Supersaturation of SLN-drug conjugates at high cooling	LDL-cholesterol conjugates	AD, PD, and cancer	US7682627
						LDL nanoparticles	Epilepsy, stroke, Trauma and AD	US20060222716
Micelles	80-100	• Self-assembly • Ring-opening polymerization	Pulmonary delivery	Receptor-mediated transport, absorption, and endocytosis	Bursting, diffusion, and cleavage	doxorubicin, vincristine sulphate loaded poly (L-histidine)-poly(ethylene glycol) block copolymer and PLEG poly micelles	Cancer	US7659314
						Paclitaxel-loaded copolymer micelle	Lung cancer	NCT01023347
Nanoliposomes	Less than 100	• High-pressure homogenization	Pulmonary delivery, intravenous,	Adsorption, fusion and diffusion/ endocytosis	Endocytosis and Adsorption to cell surface Bursting due to environmental stimuli	Glutathione encapsulated liposomes	Myoclonus	US20100166846
						Tempamine loaded liposome	Multiple sclerosis and PD	US20110027351
CNTs	Diameter of 3.5-70nm	• Arc discharge method • Chemical vapors deposition • Laser ablation method • Flame synthesis method	mainly intraperitoneal and intravenous	Endocytosis, diffusion, penetration	Electrically or chemical controlled	Streptavidin-HRP (Horseradish peroxidase) bounded SWCNT-annexin conjugates	Breast cancer	US201001846691A1
						Stem cell loaded CNT	AD, PD, and ischemia	US20090148417A1
Dendrimers	Diameter range 1.5-13.5	• Divergent method-Micheal reaction • Convergent method • Click chemistry-Diels_alder reactions, azide-alkyne reaction, and thiol-yne reactions • Hypercore & branched monomers	Oral, transdermal, topical, IV	Transcytosis and endocytosis	Degradation and environmental stimuli	Anxiolytic and antipsychotic agents	Psychotic disorder	US20100160299

Nanotechnology-based drug delivery vehicles

The nanotechnology-based drug administration has shown significant advantages over traditional drug delivery. The different nanoformulation carrier has used for targeted drug delivery, some of them are Nanoparticles (NP), lipid-based vehicle, carbon

nanostructure-based vehicle and polymer based vehicle; as shown in Figure 1. We are discussing important nano drug carrier in the following section.

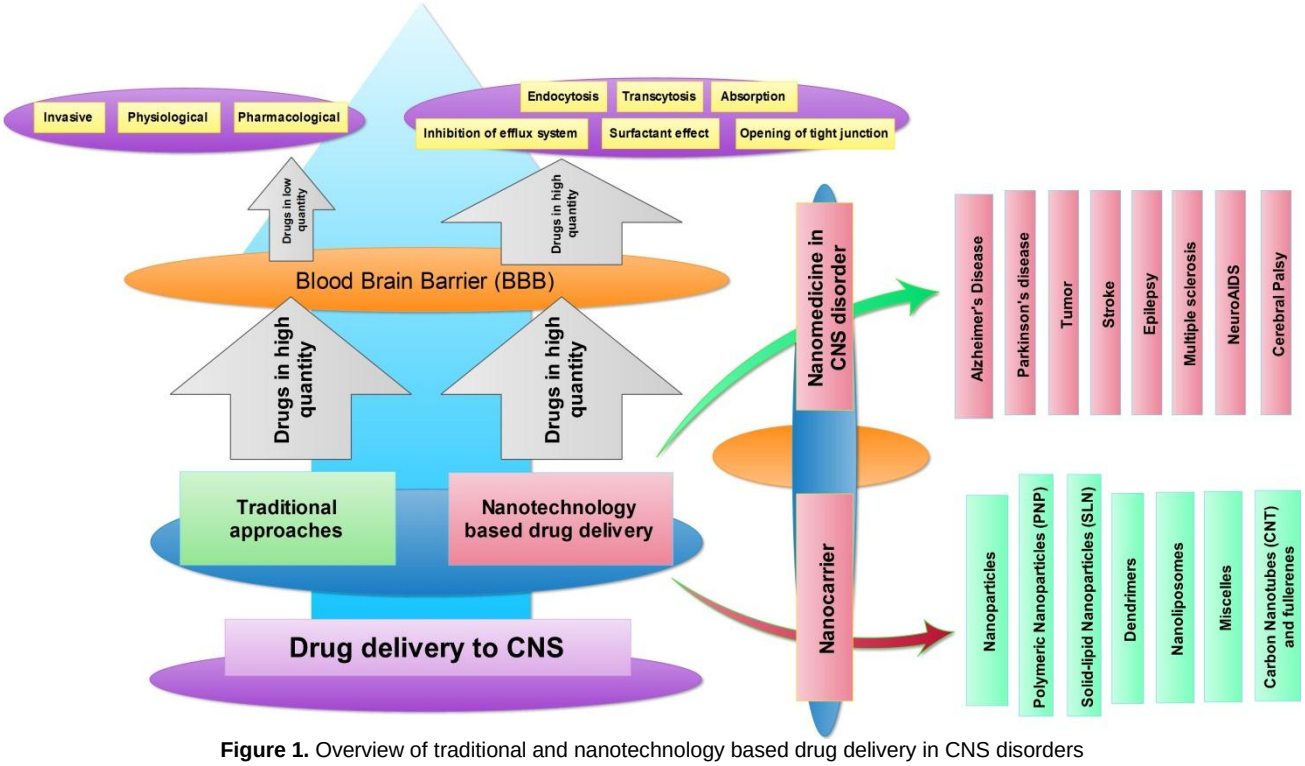

Figure 1. Overview of traditional and nanotechnology based drug delivery in CNS disorders

Nanoparticle

The inorganic nanoparticle of size 10-1000nm recently elicited much interest due to their chemical and biological properties. Several features of nanoparticles show significant advantages to overcome problems associated with traditional drug delivery, which includes: high drug carrying capacity, high stability, controlled release, high specificity and hydrophilic and hydrophobic molecules transportability.[52] Drug-loaded nanoparticles release to target site via diffusion, degradation, erosion or due to external energy input.[53] Protein and ceramic NP are most commonly used in targeted drug delivery.[54]

Easy functionalization property and good biocompatibility of modified molecule are the key requirements to select an effective route for prepare different sized NP.[55] Drug delivery through gold nanoparticles (AuNP) gives a versatile platform for effective drug delivery. Doxorubicin coated AuNP have reported making enhanced drug accumulation by overcoming multidrug resistance (MDR) in cancer treatment.[56] Similarly, curcumin conjugated AuNP also shows haemocompatibility, resulting in antitumor activity in leukemia.[57] Recent research on imatinib mesylate (IM) encapsulated, layer by layer coated functionalized AuNP, demonstrated rapid delivery into murine melanoma cells in mice.[58] This topical application for iontophoretic IM delivery shows effective cancer treatment. Chitosan derived mitochondrial targeted multifunctional NP (MNPs) performs lysosomal escape, multistage pH response, and mitochondrial and hepatocyte targeting for safe and targeted anticancer drug delivery.[59]

Polymeric nanoparticles (PNPs)

Polymeric nanoparticles are a particulate dispersion of biodegradable and biocompatible polymers with size 10-1000nm. The core-shell structure of PNP varies with hydrophilic and hydrophobic blocks present in the polymer chain.[60] The core of these PNP made up of a dense polymer matrix to encapsulate the hydrophobic drug and hydrophilic polymers in corona to serve steric stability and stealth properties to NP.[61] Drug delivery through PNP were also performed via drug encapsulation, absorption or chemically linked to surface.[62]

Availability of polymer choice and drug release from nanoparticle makes them unique candidates for drug delivery. Biologically inert polymers PEG (Polyethylene glycol), PLGA (poly-L- glutamic acid),[43] poly(alkyl cyanoacrylate), and poly(butyl) cyanoacrylate are most common used formulated nanopolymers. Level of drug release is not only controlled by molecular weight & polymer composition, drug-to-polymer ratio also affects as well.[63]

The role of PNP's in drug delivery can also consider non-replaceable. Doxorubicin loaded nanoparticles used to treat glioblastoma[64] and quinoline derivatives loaded polymeric nanoparticles used in Alzheimer's disease (AD).[65] Similarly, nano gels, a crosslinked polymer[66] and nanosuspensions, mixture of crystalline drug and non-

ionic surfactants[67] provide excellent pharmacokinetics control in CNS disorders.[68]

Solid-lipid nanoparticles (SLN)

SLN is surfactant stabilized lipid oily droplet, which is generally solid at room temperature.[54] It considered as a colloidal nano drug carrier that synthesized by homogenization of melted lipid at high pressure while dispersing in water at 70 ^{0}C with a nanometric range of 50-1000nm.[69,70] It also exhibits physical stability and easy manufacturing; hence it replaces liposomal technology in drug delivery.[71] SLN particles conjugate with lipid emulsions that can stabilize by high-level surfactant inclusions and protect from degradation.[72] The active part or drug to transported is administrated via loading or coating with nanoparticles.[73]

Recently, self-amplifying RNA in SLN nanoparticles has demonstrated the importance of lipid nanoparticle in nucleic acid vaccine development.[74] The effect of different SLN conjugated drug is widely investigated in CNS treatment. Quercetin loaded SLN shows the antioxidant property to treat AD[75] and diminazene aceturate loaded SLN particles used to treat human African trypanosomiasis (HAT).[76] Similarly, 3',5'-dioctanoyl-5-fluoro-2'-deoxyuridine (DO-FUdR) incorporated SLN used to treat neurological disorders.[77] (3H)-atazanavir loaded SLN also crossed the BBB in HIV-encephalitis treatment.[78]

Dendrimers

Highly branched dendrimers made up of a focal core, building blocks with repetitive units in interior layers and peripheral functional units.[79] Other than synthesis routes, the functionality, and efficacy of dendrimers depend on upon the used monomer and targeted polymer structure.[80] Low dispersity and high functionality of these dendrimers offer themselves as a useful therapeutic tool in biomedical and pharmaceutical science.[81] High penetration ability, high density, and peripheral functional group reactivity also considered as featured advantages as a drug vehicle.[82] The terminal surface group, biocompatibility, and multivalency of three-dimensional dendrimers have displayed their importance in emerging with Nanomedicine.[83] Polyamidoamine (PAMAM), polypropylene imine (PPI), and polylysine dendrimers are the most commonly used dendrimeric drug carrier for both hydrophobic and hydrophilic drug molecule.[84] Drug either physically entraps with dendrimer, or covalently bound with peripheral functionalized molecules of dendrimer to form dendrimer-drug conjugates.[79] The complexities of their bounding keep the chemical integrity and pharmaceutical properties of the drug.

In further research, cholesterol loaded poly (amidoamine) dendrimers reported neuroinflammation treatment.[85] Similarly, multi-functionalized CMCht/PAMAM dendrimer nanoparticles incorporation with antibody also played an important role in specific CNS targeting.[86]

Different dendrimers such as PAMAM, polyester-copolyester (PEPE) and PPI, shows anticancer and anti-inflammatory properties to treat several neurological disorders.[87]

Nanoliposome

These lipid nanoparticles are the most studied bilayer vehicle, developed in drug delivery in the 70's.[88] Less than 100nm sized nanoliposomes may consider as an advanced form of SLN that includes nanostructured lipid carrier (NLC), nanoemulsions and lipid nanocapsules (LNC).[54] The distorted structure of NLC provides enough space to accommodate active drug molecule which can develop by mixing lipid droplet into solid media at very high temperature.[54] Combination of liposomes and nanoemulsion particle gives rise to LNCs (less than 100nm) with thicker outer wall that allows more functionalization and controlled targeted drug delivery.[89]

The lipid, oily core of LNCs surrounded by lipophilic and hydrophobic surfactant that improves therapeutic drug delivery.[42] Liposomal technique emerged with pegylation for targeted brain drug delivery[41] which optimized the plasma pharmacokinetics. Neurotrophic agents loaded liposomes used in brain disorders.[90] Pegylated liposomes loaded with doxorubicin and (3H)-Prednisolone treats brain tumors[91] and autoimmune encephalitis[92] respectively. OX26 monoclonal antibody-mediated antineoplastic agent, (3H) daunomycin, conjugate with a liposome and exhibit brain drug delivery.[93] Similarly, heat shock protein (HSP) encapsulated liposomes also used in the stroke treatment.[94]

Micelles

Micelles are monolayered spherical lipid nanostructures with inwards facing hydrophobic ends and outwards facing hydrophilic ends with a range of 80-100nm.[95] Due to its small, the micelles shows short circulation time in body compares to liposomes that make them easily transportable elements.[54] Polymeric micelles considered as more stable with longevity and good biodistribution compare to traditional micelles.[96] These modified micelles show improved target penetration due to their nanoscale size, easy transportation to target location, and low critical association concentration (CMC).[97] Physically entrapped and covalently bonded micelles drug conjugate play an important role in controlled drug release system.[98] Drug loading to micelles generally depends on upon the physiochemical property of drug, the chemical composition of core forming polymers, and physical state of micelles core.[99] The release is generally affected by temperature, pH, and environment.[100]

Carbon Nanotubes and fullerenes

CNT exhibits advanced physical, mechanical property, and high aspect ratio at the nanometer scale of less than 100nm.[101] Functionalized CNT shows high solubility and high biocompatibility which generally depends on upon

surface property, size and shape of modified molecules.[102] These parameters greatly influence the internalization of therapeutic molecules inside the cell. CNT functionalization strategies include the addition of an organic group at sidewall/tip of CNTs and carboxyl group coupling after oxidation process.[103] Polymers and dendrimer conjugated CNTs also reduces aggregation, increases their solubility and biocompatibility.[104] Very few studies of the CNT in CNS treatment have been reported, yet acetylcholine loaded SWCNT (Single wall carbon nanotube) studied in the AD treatment[105] and CNT with stem cell therapy used in stroke treatment.[106] Amphotericin B loaded CNT showed lower aggregation, high solubility with reduced toxicity, and anti-fungal activity compares to administration of amphotericin B alone.[107]

Carbon nano horns and nanodiamonds modified the form of CNT which reported enhancing the nanotechnology application in biosciences and pharmaceutical industry.[54] Diamond nanoparticles also used as an important therapeutic tool in tumor patches and wound healing.[108] Fullerene has uniquely identified a class of carbon allotropes which described as 60 linked carbon with 60 vertices and 32 faces.[109] The extensive research on nanosized C60 have identified its use in drug delivery.[110] Their antioxidant and radical oxygen quenching character made them more promising than any other nanomaterial.[111] Hydrated C60 fullerene prevents astrocytes and glial fibrillary acidic proteins (GFAP) damage which caused by oxidative stress and improves cognitive function.[112]

Nanoparticle-mediated drug transport mechanism

For effective drug treatment, nanomedicine needs to cross the BBB without losing its properties. There are several possibilities for this translocation: Absorption, opening of tight junctions, endocytosis, transcytosis, surfactant effect, and inhibition of efflux system.[113]

i. Polysorbate coated dalargin nanoparticle reported to induce an antinociceptive effect (surfactant effect) and created high concentration gradient which helps to transport nanomedicine.[47]

ii. Polysorbate-80 coated nanoparticle also unfolded the tight junction and increases inulin space without disrupting BBB.[114]

iii. At present, endocytosis is considered as the most likely mechanism of nanomedicine transport. Polysorbate-80 coated PBCA nanoparticle endocytotic transport studied by laser confocal microscopy and significant and rapid uptake of coated nanoparticles were observed, rather than uncoated nanoparticle.[115]

iv. Dipalmitoyl phosphatidyl choline cholesterol-coated malto-dextrin nanoparticle transcytosis through BBB and upregulated the LDL receptor expression in a cholesterol-depleted model system.[116]

CNS disorder and nanomedicine

Recent trends of nano-therapeutics advance over traditional drug therapy in CNS disorders via its proper property to cross the BBB.[19,117] Nanotechnology used in for both diagnoses (imaging) and treatment, here we will discuss *in-vivo* drug delivery system in CNS disorders.

Alzheimer's disease

Alzheimer's disease (AD) recognized as a progressive neurodegenerative disorder, which characterized by memory loss and dementia.[118] Pieces of evidence support inclined graph of AD patients with prevalence rate 0.62% and 1.07% in people with age +55 and +65 years respectively. Estimated data are much scaring as 24.3 million people globally affected by dementia and each year 4.6 million cases reported.[119,120] Amyloid-β aggregation considered as hallmarks of AD.[121] Other than this, wide spectrum of AD pathology covers genetic change of EpoE protein, mitochondrial abnormalities, oxidative stress, and dysfunction of D-serine.[122-124]

Insufficient use of oral administrated drugs for AD, such as tacrine, memantine, rivastigmine etc, pulls the door open for nanomedicine in neurodegenerative disorders.[125,126] Cerium oxide nanoparticles,[127] SLN of ferulic acid,[128] tempol loaded PLGA nanoparticles,[129] and epigallocatechin-3-gallate (EGCG) phenol coated nanolipids[130] reported to show antioxidant property and degrade amyloid-β.[131] Thioflavin-T (ThT), charged and fluorescent biomarker, detect Aβ in senile plaques. Therefore, ThT encapsulated polymerized but cyanoacrylate NP injected directly into intrahippocampal space, and light microscopy and TEM analysis confirmed Aβ in AD brain.[132] Cu (I) chelator and MBP-PE induced D- penicillamine nanoparticles were also used tauopathies detection in AD brain.[133] Nanofabricated quinoline derivative, clioquinol (5-chloro-7-iodo-8-hydroxyquinoline,CQ), was reported to inhibit Aβ when it was functionalized with n-butyl cyanoacrylate and PBCA nanoparticle.[65] Imbalance in Ach of the cholinergic nervous system also reported in AD and free Ach could not inject into the brain directly, because it is easier to decompose in the blood and high polarities.[134] Curcumin nanoparticles have been also identified as important finding in AD treatment.[135]

Parkinson Disease

Increasing lifespan and demographic changes in population demonstrates increased prevalence of Parkinson disease (PD).[136] 50+ people in world's most 10 populous countries have around 4.6 million PD patients, which might be 9.3 million by 2030 with a rate of 1 per 100.[137,138] A hallmark of PD is gliosis and degeneration of dopaminergic neurons in the substantia nigra are not the only features of PD. It also involves selective denervation,[139] dysfunctions in the mitochondrial and ubiquitin-proteosome system, and oxidative and nitrosative stress.[140] Available drugs for PD neither surpass nor reverse disease progression[141] and BBB causes additional challenge in drug delivery.[142]

Nanotechnologies control and manipulate the drug delivery in PD to overcome these problems. Recent research has demonstrated that nerve growth factor (NGF) bound poly butyl cyanoacrylate nanoparticles[143] and L-Dopa encapsulated nanoparticles[48] crosses BBB and reduces basic symptoms of PD. Physically modified saline RNS60 with charged-stabilized nanobubbles, suppresses the proinflammatory molecules in MPTP-induced animal model of PD.[144] Similarly, coumarin-6 loaded lactoferrin conjugated PEG-PLGA nanoparticle show important role in neuroprotection in Parkinson disease.[145]

Tumor

Upward trends of brain tumor show increased incident rate with 6/100,000 for malignant brain tumors in the adult.[146] Male shows higher susceptibility than female with increasing age at a rate of 8.5 v/s 7.9 per 100,000 that have increased 5-6 folds by now.[147,148] Drug therapy is less effective in brain tumor because of less infiltration of tumor cells from normal cells[149] and less microvascular permeability of BBB.[150]

To overcome these problems, nanoformulation drug therapy is widely used an alternative approach. Gold porphyrin or camptothecin encapsulated lipid nanoparticles enhanced drug delivery to tumor tissue with a low side effect to the liver.[151] Nanotechnology-based drug delivery used in cancer treatment with a combination of gene and radiotherapy.[152] Nanotechnology in chemotherapy enhances efficacy to treat glioblastoma. DOX-loaded nanodiamond exhibit excellent cell biocompatibility and increase apoptosis of glioma cell lines.[153] MWCNTs (Multiwall carbon nanotube) showed a high level of internalization of macromolecules in microglial cells and their molecular modulation helped in immunotherapy of cancer.[154] Folic acid (as targeting agent) and methotrexate conjugated PAMAM dendritic polymers bind to tumor cell which overexpressed for folate receptor in cancer treatment.[155] Boron-enriched nanocomposites of copolymerized acetal-poly(ethylene glycol)-*block*-poly(lactide)-methacrylate with 4-vinylbenzyl substituted *closo*-carborane demonstrated high incorporation and hemocompatibility.[156]

NeuroAIDS

NeuroAIDS drags both infectious and neurological pathophysiologic pathways under one umbrella, in which HIV1 (Human Immunodeficiency Virus 1) enters in the CNS in the early stage of infection.[157] Approximately 15-30% of AIDS patients experiences several neurological and neurocognitive complications in which 7.3-11.3% and 30-60% experienced dementia and encephalopathy respectively.[158,159] BBB disruption is not the only mechanism in neuroAIDS, activated endothelial cells with decreased permeability of the barrier[160] and CD 163, Glut5 & ISG15 genes[161] are also shown deleterious effect. Currently, there are no effective vaccines or specific drug therapy for NeuroAIDS,[162] therefore, multidisciplinary approach to nanotechnology shed light on potential therapeutic approaches in HIV infection.

Nanoformulated antiretroviral therapy (ART) reported increasing blood-brain penetration in neuroAIDS treatment. Indinavir (IDV) NP loaded murine bone marrow macrophages (BMM) cause reduced HIV-1 replication in HIVE (HIV-1 encephalitis) region of the brain.[163] Their research also demonstrated the role of NP loaded BMM in studying targeted migration and antiretroviral responses. Nanotechnology-based, highly active antiretroviral therapy (HAART) also played a significant role in neurosis treatment.[164] Several antiretroviral drugs, zidovudine, delavirdine, saquinavir, and lamivudine, were nanoformulation with PBCA, MMSPM (methylmethacrylate–sulfopropyl methacrylate), polylactide (PLA) and PLGA that increases BBP 10-20 folds.[165] Liposome loaded AZT-myristate and zalcitabine were also reported with improved efficacy and longer half-life compare to traditional ARV drug treatment.[166] SLN loaded ARV drugs recently come into a highlight. Large surface area and high efficacy of SLN coated delavirdine and saquinavir ARV drug replaced MMSPM coated ARV drug treatment in neuroAIDS.[162]

Stroke

With second place, stroke is affecting mortality rates of 6,000,000 deaths annually with estimated susceptibility of 8-10% of lifetime.[167] 1.2% deaths in India reported due to this in which 87% caused by ischemia and the remaining is due to hemorrhage.[168] Glutamate excitotoxity, oxidative stress, lipid peroxidation, BBB dysfunction, leukocyte infiltration and brain injuries play an important role in the pathophysiology of stroke.[169,170] BBB and blood-cerebrospinal-fluid barrier (BCSFB) are the main issues in stroke drug delivery,[171] so optimization and efficiency of drug carriers are needed to improve.

The new, unusual perspective of nanotechnologies in stroke therapy is *'jeevandayani'* (life protecting).[37] One researcher used engineering triiodothyronine (T3) nanoparticle coated with PLGA-PEG and enhanced neuroprotection observed compared to glutathione alone.[172] Cerium oxide nanoparticles also showed neuroprotective naturally in the rodent stroke model. Cerium oxide nanoparticle reduces the 3-nitrotyrosine level, which was generally induced by peroxynitrite radical during the stroke.[173] Similarly, platinum nanoparticles showed their antioxidant property which reported lowering cerebral cortex volume and improved motor function in stroke animal model.[174] Irreversible caspase-3 inhibitor loaded transferrin targeted nanospheres provide a reduction in infarct volume in ischemic brain.[175] SiRNA loaded carbon nanotube also documented as potential therapeutics in stroke treatment.[37] Transferrin-coupled liposomes promote vascular regeneration and neuroprotection via delivering vascular endothelial growth factor (VEGF) in stroke treatment.[176] The stroke damage can also recover by

progenitor stem cell differentiation when it impregnated with CNT.[106]

Cerebral palsy

Cerebral palsy (CP) is one of the major neurodevelopmental disorders in children that considered as chronic & non-progressive in nature.[177] It causes motor dysfunction, serve paralysis[178] and musculoskeletal problems in 2-3 per 1000 children[179] with a male/female ratio of 1.4:1.[180] Unfortunately, there is no effective cure available for CP due to unknown molecular and biochemical mechanisms involvement.[181] But researchers show the wide interest to use Nanoscience used drug delivery in CP.

PAMAM dendrimers and dendrimer-based N-acetyl-L-cysteine administration suppress neuroinflammation & motor dysfunction in CP patients.[182] Stem cell therapy with nanomedicine has also come in the limelight recently to cure CP via promoting repair and regeneration of injured neurons.[183]

Epilepsy

Epilepsy is leading in all CNS disorders with a rate of 57 per 1000 people[184] which might increase as in 5.5 million patients by the year 2001 in India.[185] Abnormal neuronal discharges considered linking with oxygen deprivation, trauma, tumors and infections that cause neuronal excitability[186] and neuroinflammatory cytokine dysfunction in epilepsy.[187] The adverse effect of anti-epileptic drugs,[188] promotes the use of nanoparticle-loaded drugs with the ability to cross the BBB and direct drug delivery.[189] Carbamazepine loaded solid lipid nanoparticles of chitosan reported to be more effective than nano emulged loaded carbamazepine.[190] Similarly, poly (d,l-lactide-co-glycolide) nanoparticle loaded β-carotene anticonvulsant considered more effective when it coated with polysorbate-80.[191]

Multiple sclerosis

Multiple sclerosis (MS) considered as an autoimmune neurodegenerative disease with chronic inflammatory processes.[192] Modification of myelin basic protein (MBP) and glial fibrillary acidic protein (GFAP) triggers lesions in white matter[192] that causes MS. Advanced stage of MS causes demyelination and tissue damage due to oxidative stress are found higher in the patients.[193] Ultra sized cerium oxide nanoparticles declines oxidative stress and alleviates motor deficits in MS brain.[194]

Challenges

Emerging nanotechnology with neurosciences is like a game of risk and gain. Currently, Nanomedicine considered as a successful tool in drug delivery via crossing the BBB.[195,196] These nano drugs are in the process of clinical trials, but their proper transport and safety concerns are yet to be determined.[1,45] The composition and properties of nanoparticles may lead to oxidative stress, amino acid disturbance and BBB disruption,[196,197] that causes neurotoxicity in the brain. Although functionalized nanoparticles pose successful drug targeting, but their nano-size structure and the large surface area may result in particle aggregation and limited drug loading.[65,198] State of aggregation and mechanical properties affects nanoparticles toxicity which basically depends on preparation and purification methods. Hence, one should select a proper method to reduce toxicity.

Toxicity concerns of nanomedicine delivery based on their mode of drug administration and a measure of the drug; which causes neuroinflammation, excitotoxicity, DNA damage and allergic responses.[199] Therefore, biocompatibility and biodegradability of nano drug are also needed to understand.

As Nanomedicine need to interact with neurons at a systemic level to show their effect. But, multidimensional cellular interaction at neuronal level and restricted anatomical access increase the challenges in nano-drug delivery system.[21] The primary function of CNS needed to preserve before drug administration which also a big challenge itself.[200]

Conclusion

CNS disorders are a most serious problem in this industrialized world. Nanotechnology has proven very advanced and promising science which provides easily targeted drug delivery to the brain. But, we still need to gain more knowledge about their properties and features to evaluate their dynamic behavior in biomedical science.[201] At present, we don't have any multidimensional drug for different CNS disorders that may result of several individual biochemical pathways.[21] Nanodrugs may lead to solving this problem.

Sometimes, few diseases viz, diabetes, trauma or some of the psychotic diseases, also associated with the neurological disorder. Hence, nanomedicine requires achieving termination of these entire co-morbidity factors with fewer side effects. Other than this, Genetic manipulation in the neuronal cell is also considered as a difficult target, so nanotechnology-based drug delivery should potentially efficacious approach in CNS treatment.

Polymer-based gold nanoparticles and CNT nano drugs have very few clinical trials, but due to their noble physical and mechanical strength, they may useful to carry the drug whose transport is still unidentified.

Although, the nanoparticle-based drug has several advantages, but many aspects are still matters of concern. So far there is no specific method to identify the toxicity level and targeted drug release in the CNS. Hence, the current nanotechnology application needs to improve further, so that it can be safe and target oriented.[68]

In recent years, some nanomedicine registered for patents in complex CNS treatment, which are following: Gold nanoparticle (US2011262546, US2011111040), lipid nanoparticle (WO2008024753, WO2008018932), chitosan nanoparticle (US2010260686) and SLN (US2011208161).[1]

Increasing population and increasing brain disorders are calling for the urgent need of new promising therapies. Involvements of nanotechnology in neurosciences will unmet medical need and give a hope to patients. The new generation nanomedicine might control prolonged and targeted drug delivery in a specific manner. Instead of reduced side effect and increased viability of nano drug, we still need to improve nanotechnological methods in pharmaceuticals for better comprehension and improved life quality. It can not be denied the potential benefit of nanomedicines, but their opportunity and risk formula also point towards hazardous effects. Due to the high ongoing emergence of nanotechnology in today's research, one just cannot throw it away due to its negative points only. Specific guidelines should follow to avoid the most harmful effect of nanotechnology. It can also predict that nanotechnology-based drug delivery can revolutionize the era of traditional drugs delivery and that modified drug will be incredibly efficient from the current standard.

Ethical Issues

Not applicable.

Conflict of Interest

The authors report no conflicts of interest in this work.

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