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Review Article

Brain-Targeted Drug Delivery Systems: Overcoming the Blood–Brain Barrier

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ABSTRACT

The fact that the central nervous system (CNS) disorders are treated is a critical problem because of the existence of the blood-brain barrier (BBB), which is a highly selective and protective surface that prevents entry of most therapeutic agents into the brain. The development of brain-targeted drug delivery systems has cropped up as an ideal approach of overcoming this hurdle, which would allow the effective delivery of drugs across the BBB to access the target sites in the CNS. Using nanotechnology, molecular targeting and carrier engineering, these systems enhance drug bioavailability, minimize side effects at the systemic level and enhance therapeutic activity in neurological disease, including Alzheimer, Parkinson, brain tumours, epilepsy, and multiple sclerosis. This review notes the structural and functional properties of the BBB and describes several brain-targeting methods such as receptor-mediated transport, cell-penetrating peptides, and nanoparticle-based systems as well as discusses recent advancements in invasive and non-invasive methods. Issues of safety, biocompatibility and regulatory demands are also discussed and future outlooks of precision neuromedicine and theranostic dealing are indicated.

INTRODUCTION

The Challenge of CNS Drug Delivery

Drug transport to the CNS is limited by the BBB, among other protective barriers (e.g., blood–CSF and CSF–brain barrier). Those structures protect the brain from circulating substances and are considered as principle obstacles for drugs in CNS drug delivery [1]. Despite their vital role in preserving the CNS integrity, these barriers prevent penetration of the majority of therapeutic agents and lead to low bioavailability and little drug deposition at the pathological sites [2].

Importance of Overcoming the Blood-Brain Barrier

The BBB is essential for preventing macromolecules from reaching the brain, and maintaining normal physiological homeostasis. Blood circulating substances have difficulty permeating the BBB to gain access to brain tissue [3].

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This partition prevents 98% of drugs from entering the brain and also shields it from infections and harmful by-products. Most drugs, however, are very hydrophobic and have limited capability to interact with the highly lipophilic BBB membrane. Only very lipophilic compounds that do not form strong hydrogen bonds with non-lipids and can pass through the field are transported across the BBB. For this reason, the brain is targeted by only few drugs, which are able to cross it [4, 5].

Review Scope and Structure

The present review provides a description of BBB development, structure and function in normal and diseased nervous system as well as the nature of drug-delivery issues. It seeks to review our present understanding and recent discoveries in the field of BBB biology. The review is structured in parts terming BBB structure, pathways of formation, types of transportation mechanisms; biological functions LMTAPC (Ligand mediated targeted drug delivery system) and the different strategy in drug delivery.

Structure and function of the blood-brain barrier (BBB)

The BBB: Anatomic and Physiologic Perspective

In the Fig.1 show structure of BBB, capillary endothelial cells (ECs) express tight junctions (TJs) and adherens junctions (AJs), which restrict transcellular transport and reduce pinocytotic activity. In these cells, solute transport is supported predominantly by the paracellular route. BBB activity is also regulated by pericytes, microglia and closely associated perivascular astrocytic end-feet. These supportive cells control migration, proliferation, and vascular branching of endothelial cells that are essential for BBB development and function. The basement membrane supports both pericytes and endothelial cells of the NVU, with the basal lamina found adjacent to astrocytic end-foot membranes [6, 7].

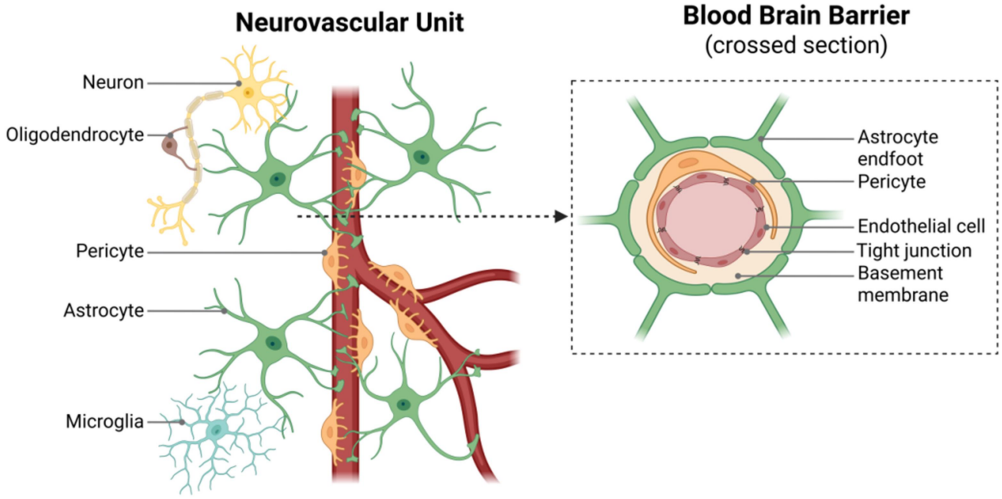

Figure 1: Neurovascular unit and BBB structure

Mechanism of Selective Permeability

BBB plays a critical role in CNS homeostasis and is responsible for protecting cerebral tissue from endogenous and exogenous harms [8]. As a semi permeable lining of blood vessels within the CNS; it controls passage of molecules between the blood and brain. Transport through the BBB is regulated by receptors, transporters or carriers, efflux pumps etc. Carrier-mediated transport and receptor-mediated transport systems control the influx and efflux of molecules into the brain parenchyma (Fig.2) [9-11].

Alterations in BBB Pathology Associated With Disease

Delivery of drugs across the BBB has been heavily researched by researchers with emphasis on utilizing NPs that could overcome or traverse through this barrier. The BBB is a blood-brain barrier that serves as a physical barrier against detrimental chemicals entering the CNS. For drugs to reach therapeutic levels at the brain, understanding how neurological diseases modify the BBB is critical. Diseases including Alzheimer's disease, stroke, neuroprotective diseases, traumatic injuries to the brain or spinal cord and CNS cancers or HIV-associated infections—and ALS, Huntington's disease, Parkinson's disease and multiple sclerosis—are all linked with changes in BBB permeability or structural integrity [11, 12].

Challenges to CNS Drug Delivery

Efflux Transporters and Metabolic Enzymes

The BBB endothelial cells comprise a number of influx and efflux transporters. Efflux transporters, especially the ATP-binding cassette (ABC) and solute carrier (SLC) systems, are major contributors to P-glycoprotein (P-gp), multidrug-resistant proteins, and breast cancer resistance protein are highly expressed in the BBB and secrete therapeutic drugs away from the CNS, lowering their levels and diminishing the efficacy of medications. Numerous approaches have been attempted in attempts to circumvent or prevent this efflux mechanism [12, 13].

Limited Paracellular Transport

Paracellular transport is the movement of solutes between tight junctions of neighbouring brain endothelial cells. This passageway permits

only the smallest hydrophilic molecules to traverse. While transient disruption of tight junctions may increase paracellular diffusion it also increases permeability to undesired agents. Furthermore, metabolic enzymes in brain capillary walls hydrolyze peptides and low molecular weight compounds as blood travels through the CNS, generating an additional passive protective layer of protection of the BBB [13, 14].

Pathophysiological Differences in BBB Permeability

The BBB is variable The disruption of the barrier will occur in while not so much in patients with Parkinson's disease (PD), ALS or CJD; the multiple sclerosis, stroke.) And epilepsy is extremely diverse. Trauma or secondary pathological conditions such as inflammation, lipid per oxidation, excitotoxicity (calicium-mediated injury) and metabolic upset may sept blood-brain barrier [14].

Strategies to Overcome the BBB

Invasive Approaches:

Intra-Cerebral and Intra-Thecal Injection

Intracranial implantation: As of right now, no completely established therapeutic medicines are targeted directly within the brain. Rats' substantia nigra (SN) was transplanted with cultured rat fibroblasts transfected with as lentivirus BDNF seven days before to intra-striatal injections of MPTP and 1-methyl-4-phenylpyridinium (MPP+), respectively. To counteract the limited availability of drug throughout the brain when drugs distribute via diffusion from an intra-cerebral injection site, multibranched catheter bundles were developed in 1988 to improve drug distribution [15, 16].

The Intra-thecal drug administration to brain or the medication injected into CSF compartment paradox is that instead of delivering medicine to the parenchyma, it is delivered to bloodstream. As the previous studies reported, drug is exclusively delivered only to ependymal surface of brain through ICV route [16].

Focused Ultrasound with Micro Bubbles

Microbubble-assisted FUS in a Brain Disorder Drug Delivery System A novel approach to treating brain disorders; micro bubble-assisted FUS uses focused ultrasound energy to temporarily breach the blood-brain barrier (BBB) in order to deliver a medication or therapeutic agent to the target region in the brain. In AD brains, FUS-mediated ultrasonography allowed aducanumab to cross the blood-brain barrier and significantly improved transport efficiency, which led to a notable drop in Aβ levels. Additionally, scientists are investigating novel methods for adhering microbubbles to brain endothelial cells, which can be utilized in conjunction with low-energy ultrasound to transport medications across the blood-blood barrier [17]. Micro bubble-mediated FUS technology is being developed for curing brain diseases, although how to make tight control of the open-close level of BBB at present remains difficult [18, 19].

Non-invasive Approaches:

Receptor-mediated transport (RMT)

The BBB, meningeal blood vessels and chimeric polymersomes (CP) each express numerous proteins and receptors. The composition of the receptors enables them to transfer vital messages and nutrients from the blood to the brain (Fig.2). Using these receptors to improve medication gateway access and engagement with BBB ECs is one strategy. Low-density lipoproteins (LDLs), rabies virus glycoprotein's (RVG), and several additional receptors are a few examples. Additionally, since this procedure is non-invasive, it may be used again. The studies that have used RMT to enhance medication penetration across the BBB will be included in this section. Many different proteins are transported by LRP and LRP-related proteins [20, 21].

Adsorptive-Mediated Transport (AMT)

Adsorptive mediated transport is enabled by electrostatic interactions in between negatively charged glycoprotein's (such heparin sulfate proteoglycans) of the BBB endothelium surface and positively charged ligand (or cationic protein, cell-penetrating peptides or nanoparticle surfaces) (Fig.2) [22]. A dual-modal probe was also developed where a small molecule inhibitor for general control non-repressed protein 5 (GCN5) was conjugated to dendrimers109. The probe can cross the blood-brain barrier efficiently via AMT, thereby providing enhanced preoperative visualization of tumor margins on MRI and intraoperative fluorescence image guidance [23].

Carrier-Mediated Transport (CMT)

PEG2000-poly (α β-polyaspartic acid) co-block polymer was used to create micelles the iso-gram moiety through, allowing passing BBB using

GLUT1 glucose to transporter, and therefore facilitate nanoparticle transiting through BBB (Fig.2). No brain uptake data were given and fluorescent microscopy showed that most of the micelles were sequestered within the brain intravascular space [24, 25].

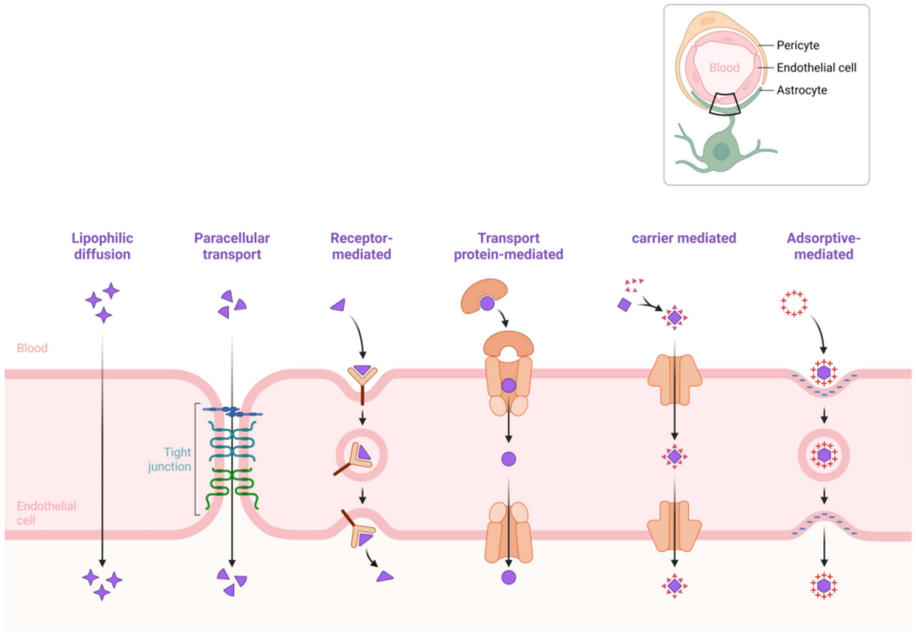

Figure 2: Non-Invasive Approaches

Nanotechnology in Brain-Targeted Drug Delivery

Polymeric Nanoparticles

It was first announced in 1995 that polymeric nanoparticles (PNP) were used to transport drugs; the process goes through by crossing the blood–brain barrier [26-28]. Hex peptide dalargin bound to poly (butyl cyanoacrylate) or PBCA PNPs. PBCA, Dalargin were vortexed and sonicated with the suspension and 0.1% PS80, a non-ionic detergent. Mice then were injected intravenously with solution immediately. It was also proved that plasma proteins including apolipoproteins B (apoB) and J were absorbed onto the surface of PS80-coated PNPs [29-32].

Liposomes and Solid Lipid Nanoparticles

Liposomes are nanosized particles formed by lipids with an entrapped aqueous core. Solid lipid nanoparticles (SLN), in contrast, are completely solid on the inside [33, 34]. The pioneer investigation with the use of liposome for brain drug delivery appeared in 1990. Fishers (F344) with intracranial 9 L glioma received theliposomes in their carotids [35, 36].

In contrary to liposomes, with aqueous core, SLNs have solid lipid matrix [37, 38]. Nanostructured lipid carriers (NLCs) have a lesser drug loading than SLNs but provide a higher total drug-loading capacity [39, 40]. The wider term, lipids periodid nanoparticles (LNPs), refers to liposomes, SLNs, NLCs and cationic lisplexes [41, 42]. In previous investigations from our laboratory on use of SLN for brain targeting, BBB traversing properties were predominantly explored using cell culture models [43]. The advantage of SLNs in drug despatch is particularly the case when loaded with poorly soluble drugs [44, 45].

Dendrimers

Dendrimers are cationic or uncharged molecules that branch like trees. The range of their molecular weight is around 1 k Da to 1000 k Da. A titrated dosage of PAMAM (poly (amidoamine)) dendrimer was administered intravenously to the mice. Because of the cytotoxicity of amine-terminated dendrimers and the aggregation of cationic dendrimers in the presence of serum, the application may be biased. The aggregation of cationic liposome/DNA complexes generated by salt is similar to that of cationic dendrimers in serum [46-48].

Inorganic Nanoparticles

Gold Nanoparticles (AuNP): 15 nm AuNPs were intravenously injected into the mice, and these AuNP were precoated with albumin and poly

(allylamine), a strong cationic charged polymer. The fluorescent microscopy indicated that the AuNPs penetrated brain, however, the fluorescence could have been due to the AuNPs aggregating on the surface of micro vasculature. Similarly in another study, AuNPs failed to enter the brain without a laser beam external to it [49].

Magnetic Nanoparticles: SPION are magnetic iron-based (Fe) nanoparticles (NP). The SPIONs were functionalized with PEG and PEI by adsorption, when PS80 was to be added for stabilization. The rat was injected with SPIONs intravenously, and an external magnetic field (EMF) was applied via a magnet placed on the surface of its skull [50].

SiNPs: SiNPs were prepared through the reaction of (CH_3CH_2O) 4-Si, or tetraethylorthosilicate, to produce SiNP. The carotid artery of rats was perfused with SiNPs in silica-specific fluorescence agent stained brains of the rats (a fluorescent chemical that specifically detects silica in natural soil) [51].

Hybrid and Multifunctional Nanocarriers

A hybrid DDS can improve both drug resistance and the therapeutic impact while taking into account the benefits and drawbacks of both organic and inorganic NPs. Lipid-polymer hybrid nanoparticles for the treatment of pancreatic, breast, and prostate cancer that has spread. The therapeutic effectiveness of this hybrid nanoparticle (hybrid NP) is higher. However, this system is easily incorporated by cancer cells and cannot be quickly removed from the reticulum endothelial system. Multifunctional nanoparticles are complexes with unique chemical and physical characteristics in relation to their size range of 1–100 nm [52-54].

Molecular and Ligand-Based Targeting Strategies

Transferrin and Lactoferrin Receptors

TfR1 is expressed at higher levels in the BBB and a limited number of cell types compared to normal tissues. Consequently, TfR1 has become an attractive candidate for therapeutic applications and conditional regulation of neurological diseases and tumors. The TfR1-targeting drug delivery carriers are used as follows, including transferrin (Tf), anti-TfR1 antibodies and TF2 recognition peptides with high specificity to TRF [55].

Since LfR is upregulated in brain endothelial cells, the brain capillaries, and neurons associated with neurodegeneration, it has also been a target for delivery of drugs into the central nervous system through transcytosis across the blood-brain barrier. Carbodiimide conjugated LF-conjugated linoleic acid-loaded micelles showed improved brain release in the AD mouse model caused by aluminum chloride, and also exerted strong cognitive activity [56].

Insulin and Leptin Receptors

These are for instance insulin, or drugs conjugated to derivatives of synthetic molecules that follow the same transport route into the brain (insulin-analogues). Fusion proteins of insulin that can be applied to hippocampal neurons have now been developed by scientists [57].

A high-affinity binding site for leptin was found with isolated human brain microvesse and radio-receptor tests. A KD for leptin binding was 5.1+/2.8 nM. Endocytosis by human brain microcapillaries could take up leptin, which was not blocked binding to these sites by insulin and IGF-1. This (Bmax----pmol/mg protein) was within the range of values obtained previously for insulin, transferrin (Tf), and IGF binding to human brain capillaries. PCR study also demonstrated that the short form of LEPR is significantly expressed on the brain endothelial cells [58, 59].

Cell-Penetrating Peptides (CPPs)

Cationic, non-targeting cell penetrating peptides (CPPs) enhance medication diffusion through the cellular membrane and also pass through the blood–brain barrier. For any number of applications, a variety of entities have been transported using the TAT peptide [60].

Antibody- and Aptamer-Mediated Targeting

Aducanumab is an IgG1 antibody that targets and promotes clearance of brain-extracellular Aβ plaques. With respect to the factors that the drug does improve cognition, it is not enough to have clinical evidence [61, 62].

For brain tumor delivery, ligands can be conjugated onto the surface of NPs to enhance their effectiveness.

Results: SELEX showed that AS1411 aptamer targeting nucleolin, a receptor overexpressed in the brain tumor. AS1411-conjugated NPs could

be 2 times more internalized by brain tumor cells than non-modified nanoparticles [63].

Emerging Technology and Innovations

Exosomes and Extracellular Vesicles

The low immunogenicity, and the high biocompatibility of exosomes what kind of construction should be prohibited in urban areas have a little President Xie suddenly sighed. Their ability to penetrate the brain-blood barrier set adds them apart from a delivery system. TanIIA-GL nanoparticles (TGM) composed of tanshinone IIA and glycyrrhizic acids are combined with the exosome which is loaded with immune activating agents to generate drug-loaded nanoparticles, namely CpG-EXO/TGM [64].

Cell-generated lipid bilayer membrane vesicles (extracellular vesicles [EVs]) have some special surface contacts with cells in their surrounding and extracellular substances, such as chemical species [65].

Gene and RNA-Based Therapies

It also describes the use of viral vector- or nanoparticle-based delivery methods to deliver CRISPR and RNA components for treating genetically and neurodegenerative brain diseases [66, 67].

Stem Cells Transfected by Lentivirus

An LV retrovirus is responsible for integrating itself permanently into the host's DNA. That means this virus poses a long-term threat of cancer [68].

Adeno-Associated Virus

Intracerebral instillation of a beta-galactosidase gene in the rat brain: Effect of type and volume of solution at the injection site. Issues of diffusion-limited IC delivery of drugs [69].

Theranostic Nanoplatforms

Theranostic -The process of combining therapy with diagnostics. It uses a variety of methods for creating 3D molecular images and an individualized diagnosis to plan treatment. Cancer experts say they could help provide cancer patients with improved prognoses by giving them alternative options for treatment. In addition, thesynchronous nanoparticles can also serve as theranostic agents to analyze treatment response post therapy and help clinicians make more accurate personalized therapydecisions [70-72].

AI for Drug Delivery Design of the CNS

"Recent development in [the] field of nanotechnology with use of AI-based approach may also be useful to handle a variety (i.e. multiple sclerosis, Alzheimer disease, Parkinson disease and brain cancer)" but without the pitfalls related to conventional modalities. These ideas are broadly relevant to many facets of illness management, including the early recognition thru discovery of biomarkers, prediction of disease course and monitoring over time, treatment construct and drug advancement [43]. In this segment, we also sidelong into a look at possible applications of AI tools in advancing Nano- medicine with its application to various aspects of brain disorder management [73].

Therapeutic Applications

Table 1 highlights these approaches enhance the delivery of drugs, genes, nanoparticles and peptides for conditions including brain tumors, neurodegenerative diseases, epilepsy, and traumatic brain injury, resulting in improved bioavailability, sustained release, and localized therapeutic action.

Challenges and Clinical Translation

Safety, Toxicity, and Immunogenicity

The safety of EV-nanomaterial hybrid systems is still major concern, which remains to be answered prior to clinical trials. Toxicity, immunogenicity, and ADR of nanomaterials are still problems after long-term administration. This danger might be potentiated by the association of nanomaterials with EV leading to inflammation, impairment in cell signaling pathways and/or conversion of their structural stability. Long-term toxicity is also concerned since nanoparticles might be accumulated in non-specific organs over time [79, 80].

Scalability and Manufacturing Constraints

Increasing the yield is a key issue for potential EV-nanomaterials hybrids clinical applications. Although these methods have demonstrated very promising results within small-scale studies, there are challenges to translating them into the clinic. For their clinical utility, EVs must maintain high yield with therapeutic properties. In addition, efficient preservation of the hybrid system function during industrial scale production is still an issue to be addressed, in particular related to nanomaterial-EV stability [80, 81].

Table 1: Therapeutic Applications

Sr No	Disease/Condition	Therapeutic Target	Delivery System	Therapeutics	Advantages	Ref
1	Brain Tumor e.g., Glioblastoma	Target tumor cells, bypass BBB, reduce tumor growth	Nanoparticle-based delivery liposomes polymeric Nps), Focused ultrasound mediated BBB opening	CRISPR/Cas9 constructs, monoclonal antibodies, siRNA, Temozolomide	Enhanced tumor penetration, reduced systemic toxicity, localized delivery	[73-75]
2	Parkinson's disease, Alzheimer's disease, and other neurodegenerative diseases	Peptides, Genes: promote neuronal survival	Lipid nanoparticles, Exosomes, iBBB targeted polymeric Nanoparticles	Donepezil, dopamine, BDNF,	Sustained release, improved brain bioavailability	[76, 77]
3	Epilepsy and Seizure Disorders	Control abnormal neuronal firing & enhance drug bioavailability	Nanoemulsion or lipid based delivery and Targeted polymeric nanoparticles	Carbamazepine , valproic acid &levetiracetam	Faster onset, reduced side effects and improved pharmacokinetics	[75, 78]
4	Neuroinfections& Inflammation	Deliver antimicrobial/ anti-inflammatory drugs across BBB	Liposomal antibiotic carriers, Magnetic nanoparticles & Targeted polymeric nanoparticles	Amphotericin B, Rifampicin & dexamethasone	Enhanced CNS penetration, localized action & lower systemic toxicity	[79]
5	Traumatic brain injury and stroke (TBI)	Neuroprotection, reduce oxidative stress and promote regeneration	Polymeric and lipid nanoparticles, Exosomes based delivery, Intranasal peptide delivery. FUS assisted delivery	Antioxidants (curcumin, resveratrol), growth factors, siRNA	Targeted delivery to ischemic regions, reduced inflammation, improved recovery outcomes	[76, 80]

Regulatory Considerations and Clinical Trials

Receptor-targeted therapy in previous clinical trials has made some promising leaps forward for the treatment of neurological disease. Bispecific anti-TfR antibodies with activity for brain uptake clearance of Aβ include gantenerumab (TfR/antiAβ): In Alzheimer's disease, PhaseIII trials for brain amyloid plaques reduction were superior to aducanumab at lower doses (Phase III NCT03444870 and NCT03443973), though cognitive benefits were also minimal. Some LDR LRP1-targeting agents, such as the PTX–peptide conjugate ANG1005 (NCT01967810), have also been evaluated in patients with brain metastases plus other TfR-targeted approaches. Receptor saturation and differences in treatment response between patient groups continue to pose problems in current clinical studies aimed at increasing receptor affinity and maximising dosing regimens.[81, 82]

Cost and Patient Accessibility

There are several factors as to why NP drug delivery system were already prevalent in the clinics and one of which is its cost-effectiveness. While these better nano-carriers have the potential to enhance drug bioavailability or target therapy, and diminish side-effects, their commercial viability shall depend on how production cost is reconciled with therapeutic value. Among others, liposome and polymeric NPs are two types of NPs that appear to be cost-effective alternatives owing to their well-established fabrication strategies, regulatory approval and biocompatibility. What are worse, metallic nanoparticles can't be biodegraded and are present in organs such as liver and spleen, which is very likely to lead to long term safety problems [82].

Future Perspectives

Personalized Neuromedicine

Personalized Neuromedicine Approaches: treatment/rehabilitation of CNS diseases. In the setting of certain CNS disorders, personalized nano-medications are also desired to be as effective as possible with few side-effects. The obstacles in personalized nano-medicine can be addressed through the learnings from nano-bioengineering. Commercially available NCs Most of the commercially available NCs are made

biocompatible by sophisticated synthetic procedures and surface functionalization. Therefore, biopolymer materials including hydro gels and liposome-based NFs are commonly prepared [82, 83].

Real-Time Imaging and Monitoring of Delivery

It is extremely difficult in theory to apply drugs directly into brain tissue because the exact site of injection and the quantity are not possible to control. Prompt visualisation and quantification of liposomes within the CNS highlight the importance of investigating time-dependent delivery. This suggests that on-line monitoring of liposomally-mediated drug infusion would be a useful tool in minimize systemic toxicity and high degree of side effect. This kind of monitoring is likely to optimize CED trials, especially when the targetization drugs to distinct anatomic brain regions [83].

Smart and Responsive Brain-Delivery Systems

"Smart and responsive-based brain-delivery systems" constitute a highly advanced category of therapeutic platforms for the delivery of drugs, genes, or bimolecular agents directly into the brain by circumventing the restraining character of blood-brain barrier (BBB)-mediated routes. These nanotechnology based systems aggregate to biomaterials, and stimuli-responsive (SR) pilimicrom environment will supply the controlled and targeted adsorbent drug release in response to external (light [18], ultrasound [19], magnetic field [20]) or internal conditions (pH gradient of enzymes red-ox potential).. Even though there are remaining requirement- s of biocompatibility, long-term safety, scalability that have always been unclear Issues of fusing nano-biotechonology with aluminium-medicine [84].

Integration with Neural Implants and Bioelectronics

Research and development activity on implantable brain interfaces has exploded in recent years. These implanted brain sensors to observe electrophysiological and neurochemical levels, or activate some activities in the brain by external electrical, optical, chemical, magnetic or ultrasound stimulation [83, 84].

CONCLUSION

Effort has been made to summarize the agents that can cross or penetrate BBB under a format for them as follows, which attempts at incorporating above discussion. BCNU wafer this was a shining star in the implantable biodegradable polymers systems. By 'target tissue specific' I mean that exosomes, for being a potential carrier of therapeutic cargo in different target tissue using the help of tissue engineering, have become an emerging tool. They can be used in combination with other biomaterials or inorganics, such as magnetic nanoparticles, for enhanced targeting or detection sensitivity. Evidence from clinical studies has been reported on the safety of FUS-induced BBB opening and its subsequent clearance of amyloidal plaques in two Alzheimer's disease trials, as well as that of FUS-assisted medication delivery of a number of neurodegenerative diseases and brain cancer tribulations.

The proximity of these delivery systems to brain enables a number of advantages for such platforms in therapeutic applications. Combined therapeutic approaches, such as FUS-mediated IN delivery, may also be prospects to enhance the therapeutic applications. However, randomized controlled trials are necessary to assess these strategies in a correct manner regarding safety and feasibility as well as their therapeutic effect. Achieving high selectivity against nanoparticles remains an important objective for targeted drug delivery. Ultimately BBB integrity is subject to integration of numerous receptor and transporter pathways. Present studies are also exploring whether novel engineered compounds would be a candidate for regulating these pathways to guide drug delivery across BBB.

ABBREVIATIONS

RMT	Receptor-Mediated Transcytosis
AMT	Adsorptive-Mediated Transcytosis
CMT	Carrier-Mediated Transport
TfR	Transferrin Receptor
INSR	Insulin Receptor
BBB	Blood-Brain Barrier
SLNs	Solid Lipid Nanoparticles
NLCs	Nanostructured Lipid Carriers
AuNPs	Gold Nanoparticles
NPs	Nanoparticles
LNPs	Lipid Nanoparticles
FUS	Focused Ultrasound
PEG-LIPs	PEGylated Liposomes
NVs	Nanovesicles
EVs	Extracellular Vesicles
EXOs	Exosomes
AD	Alzheimer's disease
PD	Parkinson's disease

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