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Modern method of drug delivery across blood brain barrier

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Abstract

Blood-brain barrier tightly regulates the flow of matter between the blood and brain, and it places restrictions on the amount of drugs that can enter the brain when taken systemically. As a consequence, brain diseases cannot be effecively treated with drugs. Treatment for various brain illnesses has not made any notable advancements recently. The BBB and achieving an adequate targeting capability for therapeutic molecules continue to be major obstacles. BBB supports the CNS's ability to maintain homeostasis. The BBB is better understood as a result of advancements in molecular biology, especially in various pathological situations. We'll examine contemporary techniques that can make use of these possibilities. Invasive and non-invasive approaches are the two primary types of drug distribution. To reduce risks, non-invasive means of drug delivery should be used to administer the medication. Utilization of nanotechnology in drug transport, receptor mediated targeting and transport and cell mediated drug transport will be covered in this review.

Keywords: Blood brain barrier; Delivery technique; Nano-Technology; Receptor and cell mediated drug transport. Dendrimer; Invasive Non-Invasive

1. Introduction

1.1. Drug Delivery across the Blood–Brain Barrier

The delivery of drugs to the central nervous system (CNS) remains a challenge in the treatment of neurological diseases such as Alzheimer's disease, Parkinson's disease, and stroke. The major challenge to CNS drug delivery is the presence of the blood–brain barrier (BBB), which limits the access of drugs to the brain parenchyma.[1,2] The BBB limits drug delivery by generally allowing only those molecules that are lipophilic and have low molecular weight (less than 400–500 Da) to enter the brain from the bloodstream through the transcellular route.3 In this context, it has been reported that approximately 98% of small molecules and nearly all large therapeutic molecules, such as monoclonal antibodies, antisense oligonucleotides, or viral vectors, cannot pass through this barrier.4 For these reasons, delivery of drugs to the brain is still a major challenge, and recent reports indicate that less than 10% of therapeutic agents for neurological diseases enter into clinical trials because of poor brain penetration.5 Attempts to overcome this barrier involve increasing drug delivery of intravascularly administered drugs by manipulating either the drug or capillary permeability,1 and/or by local administration into brain fluids, such as the cerebrospinal fluid of brain ventricles or the interstitial fluid of brain tissue.

1.2. Physiology and biology of the blood–brain barrier

The brain is well protected and dynamically regulated to provide a sanctuary for the central nervous system (CNS). There are several gateways to enter brain parenchyma, the most important two are blood circulation and cerebrospinal fluid (CSF) circulation. In the human brain, there are about 100 billion capillaries in total, providing a combined length of brain capillary endothelium of approximately 650 km and a total surface area of approximately 20 m2.Any molecules'

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entry into the brain via parenteral administration is strictly controlled by the BBB and the BCSFB. As the surface of BCSFB faces the ventricle that is filled with CSF, not the blood this, in combination with the high turnover rate of CSF, leads to continuously flushing the injected drug (i.e. those injected into the ventricle) back to the blood.[2,3] The BBB, therefore, is universally considered as the most important barrier in preventing molecules from reaching the brain parenchyma via extensive branches of blood capillary networks. The chief anatomical and functional site of the BBB is the brain endothelium. Physiologically, in addition to brain capillary endothelial cells, extracellular base membrane, adjoining pericytes, astrocytes, and microglia are all integral parts of the BBB supporting system. Together with surrounding neurons, these components form a complex and functional "neurovascular unit".[3,4]

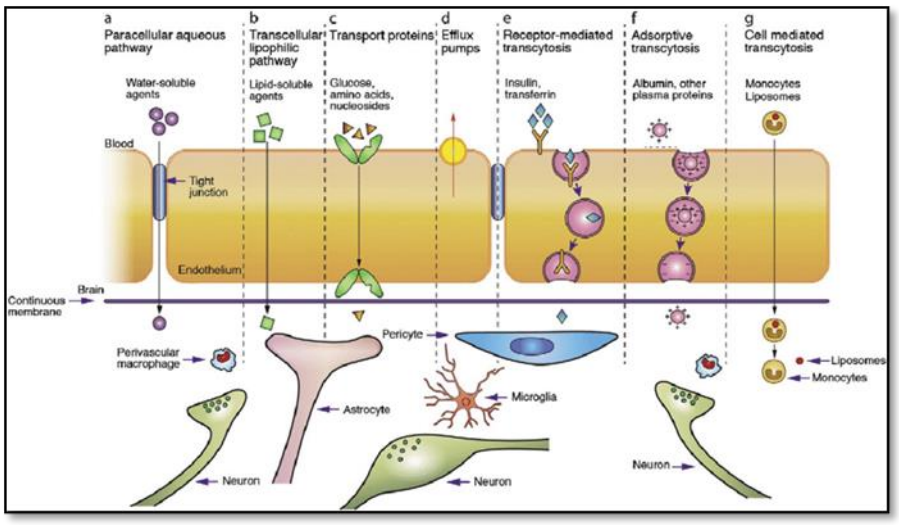

Figure 1 Physiology and biology of the blood–brain barrier

1.3. Blood–brain barrier and drug delivery

The BBB is a semi-permeable membranous barrier, lo- calized at the interface between the blood and the cere- bral tissue, composed of a complex system of endothelial cells, astroglia, pericytes, and perivascular mast cells.[4] It is mainly responsible for rigorously control- ling the exchanges between the two compartments allowing only certain molecules or ions to pass through by diffusion or occasionally by more specialized pro- cesses of facilitated diffusion, passive transport, or active transport. It is thus responsible for creating and main- taining homeostasis for neuronal functions, defending the system against toxic insults, regulating the commu- nication between the periphery and the CNS, and pro- viding the brain with nutrients[4,5]

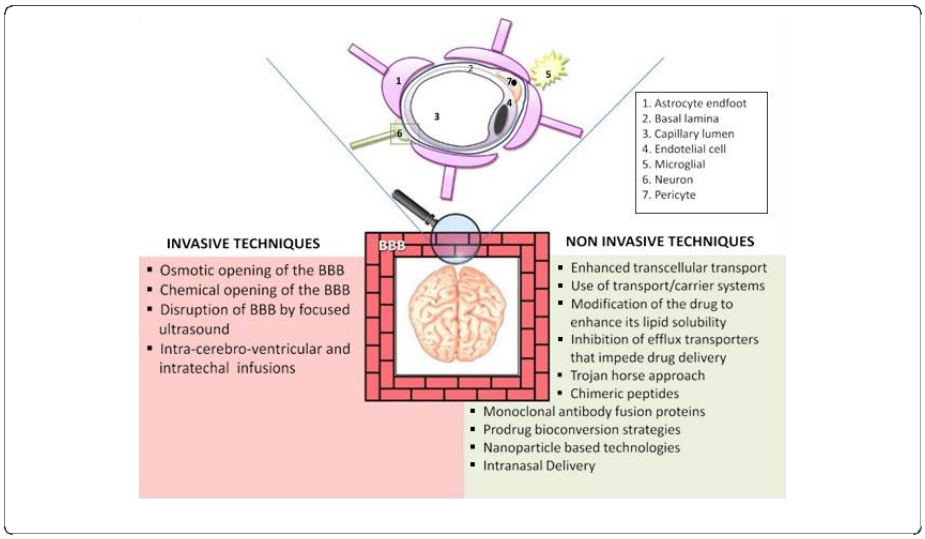

Figure 2 Blood–brain barrier and drug delivery

1.4. Invasive techniques

1.4.1. Blood–brain barrier transient disruption

This technique consists of the use of noxious agents, hyperosmotic solutions, or ultrasounds (mannitol, dimethyl sulphoxide, ethanol, metals, glycerol and polysorbate-80, X-irradiation, etc.) to shrink the brain's endothelial cells by breaking down tight junctions, allowing various molecules to pass into the cerebral tissue.5,6 Unfortunately, this technique has several limitations; it is in fact non-patient friendly, and can compromise the integrity and the physiological functions of the BBB leading to potential ac- cumulation of unwanted blood components, neurotoxic, xenobiotics, and exogenous agents, thus causing injury to the CNS.

1.4.2. Intracerebroventricular and intrathecal infusion

These strategies consist of the injection or intraventricu- lar infusion of therapeutic proteins directly into the cerebrospinal fluid (CSF).

The advantages of these methods over systemic ERT are that they allow delivery to the brain of a higher amount of enzymes and, consequently, it is not neces- sary to use massive concentrations of therapeutic drugs. Furthermore, these strategies overcome the problems re- lated to the short half-life of drugs in the blood, avoiding the ones related to systemic exposure and toxicity.Intrathecal drug administration can be accomplished by lumbar puncture or by an implanted intrathecal drug de- livery device (IDDD).6,7

Data from animal models of MPS I, II, and IIIA, and also of other LSDs such as infantile neuronal ceroid lipo- fuscinosis and Niemann-Pick A, indicate that ERT through intrathecal injection is able to distribute the re- combinant enzyme throughout the CNS where it can penetrate the brain tissue promoting the clearance of ac- cumulated material within the lysosomes. In the past few years, thanks to the availability of mouse and dog models capable of recapitulating the MPS IIIA neuropathological features, research efforts have been particularly focused on the development and testing of new therapies for brain involvement in MPS IIIA7,8 Fol- lowing the encouraging results obtained from animal studies showing that repeated direct infusion of a miss- ing enzyme via cerebrospinal fluid injection is an effect- ive treatment for pathological changes in the brain of mice and dogs , clinical trials have been initiated in humans to test the safety and tolerability of recombinant human heparan-N-sulfatase (rhHNS) administered via IDDD in patients with MPS IIIA (NCT01155778 and NCT01299727).Similarly, the safety of idursul- phase formulated for intrathecal administration (idursul- phase-IT) via IDDD has been tested on MPS II patients.Although outcomes from these studies encourage further investigational studies, the clinical application of these approaches is considered challenging due to the short half-life of the enzymes. To improve efficacy and increase the chance for clinical success, repeated admin- istrations are necessary with an increased risk of toxic effects.8,9

1.5. Non-Invasive Approaches10,11

Non-invasive approaches mostly consist of pharmacological tactics capable of altering pharmaceuticals to allow them to pass across the BBB. The primary non-invasive procedures are detailed further below.

Table 1 Strategies for Brain Drug Delivery

Type of Procedures	Strategies	Advantages	Limitations	References
Invasive approches	Blood–brain barrier transient disruption	Transient opening; can achieve therapeutic concentrations	Non-Targeted BBB Disrupted	
	Intracerebroventricular And intrathecal infusion	High gene transfection efficiency	Safety concerns,direct brain injection ,crossing bbb	
	Chemical modification of drugs	Option for personalized medicine	Difficultt to achieve therapeutic concentration in vivo	

Non Invasive approaches	Virus-mediated blood–brain barrier delivery	High gene transfection efficiency	Safety concern,direct brain injections,high dose by iv administrations	
	Exosome-mediated blood–brain barrier delivery	Gene delivery to the brain; potential ability to cross the BBB	Invivo toxicity and pharmacokinetics	
	Intranasal route of delivery	Bypass the BBB through nasal administration	Suitable for low dose	
	Modulating blood–brain barrier permeability	Transiently open the BBB	Mismatch between findings in rodents and humans	
	Focused ultrasound for brain diseases	Therapeutic concentrations; targeted to sub-millimeter regions in the brain	0nly relatively short term studies have been performed	
	Nanoparticles for brain imaging/diagnostics	Enhance imaging; cross the BBB through the hyper-permeable BBB under disease conditions	Cross the bbb ;understand dynamic changes in the bbb	
	Liposome-based strategies	Exhibit strong biocompatibility and biodegradability; minimal toxicity; drug-targeted delivery; controlled drug release	Liposomes are not currently used in clinical practice to deliver brain specific drugs	
	Solid-lipid nanoparticles	Site-specific targeted delivery (via receptor-mediated transcytosis across brain capillary endothelial cells); physical stability; ability to escape the reticulo-endothelial system; extended blood circular	Smaller drugs payload;a complicated physical state of the lipid content ;storage and administration stability issues	

1.6. Chemical Modification of Drugs

The transvascular approach preceding systemic injection is the primary limitation but the only one to consider for chronic CNS disorders, whether tumoral or neurological. Because many severe neurological disorders do not react to small-molecule treatments, large molecules, therapeutic peptides, inhibitors, or other medications are necessarAs a result, medication delivery to the brain requires methods such as nanoparticles capable of ferrying pharmaceuticals over the BBB.11,12 The BBB excludes hydrophilic medications and the vast majority of molecules, although some (but not all) tiny (300 Da) lipophilic molecules may get through via diffusion.A medicine can be lipidated to be carried to the brain, however, this strategy has had limited success since increasing lipophilicity may be efficient.but it usually comes at the expense of a greater biodistribution. As most transporters are selective, this technique requires that the medication imitate the endogenous ligand.12

Following the Maillard process, glycosylation or glycation may improve medication and peptide transport to the brain while enhancing biological stability. Due to better transport, which was likely controlled by adsorptive endocytosis instead of the glucose transporter, and retained bioactivity, Enkephalin-Ser6 b–DGlucose demonstrated higher blood stability and absorption by the brain. EGF (a ligand for differentially expressed EGF receptors in brain cancer) or BDNF (a neurotrophic component) have been linked to a monoclonal antibody against transferrin receptor, resulting in bifunctional molecules that can attach to the BBB transferrin receptor, ferry peptides throughout the vascular wall, and distribute these peptides to the brain.The activation of enzyme activities is also important in the BBB, and these functions can be changed by sickness. Aminopeptidase A activity is increased in brain tumors, but aminopeptidase N activity is reduced. These differences are crucial for transporting undamaged molecules to the brain, and enzymatically intact (pro)drugs may be necessary, such as via cyclization, halogenation, methylation, pegylation, or the inclusion of unnatural.12,13

1.7. Nano approaches toward cns drug delivery

Nanotechnology is an innovative, promising and cutting edge approach for delivering neurotherapeutics across BBB. In the last few decades, nanomedicines have shown great potential toward CNS drug delivery owing to its nanosize range, their unique physic-chemical properties and ability to exploit surface engineered biocompatible and biodegradable nanomaterials. Nanotechnology-based approaches for site-specific delivery of therapeutics and other compounds across the BBB may potentially be engineered to carry out particular functions as needed. The drug, the pharmacologically active component to be delivered, itself constitutes one part of the nanoengineered complex while remaining complex is intended to accomplish other key functions such as encapsulating the active drug protection against enzymatic degradation, drug release at specific pH, ability to cross the BBB, and targeting specific brain cells.14.15

A wide range of pharmaceutical nanocarriers including liposomes, PNPs, SLNs, micelles,dendrimers, and some others have been develop.

1.8. Micelles

Micelles, the vesicles which is made up of amphiphilic surfactants (non-polymeric micelles) or amphiphillic copolymers (polymeric micelles) have recently fascinated the researchers as a novel drug carrier system to the CNS.15,16 As compared to non- polymeric micelles, polymeric micelles are considered more stable having long duration of action and high biodistribution. They have a core-shell structural design with size ranging from 10 to 100 nm consisting outer hydrophilic environment mostly made up of polyethylene glycol (PEG) and inner hydrophobic core synthesized by means of molecules such as polycaprolactone, polypropylene glycols, phospholipids, and fatty acids, thus they allow loading of hydrophobic drugs. The external hydrophilic shell provides stability to micelles in an aqueous environment and prolongs their circulation time in bloodstream, thus protecting it from reticulo-endothelial system (RES)16,17 and further facilitate their accumulation in specific region having leaky vasculature. The class of pluronic (also known as Poloxamers) block copolymers is of particular interest as they have an ability to hinder drug efflux transporters, for instance, inhibition of P-gp efflux transporters widely expressed on BBB and enhance drug shipment to the CNS. Moreover, it was demonstrated that they facilitate the brain delivery of low molecular mass drugs incorporated into them by escalating the drug solubility and stability in plasma.

2. Organic-NP delivery systems

Organic NPs, including lipid-, polymer-, and biomolecule-based NPs which can penetrate the BBB and deliver drugs to the CNS have been developed. After surface modification to improve surface charge, lipophilicity, biocompatibility, and brain target- ing ability, these organic NPs can avoid phagocytosis by the reticuloendothelial system (RES) and significantly increase the concentration of drugs in the brain. For example, decorating with polyethylene glycol (PEG) can prolong the retention time of liposomes in blood. Targeting ligands allow NPs to get through the BBB with different transport mechanisms and realize active targeting to promote the carriers to further accumulate in the brain. Furthermore, modification of surfac- tants can alter the surface charge and improve the BBB-crossing by the enhanced electrostatic interaction.17

2.1. Lipid Based NP

2.1.1. Liposomes

Liposomes are bilayer vesicles formed by amphiphilic phospholipid with extensive use in Drug delivery because of the following advantages.

- High adaptability to loaded drugs: hydrophilic and hydrophobic drugs are loaded into the water phase and the lipid membrane, respectively, and the amphiphilic drugs are located between the phases. Thus, liposomes can simultaneously carry both hydrophilic and hydrophobic drugs, while protecting them from being diluted by body fluids and destroyed by enzymes in the body.2
- Good biocompatibility and high bioavailability: phospholipids are cell-membrane components that do not elicit toxicity upon injection into the body with a low immune response.20 The electrostatic interaction between the surface charge of cationic liposomes and the negatively charged BBB can trigger the cellular internalization of liposomes, thereby effectively pro- moting liposomes to get into the brain. In addition to the decoration with PEG and active targeting ligands, embellish- ment of some cellular membrane proteins can camouflage the surface of nanocarriers.

These multi- functional liposomes combined with other processes to open the BBB can further promote the dug-delivery system to get into the brain for improved diagnosis and treatment. Some other types of liposomes, such as temperature-sensitive liposomes, have a con- trolled drug release ability in the brain, thus can reduce the risk of pre-leakage.21,22

Conjugating liposomes with brain-specific ligands or anti- bodies can improve the targetability and promote the nanodrugs getting into the brain by RMT. For example, apolipoprotein E (ApoE) can bind to receptors (low-density lipoprotein receptors (LDLRs)) and LDLR-related proteins (LRPs) on the BBB. Trans- ferrin (Tf) is a glycoprotein that can transport iron ions into cells.22,23 Cheng et al. developed Tf-modified and PEGylated lipo- somes to encapsulate chemotherapeutic osthole (Ost) (Tf-Ost-Lip) to treat AD. Muzykantov et al. constructed vascular cell adhesion molecule 1 (anti-VCAM)-conjugated liposomes, which exhibited improved brain accumulation compared to TfR or intercellular adhesion molecule 1 (ICAM-1)-conjugated liposomes

2.2. Solid lipid NPs

SLNs are solid colloidal particles consisting of natural or synthetic solid lipids, such as lecithin and triacylglycerol that can encapsulate or embed drugs into the lipid core. SLNs can improve the physical and chemical stability of drugs, prevent drug degradation, bypass efflux transporters (such as P-gp), enhance the brain-targeting ability of drugs, and accommodate the slow release of drugs. Decora- tion with surfactants can improve the stability of SLNs, and certain surfactants can inhibit P-gp, thereby promoting the accumulation of drugs in the brain. Compared with liposomes, SLNs have higher physical and chemical stability. SLNs are compatible with multiple administration routes, including intravenous injection, subcutaneous injection,24,25 ocular adminis- tration, and pulmonary administration

Decoration with bioactive molecules can also facilitate the BBB-crossing ability. For example, Bozkir et al. used ApoE modification to improve the BBB permeability of donepezil and rhodamine B-loaded liposomes (ApoE-DON-SLNs). After 2 h of incubation, the uptake of ApoE-DON-SLNs by endothelial cells increased by over 4 fold higher than that of non-targeting liposomes.26,27 SLNs with ApoE-derived peptide (SLN-mApoE) as a specific brain-targeting ligand were also prepared via warm micro-emulsification technology

2.3. Polymer-based NPs

Polymer-based NPs are formed by the assembly of polymers. According to the building blocks, polymer-based NPs can be

PBCA NPs crossed the BBB via receptor-mediated endocytosis. Most importantly, they did not induce non-specific BBB dis- ruption. However, the use of PBCA NPs is limited due to the generation of toxic hydrolytic by-products (polyacrylic acid and alcohols). Moreover, the pharmacological effects of PBCA NPs were temporary; thus, daily intravenous injection may be required over the course of treatment.27 Polylactic-acid-based NPs. Polyester polymers, such as polylactic acid (PLA) can produce non-toxic lactic acid and glycolic acid oligomers that can be further degraded into CO2 and H2O. Wang et al. prepared Cur-encapsulated mPEG-b-PLA (NP Cur), which had a smooth surface, a spherical morphology, and a narrow size distribution (147.8 5.7 nm), to effectively deliver Cur to the brain.28,29 The Cur-loading efficiency reached as high as 51.7 3.1%. NP Cur can reduce oxidative stress and inflammation by protecting the BBB and inhibiting the activity of M1 microglia. Triphenyltetrazole (TTC) staining was used to evaluate the area and volume of infarct tissue due to inade- quate blood supply. In this study, Cur could accumulate to ischemic penumbra at 3 h post-injection. The result showed that the infarct volumes of PBS, Cur, and NP Cur groups were 40.1%, 32.4%, and 18.3%, respectively. Compared with that of the PBS- and Cur-treated groups, the infarct (dead tissue due to inadequate blood supply) volume of the NP Cur-treated group was significantly lower at 3 days after ischemia-reperfusion injury. The data indicated the successful protection of neurons against ischemia-reperfusion injury by NP Cur.30

- Amphiphilic copolymers. Amphiphilic copolymers can assemble into core–shell NPs through the amphiphilic component of hydrophilic and hydrophobic chains. Hydro- phobic drugs can be encapsulated into the hydrophobic core to enhance the water solubility of NPs.31,32 The outer layer of the hydrophilic shell can promote the stability in plasma, prolong the circulation time, and increase the bioavailability and bio- safety of NPs. In Fig. 5, four types of amphiphilic copolymers are discussed, and a brief comparison is presented.
- Poly(butyl cyanoacrylate)-based NPs. Poly(butyl cyano- acrylate) (PBCA) is a promising delivery system with high adsorption, low toxicity, and good biodegradability. Koffie et al. prepared PBCA NPs with spherical and ellipsoid geometry and a mean diameter of 48 nm, and invested their capability for crossing the BBB.58 As shown in Fig. 6A, Texas Red Glucan dissolved in PBS alone could not penetrate the BBB and remained in the blood vessel at 2 h after intravenous injection.

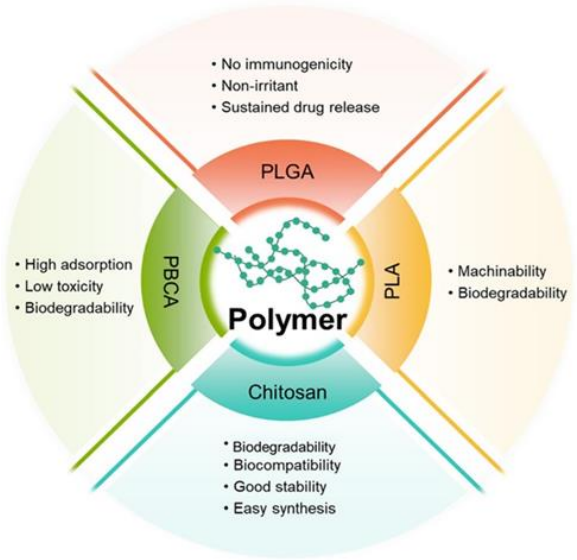

Figure 3 Polymer Based Nanoparticles

Poly(lactic-co-glycolic acid)-based NPs. Poly(lactic-co- glycolic acid) (PLGA) is formed by random polymerization of lactic and glycolic acids. PLGA has been approved as a phar- maceutical excipient for clinical use by the U.S. Food and Drug Administration.

The formation of extracellular aggregates of Ab1–42 is a sign of AD. It has been reported that Cur not only inhibits the formation of new Ab aggregates, but also shows anti-amyloid activity by breaking down existing Ab aggregates. Targeting ligand that could be separated from the nano-cleaner to promote transcytosis from endothelial cells into brain parench- yma. The exposed KLVFF could capture Ab, and in response to the presence of ROS, rapamycin was released to improve Ab degrada- tion and normalize inflammatory conditions. The physiological evaluation and behavioral experiments in an AD mice model demonstrated the effectiveness and biocompatibility of the nano-cleaner in AD therapy

2.3.1. Chitosan

Chitosan is obtained by deacetylation of chitin and is broadly utilized in biomedical applications due to the merits of degradability, biocompatibility, good stability, easy synthesis and functions, and mucoadhesivity. In 2006, chitosan was approved as a ‘‘generally recognized as safe’’ (GRAS) class of natural products by the FDA.

Trapani et al. prepared dopamine-encapsulated chitosan NPs to cross the BBB for Parkinson’s disease.77 Gu et al. designed double antibody-modified (Tf antibody and brady- kinin B2 antibody) chitosan/siRNA NPs (chitosan-NPs) with a spherical shape and an average particle size of 235.7 10.2 nm, which could target HIV-infected brain astrocytes and deliver siRNAs to inhibit HIV replication.78 Double-ligand modifica- tion of NPs is a potential strategy for improving drug-delivery efficiency. Herein, transferrin antibody and bradykinin B2 anti- body could specifically bind to transferrin and bradykinin B2 receptors, respectively, and then deliver the siRNA across the BBB into the target cells astrocytes.

2.3.2. Dendrimers

Dendrimers are novel functional polymers with highly branched three-dimensional structures. In general, dendrimers consist of an initial core (starting atoms), an inner layer with repeating units, and an outer layer with numerous terminal active groups. Dendrimers are greatly advantageous to drug delivery due to their facile surface modification, adjustable molecular weight and shape, good water solubility, and high biocompatibility and biodegradability. Moreover, dendrimers have a passive targeting effect as a result of their enhanced permeability and retention (EPR) effect, which is the characteristic conducive to BBB penetration.

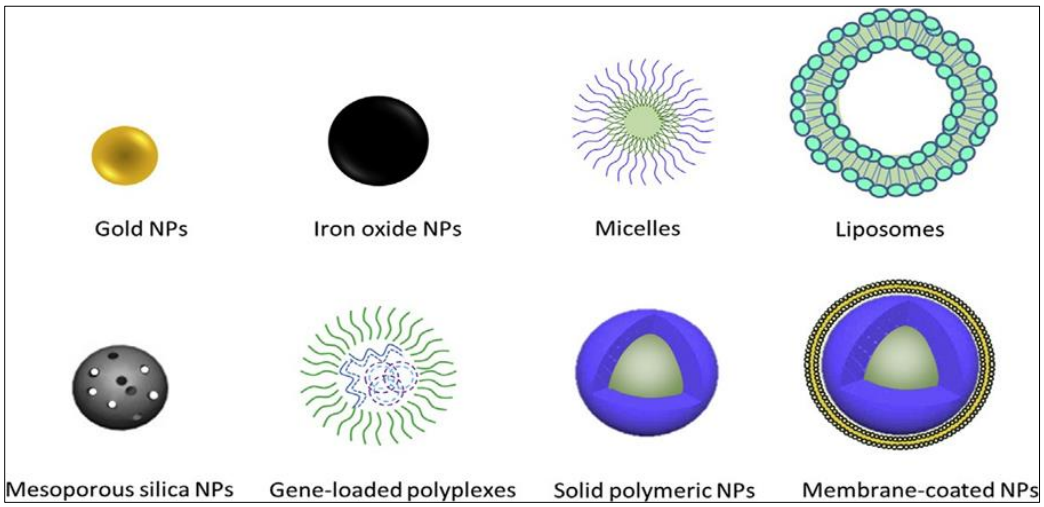

Figure 4 Different types Of Nanoparticle

2.4. Mechanism of action of drug release

The physiochemical properties of drug loaded nanocarrier like hydrophilicity, surface charge and targeting ligands of nano carrier is the deciding factor for the adsorption on the brain capillary endothelial cells. Surface charge like positive nature of the nanomaterials interacts with the negative surface charge of endothelial cells of brain, due to electrostatic interactions between carrier and cells, secondly lipophillic nature of nanocarriers also enhance and facilitates adsorption process;). These approaches reduces the clearance of nanocarrier by the fixed macrophages of the mononuclear phagocytic system (MPS), Once, the nanomaterials get absorbs either through targeting low density lipoprotein receptors present on the microvessel brain capillary endothelial cells by means of normal endocytosis and transcytosis, desorption occurs and reenter into the blood stream, where drug loaded nanocarrier releases its encapsulated or adsorbed drug on the surface of blood brain barrier and further diffuses into brain parenchyma. The average size of human cells is 10–20 μm, where as the minimal diameter of blood capillaries are 6–9 μm, due to their nano size ranges nanomaterials get easily transported and internalizes by brain capillary endothelial cells via endocytosis and transcytosis mechanism of transport. The adsorbed drug–carrier conjugates is endocytosized by the cells, at times followed by exocytosis, and further penetration of the nano carrier into the cells or brain parenchyma occurs.

The mechanism of drug delivery by nanotechnology is not still well-explored, however, various suggestions have been put forward to suggest possible mechanisms. Though the uptake of nanocarriers along with drugs into the brain has been proposed to occur by following six mechanisms.

- Increased transport across the endothelial cell layer facilitated by higher concentration gradient due to increased retention of the nanocarriers in the brain blood capillaries with an adsorption to the capillary walls. Since the diffusing drug can be effluxes out by various transporters such as P-gp, it is not a good mechanism to achieve a sufficient amount of drug inside the brain to elicit a relevant pharmacological response.
- Inhibition of the efflux system particularly P-gp.
- Toxicity to the brain vasculature.
- Solubilization of the endothelial cell membrane lipids due to general surfactant effect followed by membrane fluidization and enhanced drug permeability across the BBB.
- Permeation of nanocarrier system through the tight junctions after the opening of them.
- Endocytosis and transcytosis phenomenon through the endothelial cell layer.

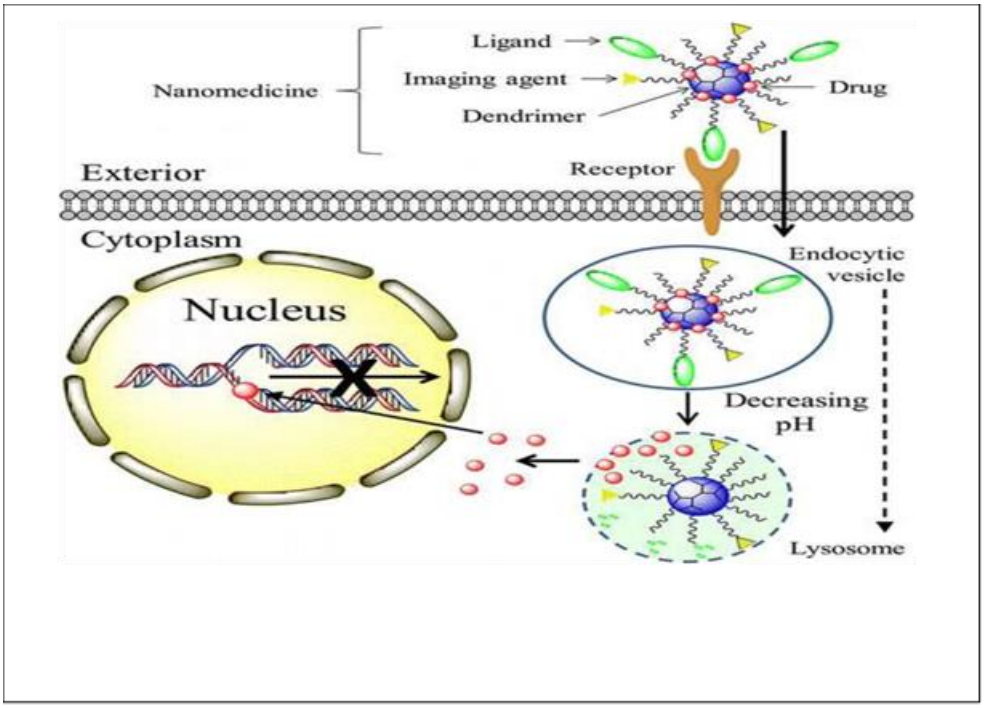

Figure 5 Mechanism Of Action of Drug Release

2.5. Applications of nanotechnology in cns disorders

Nanotechnology has revolutionized the field of treating various neurological disorders and has provided a number of new approaches that have shown potential for treating neurodegenerative disorders like AD, PD, stroke, epilepsy, HD, and brain tumor. Molecules are nano-engineered so that they have an ability to traverse the BBB, target the specific cell or signaling pathway, act as a carrier for gene delivery. Besides delivery of therapeutic drugs, nanotechnology has also gained the interest of researchers for delivery of radiocontrast agents, imaging agents for diagnosis purpose

2.5.1. Alzheimer's Disease

Alzheimer's disease is a slowly progressive neurodegenerative disorder, and is the main culprit for dementia syndrome. Pieces of evidence state that its incidence and prevalence rate is more common in elder persons. Amyloid-β plaques and Tau protein hyper-phosphorylation are considered as hallmarks of AD. The degeneration of nervous tissue in AD starts years back of the actual appearance of the symptoms of the disease. The conventional treatment approaches are not able for complete treatment of disease, thus the inability of orally administered drugs such as tacrine, rivastigmine, etc. to treat the disease, opens the door for the application of nanotechnology for AD treatment.

2.5.2. Parkinson's Disease

Parkinson's disease, illustrated by loss of dopaminergic neurons in the substantia nigra of the midbrain and the generation of α-synuclein aggregates (Lewy bodies), is the next most common neurodegenerative disorder worldwide after AD. Nowadays, it is considered that pathology of PD is not just limited to a particular part of the brain but it involves various other regions of the brain, neurotransmitters such as imbalance in ACh and dopamine, and protein aggregates other than Lewy bodi. The manifestations of PD involve motor symptoms like tremor, speech, writing changes and non-motor symptoms like cognitive, behavioral, and autonomic changes.

2.5.3. Huntington Disease

Huntington disease (HD) is described by preferential loss of neurons in striatum and other brain regions leading to progressive motor, cognitive, and psychiatric manifestations. It occurs due to monogenic mutation in the exon 1 of huntingtin gene which leads to polyglutamine (poly Q) expansion and causes misfolding and aggregation of huntingtin protein (HTT) in the brain. Several studies confirm the involvement of astrocytes in HD. Brains of HD patients and mouse models of HD demonstrates accumulation of mutant HTT in striatal astrocytes which ultimately leads to age-dependent HD-like pathology and premature mortality. Symptomatic and protective treatment strategies are available for HD but

none of them are efficacious to completely cure the disease. Currently, tetrabenazine is FDA approved drug for the symptomatic treatment of HD.

2.5.4. Tumor

Brain tumors, like other body parts tumors, may be benign, originating and residing within the brain, or metastatic, originating from a tumor outside the CNS, among which glioblastoma multiforme (GBM) – a malignant glioma, is the most prevalent. They are among the most challenging disease to treat due to poor prognosis, diagnosis, high recurrence rate, and availability of limited number of convenient methods to transport anti-cancer drugs across BBB in effective concentration. Current treatments available are just palliative, involving united approaches of surgical debulking with radiotherapy and chemotherapy, which are not sufficient for the complete treatment, and also the reversal to the tumor state again is most common.

2.5.5. Multiple Sclerosis

Multiple sclerosis (MS) is a progressive autoimmune and inflammatory disease. It is a multifactorial disease in which body's immune cells attack on the nervous system. It involves various pathogenic mechanisms leading to demyelination of myelinated axons which results into slow conduction of nerve signal. There are evidences which suggest mutual interplay of microglial, astrocyte and T-cells beside demyelination ; Ojha and. It is diagnosed on the basis of clinical findings, magnetic resonance imaging (MRI) and examination of Cerebrospinal fluid (CSF).The prevalence rate of MS ranges 2–150 per 100,000 people and females are more susceptible than males. MS attack disrupt BBB in the section of brain or spinal cord from where peripheral T lymphocytes gain access to brain and attack the myelin gradually leading to demyelination.

2.5.6. Stroke

Stroke, an acute CNS disorder, is characterized by the disruption to the vasculature supplying the brain, resulting into sudden symptoms, within seconds to hours, which usually depends on the fraction of the brain involved and the severity. There are two main types of stroke: Ischemic stroke, contributing 87% of total stroke, comprising of lacunar, cardioembolic and cryptogenic stroke, and the hemorrhagic stroke, having 13% contribution to the total stroke, comprising of 10% intracerebral and 3% hemorrhagic stroke. It is among the principal cause of mortality and morbidity, regardless of the availability of a number of treatment approaches, due to various challenges in drug treatment, which demands the development of new therapeutic approaches. The nanotechnological approach has shown great potential to overcome the major hurdles in stroke management and has provided a useful platform for the development of novel therapeutic methods for treatment.

2.5.7. Epilepsy

Epilepsy, a CNS disorder, is characterized by an abnormal increase in brain electrical activity that may be either limited to the focal area or spread throughout the brain, resulting in partial or generalized seizures, respectively. The current treatment methods, having the aim of diminishing the seizure frequency and severity while producing the minimum toxic effects to the brain and other tissues of the body, are almost failures due to various hurdles, such as the inability

3. Conclusions and BBB avoid ANCE strategies

The development of new drugs for brain diseases, much less the major diseases of the brain in aging, AD, PD, and stroke, has proven to be most difficult, particularly for biologic drugs. In 2019, there is not a single recombinant protein that is FDA approved for brain disease, wherein that drug must cross the BBB. The main factor limiting CNS drug development is the BBB, as 98% of all small molecules do not cross the BBB, and 100% of large molecule drugs do not cross the BBB. Multiple clinical trials of CNS disease have been attempted with recombinant proteins over the last 25 years, and all such clinical trials have failed. The singular feature of all these trials is that, in no case, was the biologic re-engineered to enable BBB transport prior to entry into the human clinical trial. This is a natural result of CNS drug development taking place in the absence of a parallel effort in BBB drug delivery technology.

The fact that multiple biologics have entered CNS clinical trials over the last 25 years, without any BBB drug delivery technology, seems paradoxical. These clinical trials were enabled because CNS drug developers practiced a variety of BBB avoidance strategies, wherein the brain drug delivery strategy emanated not from a foundation in BBB drug delivery technology, but rather from a basket of BBB avoidance strategies that: (i) asserted the drug crossed the BBB, (ii) employed BBB disruption strategies, (iii) bypassed the BBB by drug injection into the brain or CSF; or (iv) employed ineffective BBB delivery vehicles, such as stem cells or AAV. Such BBB avoidance strategies are generally not effective,

and with rare exceptions, the clinical trials lead predictably to failure and no FDA approval. The top 10 BBB avoidance strategies are highlighted below.

Use of drug entry into CSF as an index of drug transfer across the BBB. Therapeutic antibody-drug developers for brain claim no BBB delivery technology is needed, owing to a low, but significant, antibody delivery into the brain from the blood. The IgG concentration in the brain is said to be 0.1%–0.2% of the blood IgG concentration. However, what is being cited in this context is the concentration of antibodies in CSF, not the brain. Drug transport from blood into CSF is a function of delivery across the choroid plexus, which forms the blood-CSF barrier, whereas drug transport from blood into brain parenchyma is a function of delivery across the brain capillary endothelium, which forms the BBB. The choroid plexus epithelial barrier and the brain endothelial barrier are anatomically and functionally distinct. The blood-CSF barrier is much leakier than is the BBB. All proteins in blood enter into CSF across the leaky choroid plexus, at a rate inversely related to the molecular weight of the druG. The concentration of IgG in CSF is 0.1%–0.2% of the corresponding plasma level, whereas the concentration in brain parenchyma of a therapeutic antibody is <0.01% of the plasma concentration.

Failure to account for the cerebral blood volume. Aducanumab, the therapeutic anti-Abeta amyloid antibody, was said to cross the BBB because the brain concentration was parallel to the plasma concentration in preclinical research in mice. However, the brain/plasma ratio of this antibody was 1 μl/g, which is >10-fold lower than the brain plasma volume, 10–15 μl/g. Antibody residing in residual blood volume of brain has not crossed the BBB. For assessment of biologic uptake by the brain, it is important to correct brain drug uptake estimates for drugs trapped in the blood volume of the brain. Failure to correct for the brain-blood volume may lead CNS antibody-drug developers to conclude that no BBB delivery technology is required.

Drug-induced BBB disruption. Aducanumab reduces brain amyloid plaque in AD in a dose-dependent mechanism, which indicates this antibody crossed the BBB in patients with AD. However, aducanumab also caused a dose-dependent disruption of the BBB, as reflected in the vasogenic edema measured in these patients by MRI. The BBB disruption in AD caused by high doses of an anti-amyloid antibody parallels the cerebral micro- hemorrhage observed in transgenic AD mice administered high doses of an anti-amyloid antibody. The AAA that do not cause BBB disruption or brain edema in AD also do not lower brain amyloid plaque.

Drug injection into the CSF. Over 100 years ago, when a barrier between brain and blood was just discovered, it was believed that nutrients in blood passed first into CSF and then into the brain. These ideas were soon shown to be false and that drug entered the brain directly from blood without any intermediate passage through the CSF. Nevertheless, these ideas gave rise to the concept that drug injected into CSF easily distributed to the brain. However, a drug injected into CSF does not undergo significant penetration into the brain parenchyma , because drug diffusion into the brain from the CSF is slow compared to the rapid bulk flow of CSF out of the brain to the peripheral blood.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors have no conflicts of interest to declare.

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