

Challenges of Brain Drug Delivery and G-Technology as One of Solution

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ABSTRACT

Brain is one of the most difficult organ for efficient drug delivery for the treatment of brain related illnesses. The reason behind it the various barriers such as blood brain barrier, blood cerebrospinal fluid barrier and blood tumor barrier present in central nervous system. The blood brain barrier formed by the endothelial cells of the brain capillaries which restricts the entry of most drugs and delivery systems. Blood cerebrospinal fluid barrier and blood tumor barrier also presents a huge problem for effective delivery of therapeutics to the central nervous system (CNS) Therefore, various techniques like BBB disruption, Molecular Trojan Horse Technology, Biology Based Approach, Intranasal Delivery, Stereotactically guided insertion, Chemical Methods, Transporter mediated delivery are being developed to enhance the amount and concentration of therapeutic compounds in the brain. A new method which is called G-Technology also developed to enhance the delivery of drugs.

INTRODUCTION

Overcoming the difficulty of delivering therapeutic agents to specific regions of the brain presents a major challenge to treatment of most brain disorders. The brain (central nervous system) is protected by barriers which control the entry of compounds into the brain, thereby regulating brain homeostasis. Brain is tightly segregated from the circulating blood by a unique membranous barrier – the Blood Brain Barrier (BBB) [1,2]. Drugs that are effective against diseases in the CNS and reach the brain via the blood compartment must pass the BBB. Current estimates are that 98% of all small molecule drugs minimally cross the BBB, and miniscule amounts of large molecule drugs cross the BBB. The capillaries of the brain have evolved to constrain the movement of molecules and cells between blood and brain, providing a natural defense against circulating toxic or infectious agents. The relative impermeability of the BBB results from tight junctions between capillary endothelial cells which are formed by cell adhesion molecules. In order to develop drugs which penetrate the BBB at concentration level which required for therapeutic effects, it is of great importance to understand the mechanisms involved in uptake into and efflux from the brain [3]. The majority of drugs that are used to treat CNS disease have a molecular weight between 150 and 500 Da and a log octanol/water partition coefficient between -0.5 and 6.0 [4]. It is generally assumed that charged molecules cannot readily penetrate the BBB; thus, for a drug that is partially ionized at physiological pH 7.4, it is the uncharged fraction that determines the diffusion gradient across the BBB and forms the driving force for any passive diffusive movement of drug [5].

There is a direct relationship between the lipid solubility of a drug and its CNS penetration [6], which is thought to represent a direct correlation between BBB penetration and the ability of a drug to partition into the lipid of the cell membrane. Thus, designing a drug with optimal lipid solubility for BBB penetration and which retains a significant central pharmacological activity would be the desired solution, but this is often not possible. Therefore, various strategies are being developed to enhance the amount and concentration of therapeutic compounds in the brain.

Various Barriers to CNS Drug Delivery

There are number of barriers that inhibit drug delivery to the CNS.

Blood-Brain Barrier

The BBB is a membranous barrier that tightly segregates the brain from the circulating blood [7,8]. The blood-brain barrier acts very effectively to protect the brain from many common bacterial infections. Thus, infections of the brain are very rare. However, since antibodies are too large to cross the blood-brain barrier, infections of the brain which do occur are often very serious and difficult to treat. Viruses easily bypass the blood-brain barrier, however, attaching themselves to circulating immune cells. The blood-brain barrier is composed of high density cells restricting passage of substances from the bloodstream much more than endothelial cells in capillaries elsewhere in the body. Capillaries of brain are lined with a layer of special endothelial cells that lack fenestrations and are sealed with tight junctions [9]. These tight junctions called zona occludens [10]. The tight junctions produced by the interaction of several transmembrane proteins such as occludin and claudin that project into and seal the paracellular pathway. The interaction of these junctional proteins is complex and effectively blocks an aqueous route of free diffusion for polar solutes from blood along these potential paracellular pathways and thus denies these solutes free access to brain interstitial (extracellular) fluid [11,12,13,14,15]. The endothelial cells forming the BBB also exhibit a polarized expression of transport proteins in the luminal and abluminal membranes of the endothelial cells, with some transporters expressed exclusively in one of these interfacial membranes and some in the other, whereas some are inserted into both membranes [16,17,18,19,20]. Ependymal cells lining the cerebral ventricles and glial cells are of three types.

Astrocytes

Astrocytes form the structural frame work for the neurons and control their biochemical environment. Astrocyte cell projections called astrocytic feet (also known as "glia limitans") surround the endothelial cells of the BBB, providing biochemical support to those cells.

Oligodendrocytes

Oligodendrocytes are responsible for the formation and maintenance of the myelin sheath, which surrounds axons and is essential for the fast transmission of action potentials by salutatory conduction.

Microglia

Microglia are blood derived mononuclear macrophages [21].

Blood-Cerebrospinal Fluid Barrier

The CSF exchange molecules with the interstitial fluid of the brain parenchyma. So, the passage of blood-borne molecules into the CSF is also carefully regulated by the Blood-Cerebrospinal Fluid Barrier. Blood-CSF barrier formed by the epithelia of the choroid plexuses [13]. The choroid plexus and the arachnoid membrane act together at the barriers between the blood and CSF. On the external surface of the brain the ependymal cells fold over onto themselves to form a double layered structure which called arachnoid membrane. Within the double layer is the subarachnoid space, which participates in CSF drainage. Passage of substances from the blood through the arachnoid membrane is prevented by tight junctions [22]. The arachnoid membrane is generally impermeable to hydrophilic substances. The choroid plexus forms the CSF and actively regulates the concentration of molecules in the CSF.

Blood-Tumor Barrier

In CNS malignancies where the BBB is significantly compromised, a variety of physiological barriers common to all solid tumors inhibit drug delivery via the cardiovascular system. Drug delivery to neoplastic cells in a solid tumor is compromised by a heterogeneous distribution of microvasculature throughout the tumor interstitial, which leads to spatially inconsistent drug delivery. Furthermore, as a tumor grows large, the vascular surface area decreases, leading to a reduction in trans-vascular exchange of blood-borne molecules. In this condition intra-capillary distance increases, leading to a greater diffusional requirement for drug delivery to neoplastic cells and due to high interstitial tumor pressure and the associated peritumoral edema leads to increase in hydrostatic pressure in the normal brain parenchyma adjacent to the tumor. As a result, the cerebral microvasculature in these tumor adjacent regions of normal brain may be even less permeable to drugs than normal brain endothelium, leading to exceptionally low extra tumoral interstitial drug concentrations [23].

Various Techniques Used for Drug Delivery to Brain

Trans-cranial Drug Delivery

This includes intra cerebroventricular (ICV) injection, intracerebral implantation (IC) and convection enhanced diffusion (CED).

BBB Disruption

The idea behind this approach was to break down the barrier temporarily by injecting a sugar solution (mannitol) into arteries in the neck. The resulting high sugar concentration in brain capillaries sucks water out of the endothelial cells, shrinking them thus opening the tight junctions [24]. Low doses of solvents such as SDS (Sodium Dodecyl Sulphate), ethanol, DMSO (dimethyl sulfoxide), glycerol and Tween-80 found to cause mild disruption to BBB, by which drug can be easily administered. BBB Disruption has the potential for enhancing delivery of therapeutics to the brain for treatment of brain infection, lysosomal storage disorders, and neurodegenerative diseases [33].

Side effect: It allows leakage of plasma proteins to the brain and also cause physiological stress.

Molecular Trojan Horse Technology

In this techniques the non-transportable protein or monoclonal antibodies is fused to a Molecular Trojan Horse [25]. Molecular Trojan Horses can transport large molecules such as antibodies, recombinant proteins, nonviral gene medicines or RNA interference drugs across the BBB. The genetically engineered MAb against the BBB human insulin receptor (HIR) and monoclonal antibodies against the rodent transferrin receptor (TfR), HIRMAb and TfRMAb respectively, have been reported to undergo RMT across the BBB via the endogenous transport systems for insulin or transferrin (Tf).

Biology Based Approach

Biological approaches of CNS drug delivery primarily emanate from the understanding of the physiological and anatomical nuances of the BBB transportation. The conversion of dopamine, a water soluble catecholamine that does not cross the BBB, into the corresponding α amino acid, L - DOPA, enables dopamine delivery to the brain, which has been the mainstay of treatment of PD for nearly 40 years. The use of L -DOPA to deliver dopamine to the brain is a BBB drug delivery strategy that utilizes the type 1 large neutral amino acid transporter (LAT1) one of the CMT systems within the BBB. Upon crossing the BBB through LAT1, L -DOPA is converted back to dopamine within the brain by aromatic amino acid decarboxylase (AAAD) [26].

Transporter-mediated delivery

Peptides and small molecules may use specific transporters expressed on the luminal and basolateral side of the endothelial cells forming the BBB to cross into the brain. At least 8 different nutrient transport systems have been identified, with each transporting a group of nutrients of similar structure. Only drugs that closely mimic the endogenous carrier substrates will be taken up and transported into the brain. Drugs may be modified such that their transport is increased by using a carrier-mediated transporter expressed on the endothelial cells forming the BBB [27].

Stereotactically guided insertion

It includes the insertion of a small-caliber catheter into the brain parenchyma. Through this catheter, infusate is actively pumped into the brain parenchyma and penetrates in the interstitial space. The infusion is continued for several days and the catheters are removed at the bedside. The success of Stereotactically guided insertion depends on precise placement of the catheters [28]. The major clinical use of this method will be for targeted therapy of glioblastoma [29].

Chemical Methods

The main premise for the chemical methods remains the use of prodrugs. Prodrugs are pharmacologically inactive compounds that result from transient chemical modifications of biologically active species. The chemical change is usually designed to improve some deficient physicochemical property, such as membrane permeability or water solubility. After administration, the prodrug, by virtue of its improved characteristics, is brought closer to the receptor site and is maintained there for longer periods of time. Here it gets converted to the active form, usually via a single activating step [30].

Intranasal Delivery

A non-invasive, intranasal method of bypassing the blood-brain barrier to deliver therapeutic agents to the brain has been developed [31]. This method allows drugs that do not cross the blood-brain barrier to be delivered to the olfactory cerebrospinal fluid via transport across the olfactory region of the nasal epithelium. The surface area of the olfactory region of the nasal epithelium in rodents is large, about 50%, and is small in humans, about 5%, therefore intranasal delivery is not expected to achieve therapeutic drug levels in most brain regions [32].

Liposomes

Liposomes are colloidal particles, typically consisting of phospholipids and cholesterol, to which other ingredients may be added. These lipid molecules form concentric bimolecular layers in the form of vesicles, that may be used to entrap and deliver drugs to and through the skin [34]. Their characteristics depend on the manufacturing protocol and choice of bilayer components. They can be as small as 20nm and as large as 10µm in diameter. The liposomes can be unilamellar (meaning only one bilayer surrounds an aqueous core) or multilamellar (several bilayers oriented concentrically around an aqueous core) [35]. To use liposomes as delivery systems, drug is added during the formation process. Hydrophilic compounds usually reside in the aqueous portion of the vesicle, whereas hydrophobic species tend to remain in the lipid proteins. The physical characteristics and stability of liposomal preparations depend on pH, ionic strength, the presence of divalent cations, and the nature of the phospholipids and additives used

G-TECHNOLOGY

The G-Technology provides a new method to enhance the delivery of drugs that do not readily reach the brain at concentration level which required for therapeutic effects. G-Technology is a safest method of drug delivery [37]. Based on literature findings and on previous unpublished validation results from the drug delivery department of Dr. Maggie Lu at the Industrial Technology Research Institute (ITRI) in Hsin-Chu, Taiwan R.O.C., ITRI was the first in 2005 to file patents describing glutathione-mediated drug delivery to the brain. In 2008, to-BBB technologies BV obtained the exclusive worldwide rights to commercialize these patents for the targeted delivery of drugs to the brain [36].

Basic concept

G-Technology is based on the ability of the PEGylated liposomes to encapsulate hydrophilic as well as lipophilic compounds. G-Technology is the modification of liposomes. The addition of PEG on liposomes gives the liposomes stealth like properties as it minimizes scavenging of the liposomes by the body's defence system, thus enabling a long circulation time in the blood [38].

Structure

G-Technology is a pegylated liposomal drug delivery system. It consist of tripeptide glutathione and polyethylene glycol (PEG) molecules along with liposomes. Tripeptide glutathione present as a targeting ligand at the tips of the polyethylene glycol (PEG) molecules. Since all components are already used in clinical practice and their properties also known, so G-Technology provides a safe method to enhance drug delivery to the brain [39].

Mechanism of action

G-Technology uses GSH levels well below the endogenous GSH levels and the GSH transporter capacity, thereby ruling out potential interference with the endogenous function of GSH in the brain. Enhanced brain delivery through endogenous GSH transporters keep the neuroprotective blood-brain barrier function completely intact, which is essential for brain functioning. Cell based assays have demonstrated a glutathione specific and active endocytotic uptake mechanism for the G-Technology.

Uses

- Glutathione is an endogenous anti-oxidant tripeptide involved in cellular detoxifying mechanisms, and is specifically and actively taken up by specialized transporters at the blood-brain barrier.
- The G-Technology loaded with peptides and small molecules exerted a superior effect in models for pain, brain tumors, viral encephalitis, and neuroinflammation when compared to non-targeted liposomes and free drugs.
- Pegylated liposomes encapsulating chemotherapeutics, antifungal agents, vaccines and so on are in use for several indications [40].

CONCLUSION

The major problem in drug delivery to brain is the presence of the BBB. Capillaries of brain are lined with a layer of special endothelial cells that lack fenestrations and are sealed with tight junctions and form BBB. 98% of all small molecule drugs minimally cross the BBB, and miniscule amounts of large molecule drugs cross the BBB. Blood cerebrospinal fluid barrier formed by the epithelia of the choroid plexuses. Now different techniques have developed to enhance the amount and concentration of therapeutic compounds in the brain. G-technology combines the widely used drug delivery approach of pegylated liposomes with the endogenous tripeptide glutathione as targeting ligand in a novel and safe way. Glutathione plays an important role in G-Technology. G-Technology is used for drugs that are unable to reach the brain at systemically tolerable therapeutic doses. G-Technology enhance the delivery of drugs across blood brain

barrier. G-technology minimizes common risks like adverse immunological reactions or interference with life-essential physiological pathways.

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