Review Article

VARIOUS METHODS OF DRUG TARGETING TO THE BRAIN: A REVIEW

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ABSTRACT

The brain is very complicated as well as fragile organ and Nature has been played a very efficient role to protect it. The brain is protected from many toxic substances and various chemicals by the presence of two barriers namely blood brain barrier (BBB) and blood cerebrospinal fluid barrier (BCSFB). Various routes of drug targeting to the brain now become an important tool in the pharmaceutical field because of many complicated disease of the brain like Alzheimer, Huntington disease, epilepsy etc. Therefore various routes like craniotomy, non invasive route including osmotic disruption, colloidal drug delivery, intranasal route of administration and nanotechnology have been proposed to favors brain drug delivery. Novel drug delivery is the decisive part of this review. This review includes general methods that can enhance drug delivery to the brain and discussed the appropriate route by which such a drug delivery can be possible.

Keywords: Drug targeting routes to brain, Invasive, Non- invasive, Nano Technology.

1. INTRODUCTION

Treating central nervous system diseases is very challenging because of the presence of a variety of formidable obstacles that obstruct drug delivery. Physiological barriers like the blood-brain barrier and blood-cerebrospinal fluid barrier as well as various efflux transporter proteins make the entry of drugs into the central nervous system very difficult.[1] Various drugs like antibiotics, antineoplastic agents, and a variety of central nervous stimulant (CNS)-active drugs can not easily enter into brain because of Blood Brain Barrier (BBB). However, there are only a few diseases of the brain that consistently respond to this category of small molecules[2, 3], and these include depression, affective disorders, chronic pain, and epilepsy. In contrast, many other serious illness disorders of the brain do not respond to the conventional lipid-soluble low M_r small-molecule therapeutics, and these include Alzheimer disease, stroke/neuroprotection, brain and spinal cord injury, brain cancer, HIV infection of the brain, various ataxia-producing disorders, amytrophic lateral sclerosis (ALS), Huntington disease, and childhood inborn genetic errors affecting the brain. Blood Brain Barrier (BBB) is the main obstacle in the brain drug delivery. Therefore various strategies like liposomes, colloidal drug carrier, micelles, intranasal and olfactory route of administration and nano technology have been proposed to favors brain drug delivery.[4] The brain micro vessel endothelial cell (BMEC) that form the BBB, display important morphological characteristics such as the presence of tight junctions between the cells, the absence of fenestrations and a diminished pinocytics activity, that together help to restrict the passage of compounds from the blood into the extra cellular environment of the brain.[5]

2. BLOOD BRAIN BARRIER (BBB)

The brain is shielded against potentially toxic substances by the presence of two barrier systems: the blood brain barrier (BBB) and the blood cerebrospinal fluid barrier (BCSFB).[6] the term "blood brain barrier" was first coined in 1900 by Lewandowsky, while studying the limited penetration of potassium ferrocyanate into the brain.[6] The structure of the BBB is subdivided into two components: the endothelial or capillary barrier and the ependymal barrier. The structure of the BBB is subdivided into two components: the endothelial or capillary barrier and the ependymal barrier. The BBB is considered to be the major route for the uptake of serum ligands since its surface area is approximately 5000-fold greater than that of BCSFB. The BBB is formed by a complex cellular system of endothelial cells, astroglia, pericytes, perivascular macrophages, and a basal lamina.

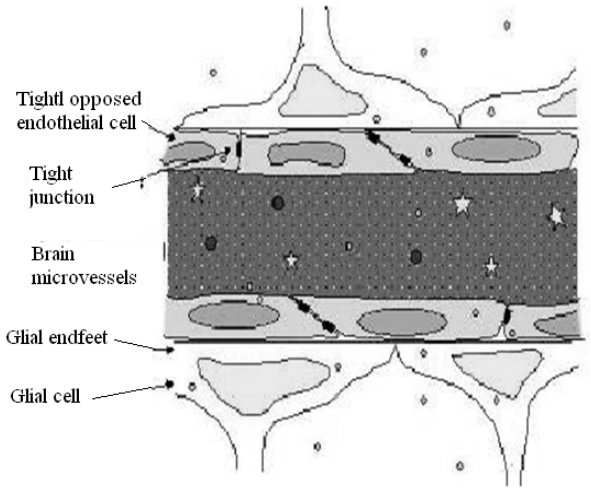

Figure 1: Structure of BBB

3. POSSIBLE ROUTES OF DRUG TARGETING TO THE BRAIN

3.1 NOVEL METHODS FOR DRUG DELIVERY

3.1.1 Colloidal drug carriers

Colloidal drug carrier systems such as micellar solutions, vesicle and liquid crystal dispersions, as well as nanoparticle dispersions consisting of small particles of 10–400 nm diameter show great promise as drug delivery systems. The goal is to obtain systems with optimized drug loading and release properties, long shelf-life and low toxicity. The incorporated drug participates in the microstructure of the system, and may even influence it due to molecular interactions, especially if the drug possesses amphiphilic and/or mesogenic properties[7].

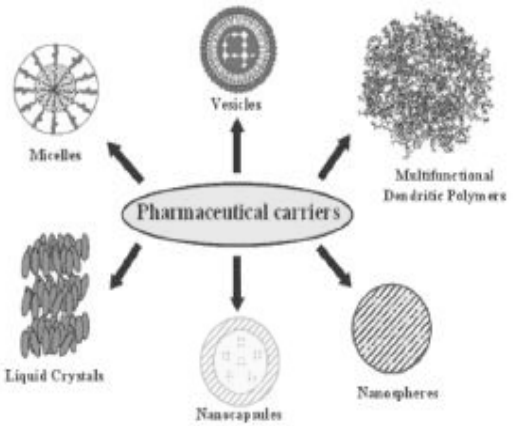

Figure 2: Colloidal Drug Carrier

3.1.2 Liposomes

Liposomes were first produced in England in 1961 by Alec D. Bangham.[8] One end of each molecule is water soluble, while the opposite end is water insoluble. Water-soluble medications added to the water were trapped inside the aggregation of the hydrophobic ends; fat-soluble medications were incorporated into the phospholipid layer.[9] In some cases liposomes attach to cellular membranes and appear to fuse with them, releasing their or drugs into the cell.[10] In the case of phagocytic cells, the liposomes are taken up, the phospholipid walls are acted upon by organelles called lysosomes, and the medication is released. Liposomal delivery systems are still largely experimental; the precise mechanisms of their action in the body are under study, as are ways in which to target them to specific diseased tissues.[11]

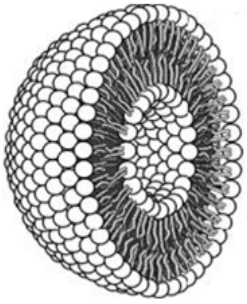

Figure 3: Liposomes

3.1.3 Polymeric Micelle

Polymeric micelles as drug delivery systems are formed by amphiphilic copolymers having an A-B diblock structure with A, the hydrophilic (shell) and B, the hydrophobic (core) polymers. The polymeric micelles are thermodynamically and kinetically stable in aqueous media. They have a size range of several tens of nanometers with a considerably narrow distribution. This narrow size range is similar to that of viruses and lipoproteins. Several reviews have analyzed in great detail, the properties of the different copolymers used in the preparation of the polymeric micelles, as well as the physical chemistry of these systems, which may influence their properties such as their size distribution, stability, drug loading capacity, drug release kinetics, blood circulation time and biodistribution.[12]

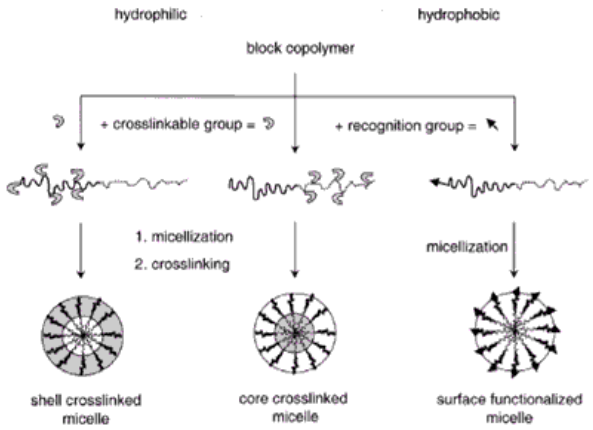

Figure 4: Polymeric Micelles

3.1.4 Polymeric Nanoparticles

Therapeutic strategies to probe the CNS are limited by the restrictive tight junctions at the endothelial cells of the BBB. To overcome the impositions of the BBB, polymeric biocompatible drug carriers, e.g., nanoparticles, liposomes have been applied to the CNS for many applications such as cancers. Nanoparticles mostly consist of polymers and are about 10 to 200 nm in size. Some researchers managed to produce efficient nanoparticles that ensure rapid transport of drug-charged particles across the BBB. Nanoparticles from polybutyl cyanoacrylate are able to transport drugs by encapsulating or binding them to the surface of the nanoparticles. Compared with other colloidal carriers, polymeric nanoparticles present a higher stability when in contact with the biological fluids. Also, their polymeric nature permits the attainment of the desired properties such as controlled and sustained-drug release.[13]

3.2 INVASIVE METHODS

Although, the ease and compliance of non-invasive delivery methods is often not associated with direct or invasive delivery of drugs to the brain, it often shows up as the sole alternative wherein the drugs elicit right

physicochemical properties. Generally, only low molecular weight, lipid-soluble molecules and a few peptides and nutrients can cross this barrier to any significant extent, either by passive diffusion or using specific transport mechanisms.[14] for most drugs it is not possible to achieve therapeutic levels within the brain tissue following intravenous or oral administration. In addition, highly potent drugs (e.g., anticancer drugs and neurotrophic factors) that may be necessary to be delivered to the CNS, often cause serious toxic side effects when administered systemically. The drug can be administered directly into the brain tissue.[15] Many ways are explored for direct intracranial drug delivery by intracerebroventricular, intracerebral or intrathecal administration after creating holes in head or Disrupting the BBB integrity by osmotic blood brain barrier disruption or biochemical BBB disruption and also by employing controlled release biodegradable drug delivery systems which are able to control the release rate of an incorporated drug in a pre-determined manner over periods of days to months.

3.2.1 Disruption of the BBB

Disruption of BBB means to break down the barrier by systemic administration of drugs in conjunction with transient BBB disruption (BBBD) agents. Mechanism of the drug to the BBB is that systemically administered drugs can undergo enhanced extravasation rates in the cerebral endothelium, leading to increased parenchymal drug concentrations. The other example of such a agent are the infusion of solvents such as dimethyl sulfoxide or ethanol and metals such as aluminium, X-irradiation, and the induction of pathological conditions including hypertension, hypercapnia, hypoxia or ischemia.[16] The example of this is the injection of mannitol solution to the arteries in the neck. The resulting high sugar concentration in brain capillaries takes up water out of the endothelial cells, shrinking them thus opening tight junction. The effect lasts for 20-30 minute, during which time drugs diffuse freely, that would not normally cross the BBB. This method permitted the delivery of chemotherapeutic agents in patients with cerebral lymphoma; malignantglioma and disseminated CNS germ cell tumors.[17]

3.2.2 Intraventricular or Intrathecal Route

Drugs can be infused intraventricularly using an Ommaya reservoir, a plastic reservoir implanted subcutaneously in the scalp and connected to the ventricles within the brain via an outlet catheter. Drug solutions can be subcutaneously injected into the implanted reservoir and delivered to the ventricles by manual compression of the reservoir through the scalp. Clinical examples of intrathecal small drug delivery are the ICV administration of glycopeptide and aminoglycoside antibiotics in meningitis, the intraventricular treatment of meningeal metastasis, intrathecal injection of Baclofen for treatment of spasticity and the infusion of opioids for severe chronic pain. The greatest utility of this delivery methodology has been in cases where high drug concentrations in the CSF and/or the immediately adjacent parenchyma are desired, such as in the treatment of carcinomatous meningitis or for spinal anesthesia or analgesia.[16]

3.2.3 Intranasal Route

In nasal drug delivery the drug first passes to the respiratory epithelial, from this drug is absorbed into the systemic circulation by Tran cellular and Para cellular passive absorption, carrier mediated transport, or absorption through transcytosis.[18] Drugs delivered intranasally are transported along olfactory sensory neurons to yield significant concentrations in the CSF and olfactory bulb. In recent studies, intranasal administration of wheat germ agglutinin horseradish peroxidase resulted in a mean olfactory bulb concentration in the nanomolar range. In theory, this strategy could be effective in the delivery of therapeutic proteins such as brain-delivered neurotropic factor (BDNF) to the olfactory bulb as a treatment for Alzheimer's disease.[19] Although absorption across the respiratory epithelium is the major transport pathway for nasally-administered drugs and may represent a potentially timesaving route for the administration of certain systemic drugs delivered in cryonics medication protocols (e.g., epinephrine or vasopressin), problem of BBB-mediated exclusion of brain-therapeutic agents to be of greater immediate concern. When a nasal drug formulation is delivered deep and high enough into the nasal cavity, the olfactory mucosa may be reached and drug transport into the brain and/or CSF via the olfactory receptor neurons may occur.[20]

Axonal transport is considered a slow route whereby an agent enters the olfactory neuron via endocytotic or pinocytotic mechanisms and travels to the olfactory bulb by utilizing the same antero grade axonal transport mechanisms the cell uses to transport endogenous substances to the brain.[21] Depending on the substance administered, axonal transport rates range from 20-400 mm/day to a slower 0.1-4 mm/day.[22] The epithelial pathway is a significantly faster route for direct nose-to-brain transfer, where by compounds pass paracellularly across the olfactory epithelium into the perineural space, which is continuous with the subarachnoid space and in direct contact with the CSF. Then the molecules can diffuse into the brain tissue or will be cleared by the CSF flow into the lymphatic vessels and subsequently into the systemic circulation.[23]

3.2.4 Craniotomy

There are examples of CNS drug development programs that go forward even though it is known that the drug does not cross the BBB and that no BBB drug delivery strategy is available. In this setting, the strategy for dealing with the BBB problem is to administer the drug after drilling a hole in the head, a process called craniotomy. With this approach, the small- or large-molecule drug may be administered either by intracerebroventricular (ICV) or intracerebral (IC)

injection. With IC administration, the drug stays at the depot site at the tip of the injection needle or at the margins of the polymeric implant.[24] An advantage of this route is that a wide range of compound and formulation can be considered for ICV or IC administration. Thus, both large and small-molecule can be delivered, either alone or in various polymer formulation, to achieve sustained release. Hoistad et al reported a diffusion distance of only 1mm following striatal IC infusion of radio labelld dopamine and mannitol in rats.[25]

3.3 NON-INVASIVE METHOD

3.3.1 Chemical Method

The aim of chemical drug delivery to the brain is the use of prodrug. There are two ways that a drug can be lipidated. First, the polar functional groups on the water-soluble drug can be masked by conjugating them with lipid-soluble moieties. Second, the water-soluble drug can be conjugated to a lipid-soluble drug carrier. For BBB transport, the upper limit in molecular area appears to be about 80 $Å^2$, which corresponds to a M_r of less than 300–400 Da. If the size of the drug is doubled from 50 $Å^2$ (M_r about 250-Da) to 100 $Å^2$ (M_r about 400-Da), the BBB permeation decreases by 100-fold.[6] Thus, if the lipidation of a drug causes a significant increase in square area of the molecule, the drug may be too large to effectively cross the BBB. The fact that membrane permeation does not increase in proportion to the increase in lipid solubility.[26]

3.3.2 Biological Methods

Biological approaches of CNS drug delivery primarily emanate from the understanding of the physiological and anatomical nuances of the BBB transportation. Of the many available approaches, conjugation of a drug with antibodies is an important mechanism. Other biological methods for targeting exploit ligands in the form of sugar or lectins, which can be directed to specific receptors found on cell surfaces.[27,28] Antibodies are particularly well suited for targeting BBB receptor-mediated transcytosis systems given their high affinity and specificity for their ligands.[29] As examples, appropriately-targeted antibodies that recognize extracellular epitopes of the insulin and transferrin receptors can act as artificial transporter substrates that are effectively transported across the BBB and deposited into the brain interstitium via the transendothelial route.[30]

3.3.3 Carrier and Receptor Mediated Drug Delivery

Carrier-mediated transport (CMT) and receptor-mediated transport (RMT) pathways are available for certain circulating nutrients or peptides. The availability of these endogenous CMT or RMT pathways means that portals of entry to the brain for circulating drugs are potentially available. In the brain capillary endothelial cells, which make up the BBB, there are several transport systems for nutrients and endogenous compounds.[12] Receptor-mediated drug delivery to the brain employs chimeric peptide technology, wherein a non-transportable drug is conjugated to a BBB transport vector. Conjugation of drug to transport vector is facilitated with chemical linkers, avidin-biotin technology, polyethylene glycol linkers, or liposomes. Multiple classes of therapeutics have been delivered to the brain with the chimeric peptide technology, including peptide-based pharmaceuticals, such as a vasoactive peptide analog or neurotrophins such as brain-derived neurotrophic factor, anti-sense therapeutics including peptide nucleic acids (PNAs), and small molecules incorporated within liposomes.[31]

4. CONCLUSION

From the above discussion we can conclude that we can treat the CNS disorder or brain diseases simply by formulating the dosage form in suitable formulation as per the disease and the nature of the drug. We can treat such a complicated brain disorder by using colloidal drug carrier, liposomes, or micelles. This review is evidence for drug administration through intra nasal and by using nanotechnology drug can penetrate the BBB competently with minimum side effects. By using invasive route like craniotomy we can deliver drug with large molecular weight while invasive method offers various advantages such as reduced dose, decreased side effects and more patient compliance. We still pursue such a development programs which gives elevated clinical significance and should be a cost effective.

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