A Review: Methods of Drug Targeting to the Brain

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ABSTRACT

Treating central nervous system diseases is very challenging because of the presence of a variety of formidable obstacles that obstruct drug delivery. 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, 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.

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INTRODUCTION

The brain is the center of the nervous system in all vertebrate, and most invertebrate, animals. Brains can be extremely complex. The cerebral cortex of the human brain contains roughly 15–33 billion neurons, perhaps more, depending on gender and age, linked with up to 10,000 synaptic connections each. Each cubic millimeter of cerebral cortex contains roughly one billion synapses. These neurons communicate with one another by means of long protoplasmic fibers called axons, which carry trains of signal pulses called action potentials to distant parts of the brain or body and target them to specific recipient cells. The brain controls the other organ systems of the body, either by activating muscles or by causing secretion of chemicals such as hormones. This centralized control allows rapid and coordinated responses to changes in the environment. Some basic types of responsiveness are possible without a brain: even single-celled organisms may be capable of extracting information from the environment and acting in response to it. Sponges, which lack a central nervous system, are capable of coordinated body contractions and even locomotion. In vertebrates, the spinal cord by itself contains neural circuitry capable of generating reflex responses as well as simple motor patterns such as swimming or walking. However, sophisticated control of behavior on the basis of complex sensory input requires the information-integrating capabilities of a centralized brain.

2 BLOOD-BRAIN BARRIER (BBB)

The blood-brain barrier (BBB) is the specialized system of capillary endothelial cells that protects the brain from harmful substances in the blood stream, while supplying the brain with the required nutrients for proper function. Unlike peripheral capillaries that allow relatively free exchange of substance across between cells, the BBB strictly limits transport into the brain through both physical (tight junctions) and metabolic (enzymes) barriers. Thus the BBB is often the rate-limiting factor in determining permeation of therapeutic drugs into the brain. Additionally, BBB breakdown is theorized to be a key component in central nervous system (CNS) associated pathologies. BBB investigation is an ever growing and dynamic field studied by pharmacologists, neuroscientists, pathologists, physiologists, and clinical practitioners.

3. POSSIBLE ROUTES OF DRUG TARGETING TO THE BRAIN

3.1 Novel Methods For Drug Delivery

1.1.1 Colloidal Drug Carriers

Colloidal drug carrier systems such as micellar solutions, vesicle and liquid crystal dispersions, as well as nanoscale 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.

1.1.1.1 Micelles

Micelles formed by self-assembly of amphiphilic block copolymers (5-50 nm) in aqueous solutions...
are of great interest for drug delivery applications. The drugs can be physically entrapped in the core of block copolymer micelles and transported at concentrations that can exceed their intrinsic water-solubility. Moreover, the hydrophilic blocks can form hydrogen bonds with the aqueous surroundings and form a tight shell around the micellar core. As a result, the contents of the hydrophobic core are effectively protected against hydrolysis and enzymatic degradation. In addition, the corona may prevent recognition by the reticuloendothelial system and therefore preliminary elimination of the micelles from the bloodstream. The fact that their chemical composition, total molecular weight and block length ratios can be easily changed, which allows control of the size and morphology of the micelles. Functionalization of block copolymers with cross linkable groups can increase the stability of the corresponding micelles and improve their temporal control.

3.1.3 Liposomes: Liposomes were first produced in England in 1961 by Alec D. Bangham. 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. In some cases, liposomes attach to cellular membranes and appear to fuse with them, releasing their drugs into the cell. 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.

1.1.2 3.2 Strategies For Enhanced Brain Drug Delivery

1.1.2.1 3.2.1 Prodrugs

Brain uptake of drugs can be improved via prodrug formation. 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. Unfortunately, simple prodrugs suffer from several important limitations. Going to extremes on the...
lipophilic precursor scale, a possible choice for CNS prodrugs is coupling the drug to a lipid moiety, such as fatty acid, glyceride or phospholipids. Such prodrug approaches were explored for a variety of acid-containing drugs, like levodopa, GABA, Niflumic acid, valproate or vigabatrin are coupled to diglycerides or modified diglycerides. While increased lipophilicity may improve movement across the BBB, it also tends to increase uptake into other tissues, causing an increased tissue burden.

1.1.2.2 Chemical Drug Delivery

Chemical drug delivery systems (CDDS) represent novel and systematic ways of targeting active biological molecules to specific target sites or organs based on predictable enzymatic activation. They are inactive chemical derivatives of a drug obtained by one or more chemical modifications so that the newly attached moieties are monomolecular units (generally comparable in size to the original molecule) and provide a site-specific or site enhanced delivery of the drug through multi-step enzymatic and/or chemical transformations. During the chemical manipulations, two types of bio removable moieties are introduced to convert the drug into an inactive precursor form. A targetor (T) moiety is responsible for targeting, site-specificity, and lock-in, while modifier functions (F1...Fn) serve as lipophilizers, protect certain functions, or fine-tune the necessary molecular properties to prevent premature, unwanted metabolic conversions. The CDDS is designed to undergo sequential metabolic conversions, disengaging the modifier functions and finally the targetor, after this moiety fulfils its site- or organ-targeting role.

1.1.2.3 Carrier 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. They are the hexose transport system for glucose and mannose, the neutral amino acid transport system for phenylalanine, leucine and other neutral amino acids, the acidic amino acid transport system for glutamate and aspartate, the basic amino acid transport system for arginine and lysine, the b-amino acid transport system for b-alanine and taurine, the monocarboxylic acid transport system for lactate and short-chain fatty acids such as acetate and propionate, the choline transport system for choline and thiamine, the amine transport system for mepyramine, the nucleoside transport system for purine bases such as adenine and guanine, but not pyrimidine bases, and the peptide transport system for small peptides such as enkephalins, thyrotropin-releasing hormone, argininevasopressin etc. Utilization of differences in the affinity and the maximal transport activity among these transport systems expressed at the BBB is an attractive strategy for controlling the delivery and retention of drugs into the brain.

1.1.2.4 Biochemical Blood-Brain Barrier Disruption

Recently, new and potentially safer biochemical techniques have been developed to disrupt the BBB. Selective opening of brain tumor capillaries (the blood–tumor barrier), by the intracarotid infusion of leukotriene C4 was achieved without concomitant alteration of the adjacent BBB. In contrast to osmotic disruption methods, biochemical opening utilizes the novel observation that normal brain capillaries appear to be unaffected when vasoactive leukotriene treatments are used to increase their permeability. However, brain tumor capillaries or injured brain capillaries appear to be sensitive to treatment with vasoactive leukotrienes, and the permeation is dependent on molecular size.

3.3 Alternative Routes To Cns Drug Delivery

1.1.2.5 Intra-ventricular / Intra thecal Route

One strategy for bypassing the BBB that has been studied extensively both in laboratory and in clinical trials is the intralumbar injection or intreventricular infusion of drugs directly into the CSF. 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.

When compared to vascular drug delivery, intra-CSF drug administration theoretically has several advantages. Intra-CSF administration bypasses the BCB and results in immediate high CSF drug concentrations. Since, the drug is somewhat
contained within the CNS, a smaller dose can be used, potentially minimizing systemic toxicity. Furthermore, drugs in the CSF encounter minimized protein binding and decreased enzymatic activity relative to drugs in plasma, leading to longer drug half-life in the CSF. Finally, because the CSF freely exchanges molecules with the extracellular fluid of the brain parenchyma, delivering drugs into the CSF could theoretically result in therapeutic CNS drug concentrations.

However, this delivery method has not lived up to its theoretical potential for several reasons. These include a slow rate of drug distribution within the CSF and increase in intracranial pressure associated with fluid injection or infusion into small ventricular volumes. It results in high clinical incidence of hemorrhage, CSF leaks, and neurotoxicity and CNS infections. The success of this approach is limited by the CSF-brain barrier, composed of barriers to diffusion into the brain parenchyma. Because the extracellular fluid space of the brain is extremely tortuous, drug diffusion through the brain parenchyma is very slow and inversely proportional to the molecular weight of the drug. For macromolecules, such as proteins, brain parenchymal concentrations following intra-CSF administration are undetectable. For these reasons, intra-CSF chemotherapy in the treatment of intraparenchymal CNS tumors has not proven to be effective. 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/analgesia.

Interstitial Delivery

The most direct way of circumventing the BBB is to deliver drugs directly to the brain interstitium. By directing agents uniquely to an intracranial target, interstitial drug delivery can theoretically yield high CNS drug concentrations with minimal systemic exposure and toxicity. Furthermore, with this strategy, intracranial drug concentrations can be sustained, which is crucial in treatment with many chemotherapeutic agents.

Intrathecal and intracerebral drug administration differs fundamentally from systemic drug administration in terms of pharmacokinetic characteristics determining brain tissue concentration, where the available dose reaching the target organ is 100%. However, there are large gradients inside the tissue with very high local concentrations at the site of administration (the ventricular surface or tissue site of injection) and zero concentration at some distance for macromolecules. Since, they have low diffusion coefficients, the gradients will be even steeper than what has been measured for small molecular weight drugs. After intracerebroventricular (icv) injection, the rate of elimination from the CNS compartment is dominated by cerebrospinal fluid dynamics. 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. These examples have in common the fact that the drug targets in all instances are close to the ventricular surface. Superficial targets may also be accessible for some macromolecular drug.

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that this delivery system is without significant pathological effects at the dose of 10mg/ml morphine after repeated epidural delivery in dogs.

### 1.1.2.8 3.3.4 Nasal Transport Routes

After nasal delivery drugs first reach the respiratory epithelium, where compounds can be absorbed into the systemic circulation utilizing the same pathways as any other epithelia in the body: Tran cellular and Para cellular passive absorption, carrier-mediated transport, and absorption through transcytosis. 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. Accordingly, the remainder of this article will deal primarily with the transport of drugs to the CNS by way of the olfactory epithelium. 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. The olfactory pathways may be broadly classified into two possible routes: the olfactory nerve pathway (axonal transport) and the olfactory epithelial pathway. 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 sameanterograde axonal transport mechanisms the cell uses to transport endogenous substances to the brain. Depending on the substance administered, axonal transport rates range from 20-400 mm/day to a slower 0.1-4 mm/day. The epithelial pathway is a significantly faster route for direct nose-to-brain transfer, whereby compounds passparacellularly across the olfactory epithelium into theperineurial 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 circulations. 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 sameanterograde axonal transport mechanisms the cell uses to transport endogenous substances to the brain. Depending on the substance administered, axonal transport rates range from 20-400 mm/day to a slower 0.1-4 mm/day. 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### 1.1.3 11. CONCLUSION

Brain Targeting has got the attention of the many researchers due to its application in various diseases related to CNS. Only few drugs can penetrate the BBB and enters the CNS, so various systems are developed for drug delivery. It emerges that the nanotechnology and by using other routes of drug administration like intra nasal technique drug can penetrate the BBB efficiently. Further the modified colloidal particles and various modified liposomes enhance exposure of the BBB due to prolonged blood circulation, which favors interaction and penetration into brain endothelial cells. This system has clinical benefits like reduced drug dose, decreased side effects, non invasive routes, and more patient compliance. We still require developing a cost effective system that can be used in various CNS disorders efficiently with minimum side effect.

### REFERENCES


