Research Article

Recent Drug Designs to Enhance the Drug Delivery to Brain -A Review

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ABSTRACT

Brain is a delicate organ .The brain is shielded against potentially toxic substances by the presence of two barrier system such as the blood brain barrier and cerebrospinal fluid barrier.BBB is a complex system of endothelial cells, astroglia,pericytes, perivascular macrophages and a basal lamina. Clinical failure of potentially effective therapeutics is often due to insufficient amount of delivery to brain. At the same time people suffer by so many brain disorders such as ischemic stroke , giloma , Parkinson's diseases and Alzheimer's disease. To enhance bioavailability and targeting action of brain pharma field people have recently focus their faces on the development of new strategies to more effectively deliver molecules to CNS. This review intends to detail about drugtranspot, different route of drug delivery, recent drug design approaches, and brain- targeting of CNS drugs.Targeted drug delivery could improve therapeutic ratio by delivering high concentration of drug wherever it is needed. This review helps to know about types of different drug designs are used to enhance the direct delivery to brain.

Keywords: BBB, Brain-targeting, drug designs, different route of delivery, seizure activated drugs.

INTRODUCTION

Most brain disease leads to be localized loss of neurons[1]. At present most Brain and CNS disorders such as neuro degeneration, malignant brain Brain is a delicate organ .The brain is shielded against potentially toxic substances by the presence of two barrier system such as the blood brain barrier and cerebrospinal fluid barrier.BBB is a complex system of endothelial cells, astroglia,pericytes, perivascular macrophages and a basal lamina. Clinical failure of potentially effective therapeutics is often due to insufficient amount of delivery to brain. At the same time people suffer by so many brain disorders such as ischemic stroke, giloma, Parkinson's diseases and Alzheimer's disease. To enhance bioavailability and targeting action of brain, pharma field people have recently focus their faces on the development of new strategies to more effectively deliver molecules to CNS. This review intends to discuss about tumours, and brain infection are required more hospitalization and prolonged care than almost all other disease[2]. Blood Brain Barrier is now well established that it is a unique membrane barrier that tightly segregates the brain from circulating blood .This barrier is composed of different cell types such as endothelial cells,Pericytes ,astrocytes microgilial cells[3]. That are responsible for brain properties and limit the transfer of almost all drugs[4, 5]. CNS capillaries which are structurally different from blood capillaries. Structural difference results in a permeability barrier between blood and brain capillaries and extracellular fluid in brain tissues.These capillaries are lined with a layer of special endothelial cells that lack fenestration and sealed with tight junction. Brain interstial fluid concentration is determinant for effect of drug. For direct measurement of brain ISF drug concentration micro dialysis is useful technique[6]. When a drug is delivered via circulatory system for treatment of CNS disease a delicate balance between cerebro-vascular permeability and plasma solubility is required[7].Some factors such as blood flow to organ ,amount of drug available for uptake , permeability of micro vascular wall which will determine the brain uptake. To enhance drug delivery to brain different routes of delivery and different methodologies have been investigated.

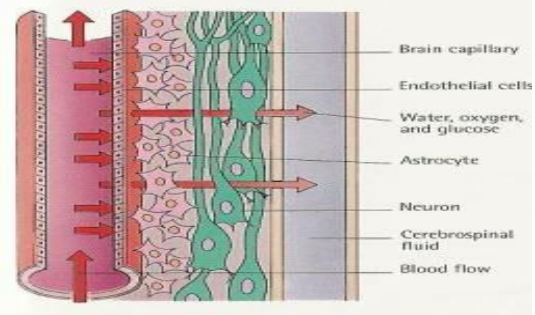
DRUG TRANSPORT MECHANISM THROUGH BBB

Most of research studies revealed that drugs are reaching brain by some diffusion mechanism such as trasncytosis, endocytosis and passive diffusion, carrier mediated endocytosis.Passive diffusion of molecule is dependent on its structural and physico-chemical properties such as molecular size, charge, hydrogen bonding potential, lipophilicity[(8)]. The essential compounds for brain such as amino acids, hexoses, neuropeptides, protein which are transported

into brain via specific carriers[9, 10, 11]. Only less than 500 da are able to cross this barrier.Generally clathrin mediated endocytosis was suggested to be predominant pathway for uptake of small particles below 200nm, whereas uptake of larger particles upto asize of 500nm seems to be caveolae – mediated[12]. Generally Nanoparticles cross the blood brain barrier by following aspects

1. An increased retention of nanoparticles in the brain blood capillaries creates higher concentration gradient which enhances the transport of drugs across endothelial cell layer.
2. Addition of surfactants for formulation of nanoparticles which fluidize the endothelial cell membrane and enhance drug permeability through BBB.
3. The nanoparticles lead to an opening of the tight junction between endothelial cells and permeate through this.
4. The polysorbate 80 used as the coating agent could inhibit the efflux system, especially P-glycoprotein[13].

Blood Brain Barrier



Different routes of delivery to Brain

- Rectal
- Skin
- Nasal
- Inhaled
- buccal
- Direct delivery to brain.

Possible Methodologies for direct delivery of CNS drugs to brain

- CSF Delivery
- Drug Wafers
- Seizure –activated drugs
- Local perfusion
- Nanoparticles
- Liposomes
- Polymeric micelles
- Cell encapsulation therapy
- Gene therapy

STRATEGIES FOR ENHANCEMENT OF DRUG CONCENTRATION IN BRAIN

Numerous drug delivery strategies have been developed as per invasive and non-invasive methods. Some strategies are manipulatory drugs, disrupting the BBB , finding alternative route for drug delivery, analogues of CNS, lack of ionization at physiological pH , penetration is favored by low molecular weight, lipophilicity[14] and others are transient osmotic opening of BBB , high dose chemotherapy, biodegradable implants.

CSF DELIVERY

CSF Delivery is one of the strategies for bypassing BBB has been studies extensively in laboratory and clinical trials. Intrathecal and Intracerebral differs fundamentally from systemic drug administration in terms of pharmacokinetic characteristic determining brain tissue concentration where available dose reaching target organ is 100%. CSF delivery can be intraventricular or intrathecal. The intrathecal route is easier and safer. Since the medication can be administered into CSF without need for surgical trauma to the brain. At present commercially available infusion pumps are used in conjunction with catheters to deliver morphine into epidural or subarachnoid of spinal cord for treatment of intractable pain or spasticity. Medication move very slowly through brain by direct diffusion, but may penetrate faster when under pressure or moving via bulk convection[15, 16].

IMPLANTS

A drug eluting wafers is a polymer matrix with interwoven drug. It slowly releases the medication over a period of time months, or weeks or few years. Drug releasing wafers have become well known to neurologist and neuro surgeons from BCNU, containing gliadel wafers which is left in the bed of tumour resection[17]. Recently several implantable pumps have been developed that possess several advantages. This can be implanted subcutaneously and refilled by subcutaneous injection capable of deliver the drugs as a constant infusion are extended the period of time. The infused pumps use the vapour pressure of compressed Freon to deliver drug solution at a constant rate. Minimed PIMS system uses a solenoid pumping mechanism and Medtronic synchromed system delivers drug via peristaltic mechanism. Distribution of small and larger molecules in the brain can be enhanced by maintaining pressure gradient [18].

LOCAL PERFUSION BY CATHETER

Delivery of a medication via an implanted catheter attached to a pump. Pump can be programmed to infuse medication at a

constant ratio.Local infusion of diazepam also can shorten or prevent ongoing seizures produced by application of convulsant chemicals [19, 20].

SEIZURE –ACTIVATED DRUGS

In this strategy an inactive precursor drug activated by a substance released at the seizure focus. This result highly specific concentration at seizure focus.The drug designed by this strategy is DPVPA which is an analogue of valporicacid. When seizure occurs elevated activity of enzyme phospholipase A2 cleaves phosphono moiety and generate locally high concentration of valporic acid [21].

NANOCARRIERS

NANO PARTICLES

Nano technology may provide a solution to overcome the diagnostic and neuro therapeutic challenges for neurodegenerative and neurological disease. In recent years Nano carriers such as liposome, Nanoparticle and micelles have been employed to deliver therapeutic agents to CNS[22]. Nanoparticles of poly butyl acrylate are able to transport drugs by encapsulation' Nanoparticles consist of polycyanocacrylate that were coated with polyethylene glycol could overcome the BBB [23]. Transport of nano particles via Poly (butyl cyano acrylate) were reported to be able to induce non specific opening of the tight junction of BBB[23]. Polymeric micelles such as pluronic or PEGylated phospholipids micelles could increase the delivery of agents to brain [24]. Poly phospho esters is (PPE) a class of biodegradable polymer which could degrade under physiological condition via hydrolysis or enzymatic cleavage of phosphoester bonds and PPE shows good biocompatibility to neuron[25].Poly caprolactone -poly ethyl ethylene phosphate (PCL-PEEP) micelles showed significantly increased brain distribution of coumarin-6 with no obvious cytotoxity to BMEC and BBBmodel[26]. Polymeric micells such as pluronic or PEGylated phospholipid micelles could increase the delivery of agents to brain. Paclitaxel is a potent anti giloma drug is impermeable. Nanoencapsulation by PCL-PEEP and transferrin modified PEG-PCL will make the paclitaxel permeable to BBB[27].PEG-PHDCA nanoparticles have more significant permeability than PS-80 nanoparticles. They have long circulating properties[28]. Low density lipoprotein receptor of brain endothelial cells after adsorption of lipoprotein from blood plasma to nanoparticles is used for transport of drug across BBB. P-glycoprotein is one of the ATP dependent efflux transportors that has an important physiological role in limiting drug entry in to brain[29].Different methods are used to preparation of nano particles are nano precipitation, emulsion polymerization, emulsion solvent evaporation, super critical fluid expansion method ,complex co-cervation , salting out method , denaturation[30].

LIPOSOME – POLYSOME

Liposome is a fatty bubble filled with a medication of interest colloidal particle composed of phospholipids molecule assembled in a cell membrane like bilayer or multilayer sheet disk configuration[31]. Liposomes are targeting to brain by exploiting receptor mediated trancytosis[32].recent study shows that epidermal delivery of morphine encapsulated in multivesicular liposome (depofoam dry delivery system) powdered a sustained clearance of morphine and a prolonged analgesia, and result suggest that this delivery system is without significant pathological effect af the dose 10mg/ml morphine after repeated epidermal delivery in dog[33].

POLYMERIC MICELLS

Polymeric Micells as drug delivery system are formed by amphiphilic copolymers that are thermodynamically and kinetically stable. Earlier studies have shown that poloxamer micells conjucated with antibodies may improve brain distribution of haloperidol, a neuroplastic agent. This approach has resulted in a dramatic improvement of drug efficacy. This poloxamer micells provide an effective transport of solubilized neuroleptic agents across the BBB[34].

CELL ENCAPSULATION THERAPY

Cell encapsulation therapy is a delivery of therapeutic substance using cells in capsulated in a semi permeable membrane[35]. It was investigated as a method for providing chronic insulin delivery to treat diabetes without the need of immunosuppressant using pancreatic islets encapsulated in a semi permeable membrane. Cell encapsulation therapies have also been developed as potential treatment for a variety of neurological disease. Numerous neurological studies have demonstrated that cell encapsulation therapies are safe and efficacious in preclinical and clinical studies. The first phase I clinical trials to be conducted using cell encapsulation therapies for neurological disease were completed in 1990 in the context of amyotrophic lateral sclerosis and chronic pain[36]. Encapsulated cells must not proliferate

within the encapsulation device to such a degree that compromise the integrity them to the immune system. The encapsulated cells must also be capable of time depending on therapy[37].

GENE TRANSFER

Recombinant adeno- associated virus vectors have shown significant promise as vehicles for in vivo gene transfer, particularly for transduction of organs composed primarily on non- diluting cells(i.e., muscle, CNS and liver)[38].Adeno-associated virus (AAV) vectors are derived from nonpathogenic and defective human parvovirus. The recombinant AAV system has continued to attract enormous interest primarily due to its unique features such as safety, high titres, broad host range, transduction of quiescent cells and vector integration. Recently rAAV-modified in vivo gene transfers have demonstrated efficient long term transduction from (3months to more than 15 years) and lack of toxicity and cellular immune response in the target tissues especially in CNS[39].Insertion of HS-tk into tumors and subsequent treatment with GCV has successfully eliminated tumors in experimental animal model[40].

CONCLUSION

The treatment of brain disease is particularly challenging one, because the delivery of drugs molecules to the brain is precluded by a variety of physiological, metabolic and biochemical obstacles that comprise the BBB, BCB and BTB. Maximum CNS drugs in market are poor drug delivery system. In this circumstances people suffering by many types of CNS disease. Recent drug designs provide reasonable hope to suffering people. Recent drug designs such as Liposomes, Nano particles, gene therapy,implants,enzymatic activation seizure activated drugs, encapsulation therapy are the promising strategies to promote drug delivery to brain. Especially nanoparticles act like the Trojan horse and it is a novel platform technology for the treatment of CNS diseases and has significant promise in delivery of therapeutic molecules across the BBB. Cell and gene therapies will play on important role in the treatment of neurological disorders in the future.

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