TARGETED DRUG DELIVERY FOR CENTRAL NERVOUS SYSTEM: A REVIEW

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ABSTRACT

Targeted drug delivery is a method of delivering medication to a patient in a manner that increases the concentration of the medication in some parts of the body relative to others. Targeted drug delivery seeks to concentrate the medication in the tissues of interest while reducing the relative concentration of the medication in the remaining tissues. This improves efficacy of the while reducing side effects. It is very difficult for a drug molecule to reach its destination in the complex cellular network of an organism. Targeted delivery of drugs, as the name suggests, is to assist the drug molecule to reach preferably to the desired site. The inherent advantage of this technique has been the reduction in dose & side effect of the drug. Research related to the development of targeted drug delivery system is now a day is highly preferred and facilitating field of pharmaceutical world. The brain is a delicate organ, and evolution built very efficient ways to protect it. Unfortunately, the same mechanisms that protect it against intrusive chemicals can also frustrate therapeutic interventions. Many existing pharmaceuticals are rendered ineffective in the treatment of cerebral diseases due to our inability to effectively deliver and sustain them within the brain. General methods that can enhance drug delivery to the brain are, therefore, of great interest. Despite aggressive research, patients suffering from fatal and/or debilitating central nervous system (CNS) diseases, such as brain tumors, HIV encephalopathy, epilepsy, cerebrovascular diseases and neurodegenerative disorders, far outnumber those dying of all types of systemic cancer or heart disease. The clinical failure of much potentially effective therapeutics is often not due to a lack of drug potency but rather to shortcomings in the method by which the drug is delivered. Treating CNS diseases is particularly challenging because a variety of formidable obstacles often impede drug delivery to the brain and spinal cord. By localizing drugs at their desired site of action one can reduce toxicity and increase treatment efficiency. In response to the insufficiency in conventional delivery mechanisms, aggressive research efforts have recently focused on the development of new strategies to more effectively deliver drug molecules to the CNS. This review intends to detail the recent advances in the field of brain-targeting, rational drug design approach and drug delivery to CNS. To illustrate the complexity of the problems that have to be overcome for successful brain targeting, a brief intercellular characterization of the blood–brain barrier (BBB) is also included.

Keyword: Targeted drug delivery, Central nervous system (CNS), Brain tumors, Cerebrovascular diseases, HIV encephalopathy, Epilepsy, Blood–brain barrier (BBB)

INTRODUCTION

It is estimated that about 1.5 billion people worldwide are suffering from some type of central nervous system (CNS) disorder. Therefore, there is a strong demand from patients for effective treatments. Targeted drug delivery is a method of delivering medication to a patient in a manner that increases the concentration of the medication in some parts of the body relative to others. Targeted drug delivery seeks to concentrate the medication in the tissues of interest while reducing the relative concentration of the medication in the remaining tissues. This improves efficacy of the while reducing side effects. This improves efficacy of the while reducing side effects. Drug targeting is the delivery of drugs to receptors or organs or any other specific part of the body to which one wishes to deliver the drugs exclusively. The desired differential distribution of drug its targeted delivery would spare the rest of the body and thus significantly reduce the overall toxicity while maintaining its therapeutic benefits. The targeted or site-specific delivery of drugs is indeed a very attractive goal because this provides one of the most potential ways to improve the therapeutic index of the drugs. The major problem in drug delivery to brain is the presence of the BBB. Drugs that are effective against diseases in the CNS and reach the brain via the blood compartment must pass the BBB. In order to develop drugs which penetrate the BBB well and exhibit the expected CNS therapeutic effects, it is of great importance to understand the mechanisms involved in uptake into and efflux from the brain. The function of the BBB is dynamically regulated by various cells present at the level of the BBB. This realization implies better understanding of the relationship of transport at the BBB to drug structure and physicochemical properties. The brain is probably one of the least accessible organs for the delivery of active pharmacological compounds. The same mechanisms that protect the brain from foreign substances also restrict the entry of many potential therapeutic agents. Despite its relatively high blood flow, there are two physiological barriers separating the brain from its blood supply and they control the entry and exit of endogenous and exogenous compounds. One is the blood–brain barrier (BBB) and the other is the blood–cerebrospinal fluid barrier (BCSFB). The BBB allows the creation of a unique extracellular fluid environment within the central nervous system (CNS) whose composition can, as a consequence, be precisely controlled. The extracellular fluid compartments of the CNS comprise the brain and spinal cord parenchymal interstitiumal fluid (ISF) and the cerebrospinal fluid (CSF), contained within the ventricles of the brain and the cerebral and spinal subarachnoid spaces. The main challenge is to develop drug delivery strategies that will allow the passage of drug molecules through the BBB in a safe and effective manner. This paper focuses on the review of various barriers for delivering the drug to CNS & different strategies developed to enhance targeted drug delivery across these barriers.

BARRIERS TO CNS DRUG DELIVERY

The failure of systemically delivered drugs to effectively treat many CNS diseases can be rationalized by considering a number of barriers that inhibit drug delivery to the CNS.

Blood-Brain Barrier (BBB)

The major challenge to CNS drug delivery is the blood-brain barrier (BBB), which limits the access of drugs to the brain substance. Advances in understanding of the cell biology of the BBB have opened new avenues and possibilities for improved drug delivery to the CNS. It is now well established that the BBB is a unique membranous barrier that tightly segregates the brain from the circulating blood. The CNS consist blood capillaries which are structurally different from the blood capillaries in other tissues; these structural differences result in a permeability barrier between the blood within brain capillaries and the extracellular fluid in brain tissue. Capillaries of the vertebrate brain and spinal cord lack the small pores that allow rapid movement of solutes from circulation into other organs; these capillaries are lined with a layer of special endothelial cells that lack fenestrations and are sealed with tight
Blood-Cerebrospinal Fluid Barrier

The second barrier that a systemically administered drug encounters before entering the CNS is known as the blood-cerebrospinal fluid barrier (BCB). Since the CSF can exchange molecules with the interstitial fluid of the brain parenchyma, the permeability of blood-brain barrier is also carefully regulated by the BCB. Physiologically, the BCB is found in the epithelium of the choroids plexus, which are arranged in a manner that limits the passage of molecules and cells into the CSF. The choroid 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 lies between the dura and pia, this is called the 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.

Blood-Tumor Barrier

Intracranial drug delivery is even more challenging when the target is a CNS tumor. The presence of the BBB in the microvasculature of CNS tumors has clinical consequences. For example, even when primary and secondary systemic tumors respond to chemotherapeutic agents delivered via the cardiovascular system, intracranial metastases often continue to grow. 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. At the same time, intra-capsular 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. Brain tumors may also disrupt BBB, but these are also local and non-homogeneous disruptions.

METHODS TO QUANTITATE DRUG TRANSPORT INTO/OUT OF THE CENTRAL NERVOUS SYSTEM -IN VIVO AND IN VITRO METHODS

In Vivo Models to Study Drug Transport across the Blood-brain Barrier and the Choroid Plexus

In vivo and in vitro techniques utilized to examine drug transport in the brain will only be briefly discussed as a review of these methods is beyond the scope of this paper and can be found elsewhere. In vivo BBB models of drug transport can be broadly categorized according to methodological approach. Single passage techniques, such as the indicator diffusion/dilution, brain uptake index, and external registration measure the uptake of substances into the CNS following a single passage through the brain upon injection into the blood stream. A major disadvantage of the single passage techniques is that transport estimates of drugs or solutes with extremely slow uptake may be inaccurate due to the short solute exposure times. Multi passage techniques, then, can be used to allow the test substance longer circulation times. Intravenous administration and micro dialysis methods are examples of multi passage techniques. These methods are model dependent, and the method of data analysis (i.e. two compartment model, three compartment model, etc. is normally chosen prior to the experiment. Therefore, once chosen, the results are model specific and may not necessarily be indicative of the active transport parameters. Metabolic processes within the tissue Finally, perfusion techniques, such as the in situ perfusion method, expose The brain tissue to the test substance by perfusion with a physiological buffer. This model was developed to provide further control over the experimental conditions (pH, temperature, etc.) and to avoid metabolism of the test substance during transfer across the BBB. Compared with single or multi passage methods, permeability coefficients can be measured accurately over a 100-fold range making this method100-fold more sensitive. Therefore measurements of brain uptake of poorly penetrating compounds (P<10^-10cm/s) or rapidly penetrating compounds(P>10^-4 cm/s) can be determined using the characterization of carrier mediated transport at the BBB. The involvement of complex surgery and the requirement of mathematical models are the main disadvantages of the perfusion models.

In Vitro Models to Study Drug Transport in the Brain

In general, in vivo methodologies to study drug transport in the CNS are costly. Furthermore, it is often difficult to maintain control of environmental factors such as pH, temperature, osmotic pressure, oxygen, carbondioxide, as well as physiological responses (metabolism, tissue distribution, excretion) that occur in the animal under normal and experimental conditions. An alternative to in vivo studies of drug transport is in vitro cell and tissue culture systems. Tissue culture techniques were developed as a method for studying the behaviour of a specific population of cells free of systemic variations that may arise in the animal both during normal homeostasis and under stress of an experiment. The development of tissue culture transport systems has revolutionized the drug transport field and has resulted in an explosion of research over the last 50 years. Not only do cell cultures provide a level of control over the environment and variables physiological responses, they also provide specific information on the type of transporter(s) involved and relative pharmacokinetic parameters such as carrier affinity and specificity. Nevertheless, these systems are limited in that many of the functional and receptor characteristics or the original tissue may be lost (i.e., tight junctions in brain endothelial cells, production of specific factors by cells , expression and activity of various transporters) due to culture conditions and the absence of endogenous factors and signals. For example, gene expression that sometimes occurs in culture may be a consequence of a variety of factors such as culture conditions (presence of serum in media and nature of sub stratum) and the absence of endogenous factors and signals that are present in vivo. Consequently caution must be taken when extrapolating in vitro tissue culture data to either in vivo models or clinical practice. A common method of studying in vitro drug transport of non polarized cells involves culture and growth of isolated cells on impermeable poly styrene strata (e.g., 24-wellplates) and measurement of the cellular uptake/ accumulation or efflux of a radio labeled substrate or fluorescent probe. Specific transporter characteristics can then be examined utilizing known transporter inhibitors, metabolic inhibitors, etc., which are appropriate for the transporter of interest. Polarized cells, such as epithelial and endothelial cells, can also be grown on porous filter membranes which provide the option of examining both basal-to-apical and apical-to-basal transport of substrates.

MECHANISMS IN DRUG TRANSPORT TO THE BRAIN

It was originally believed that membrane carriers localized at the brain barriers were solely responsible for the transport of
endogenous substances into and out of the brain and that drug transport across the brain barriers was largely dependent on the physicochemical characteristics of the drug such as lipophility, molecular weight, and ionic state. Generally, small, nonionic, lipid-soluble molecules penetrate easily across the BBB whereas larger, water-soluble, and ionized compounds are less likely to be transported by these diffusion processes. For some drugs the rate of entry and distribution in the CNS cannot be explained by passive processes that depend on the physicochemical characteristics listed above. Many drug transporters that have been well characterized in peripheral tissues and are known to be involved in the influx and efflux of drugs (i.e., the organic cation, organic anion, nucleoside, P gp, and MRP transporters), have now been identified in the brain. It is now recognized that these drug transporters may influence many pharmacokinetic characteristics of drugs in the processes of absorption, distribution, and elimination.

Organic Cation Transport Systems

A diverse group of organic cations including endogenous bioactive amines (i.e. acetylcholine, choline, dopamine, epinephrine, norepinephrine, guanidine, methyl nicotinamide, thiamine), therapeutic drugs (i.e. cimetidine, amiloride, meperiphenidol, morphine, quinine, quindidine, tetraethylammonium, verapamil, trimethoprim, tetracyclines and antibiotics (i.e., paraquat), are actively transported by the OCT system primarily in the liver and kidney. At physiological pH, the nitrogen moiety of these compounds (generally primary, secondary, tertiary, or quaternary amines) bears a transient or permanent net positive charge, which is determined by the compound's pKₐ value. Two distinct classes of OCT systems have been defined: a potential-sensitive transporter usually involved in the influx of organic cations and an H⁺ gradient-dependent transporter, mediating efflux. The concerted action of these two OCT subtypes results in the vectorial transfer of cationic compounds from the blood into the luminal fluid across the renal tubular cells or from the blood into the bile across the hepatocyte, intestinal epithelium, and the placental syncytiotrophoblast. In the brain, the physiological role of the OCT systems includes transport of cationic neurotransmitters and neurotransmitters.

Organic Anion Transport Systems

The liver and kidney are organs central to the elimination of endogenous and exogenous organic anions, many of which are harmful to the body. Several families of multi specific organic anion transporters have been identified, of which the two main families, i.e., the organic anion transporter polypeptide (oatp), and the organic anion transporter OAT will be discussed. To date, seven isoforms [oatp1, oatp2, oatp3, OAT-K1, OAT-K2, OATP, prosta glandin transporter (PGT), and the liver-specific transporter L (LST-1)] have been identified in the oatp family. In the liver, oatp1 and oatp2 are multi specific organic anion carriers that transport structurally unrelated anionic compounds in a sodium-independent manner. Both are expressed in the brain. oatp1, a bidirectional organic anion/HCO₃ and/or organic anion/glutathione exchanger, is expressed at the apical membrane of the CP in contrast to its basolateral localization in the hepatocyte. It possesses aberrant substrate specificity and mediates the transport of bile salts, steroid hormones, and a variety of organic anions and amines. However, whether oatp1 is responsible for the uptake or efflux of organic anions across the CP remains to be elucidated. oatp2, cloned from rat brain, is expressed in liver, kidney, brain capillaries, and the basolateral membrane of the CP. It mediates the uptake of bile acids taurocholate, cholate, estrogen conjugates, ouabain, and digoxin. oatp3, isolated from rat retina and expressed in kidney and retina, was shown to transport thyroid hormones and taurocholate. OAT-K1 and OAT-K2 are both localized to the luminal membrane of the renal proximal tubule, OAT-K1 is involved in the transport of methotrexate and folate whereas OAT-K2 transports hydrophobic organic anions such as taurocholate, methotrexate, folate, and prosta glandin E2. OATP is the cloned human liver organic anion carrier that transports bromosulfophthalein, cholate, taurocholate, glycolyche, taurochenodeoxycholate, and tauroursodeoxycholate in a sodium-independent manner. It is expressed in human lung, kidney, and testes. Recently, OATP was shown to be expressed along the BBB in cultured human brain endothelial cells. This transporter was found to transport two opioid peptides, deltorphin II (Kₐ ~ 300 μM) and the enkephalin analog, [d-Pen2,d-Pen5]-enkephalin (Kₐ ~ 20 μM), the latter also transported by rat oatp2 at the BBB. On the basis of sequence homology, PGT and LST-1 are believed to be oatp isoforms, of which the latter may be important for bile clearance.

Nucleoside Transport Systems

Purine and pyrimidine nucleosides and their metabolic products are the precursors of the nucleic acids, DNA and RNA, and participate in numerous biological brain processes. For example, the nucleoside adenosine modulates neuronal and cerebral vascular functions by interacting with specific receptors on brain cells and blood vessels. In general, nucleosides are synthesized endogenously via de novo synthetic pathways. However, a number of tissues including brain are deficient in de novo nucleotide synthetic pathways and rely on the salvage of exogenous nucleosides to maintain nucleoside pools and to meet their metabolic demands. Therefore, the brain is dependent on a continuous and balanced supply of purine and pyrimidine nucleoside constituents from both synthesis in situ and the blood. Nucleosides and their analogs form the basis of a wide variety of clinical agents that are used in the treatment of brain cancers, cardiac disorders, parasitic and viral diseases. The purine nucleoside, adenosine, exerts significant cardiac effects and is used clinically in the treatment of cardiac arrhythmias. Nucleoside analogs (i.e., zidovudine, lamivudine, didanosine, and abacavir) are currently used in the treatment of patients with HIV infection. Most nucleosides and their analogs exert their biological activity intracellularly, but due to their hydrophobic nature do not readily permeate the lipid bilayer. Therefore, the uptake or release of nucleosides and/or nucleoside analogs in mammalian cells is mediated by multiple distinct transporters.

Efflux Transport Systems

P-Glycoprotein

P-gp is a 170-kDa plasma membrane, energy-dependent efflux pump that belongs to the ABC superfamily of transporters. Originally discovered in Chinese hamster ovary cells selected for colchicine resistance, these cells exhibited broad cross-resistance to a number of naturally occurring structurally diverse antineoplastic agents including anthracyclines, vinca alkaloids, and taxanes. Consequently, this phenomenon was termed multidrug resistance (MDR). P-gp is a product of the MDR gene. In humans, two MDR genes, MDR1 and MDR2 (also called MDR3), have been cloned and sequenced.

Multidrug Resistance Protein Family

A second efflux transport protein subfamily, which belongs to the ABC protein super family and can confer MDR, is the MRP. Thus far the mammalian MRP family consists of seven proteins ranging from 1325 to 1545 amino acids. All MRPs contain two Transmembrane domains of six α helices each (P-gp-like core) connected to a cytoplasmic linker (Lo) region. In addition, MRP1, -2, -3, and -6 contain up to six additional membrane-spanning helices (TMDs) at the NH₂ terminus. Although this extra N-terminal domain is not required for drug transport, the linker region is absolutely necessary to maintain the protein transport properties. MRP1, -2, and -3 appear to have overlapping substrate specificities, but differ with respect to kinetic properties. Most cells appear to express multiple MRP family members, with high levels of one MRP generally dominating. While MRP2, -3, and -6 are found mainly in the liver and kidney, and MRP4 is found in high concentrations in the prostate, MRP1 and -5 appear to be ubiquitous, and both proteins are expressed in the brain. Within polarized cells (e.g. kidney and liver) MRP2 is the only homolog (defined in terms similar to P-gp), MRP1, -3, and -5 are all routed to the basolateral membrane.

PHYSICOCHEMICAL FACTORS THAT INFLUENCE BRAIN UPTAKE

Brain penetration, brain uptake, and ability to cross the BBB need to be defined exactly to understand concepts involved in brain uptake. Hence, the various ways in which transfer across the BBB are defined in table-1.
that this equation does not take into account efflux of either intact
under the plasma concentration time curve. It should be mentioned
expression equivalent to the organ clearance and AUC is the area
the phase of unidirectional uptake, the following equation-2 holds:

\[ BUI = \frac{100 \times M_{CPU}/M_{H}}{PS \times \text{saline}} \]  

\[ (\text{IC}^+\text{H})\text{saline} \]

Where, the BUI for water is 100. Although, the BUI is useful as a rank
order index of brain uptake, it is not easily amenable to analysis by
physicochemical methods. A more well-defined measure of rapid
brain uptake is the permeability, expressed either as a permeability-
surface area product (PS) or as a permeability coefficient (PC),
obtained by intravenous injection and measurement of the drug
profile in arterial blood. Both the PS product and PCare quantitative
measures of the rate of transport obtained by in-situ vascular
perfusion technique and so are amenable to analysis through
standard physicochemical procedures. An advantage of the
perfusion technique as a measure of brain uptake is that the time
scale for determination of PS products is very short, so that back
transport and biological degradation are minimized. Although there
are numerous physicochemical studies on brain perfusion, it is not
possible to reach any general conclusions. Following systemic drug
administration, uptake from the circulation into parenchyma by a
specific organ of interest will be determined by the following factors:
(a) blood flow to the organ, (b) permeability of the micro-vascular
wall, and (c) the amount of drug available for uptake, which is
inversely related to systemic clearance and is represented by the
area under the plasma concentration time curve (AUC). For the
quantification of brain tissue accumulation (C_{tissue}) at time T during
the phase of unidirectional uptake, the following equation-2 holds:

\[ C_{tissue} (T) = PS \times AUC \times T \]  

Where PS is the brain capillary permeability surface is a product, an
expression equivalent to the organ clearance and AUC is the area
under the plasma concentration time curve. It should be mentioned
that this equation does not take into account efflux of either intact
drug or metabolism and efflux of degradation products from the
brain. Based on the relationship between the octanol / water
partition coefficient (PC) divided by the square root of the molecular
weight (PC / MW1/2) and the BBB permeability coefficient (PS), one
can classify at least three different groups: (a) substrates exhibiting a
good correlation, (b) substrates exhibiting a significantly greater
PS value than indicated by their lipophilicity, and (c) substrates exhibiting a significantly smaller PS value than indicated by their
lipophilicity. The transport mechanism for groups (a) and (b) is
passive diffusion and facilitated transport, respectively. The
molecular weight of the compounds in group (c)is greater than 400
Da, the absolute cut-off for significant BBB passage regardless of
lipophilicity. This molecular weight threshold hypothesis was
proposed to explain the mechanism operating in the case of group
(c). Brain uptake can be positively correlated with lipid solubility or
negatively correlated with hydrogen bonding.

### STRATEGIES FOR BRAIN DELIVERY OF DRUG:

#### 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

**Intracerebral Implants**

Intracerebral chemotherapeutic delivery by polymeric implants
increases the survival of human with recurrent malignant gliomas
and of animals with transplanted gliomas 86. Drug added to polymer
pellet implants intra cranially bypasses the BBB and release drug
molecules locally in the brain in a sustained fashion.

**Intra ventricular / Intrathecal Route**

One strategy for bypassing the BBB that has been studied
extensively both in laboratory and in clinical trials is the intra
lumbar injection or intraventricular infusion of drugs directly into
the CSF. Drugs can be infused intra ventricularly 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. 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
meninigitis or for spinal anesthesia/analgesia 81.

#### Disruption of the BBB

One of the earliest techniques to circumvent the BBB for therapeutic
purpose and the first to be used in humans was developed by
Neuwelt (1989). 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 82. In current practice, the effect lasts
for 20-30 min, during which the drugs that would not normally cross
the BBB diffuse freely. This method allows the delivery of
chemotherapeutic agents in patients with malignant glioma, cerebral
lymphoma and disseminated CNS germ cell tumours, with a
subsequent decrease in morbidity and mortality compared with
patients receiving systemic chemotherapy alone. However, this
approach also causes several undesirable side effects in humans,

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**Table 1: Measures of ‘Brain Uptake’**

| Biological activity: Maximum brain concentration | The brain uptake index from single pass experiment |
| PSU product & permeability coefficient from: | Indicaoter dilution during single pass |
| | Intra venous infusion & bolus injection |
| | Vascular perfusion of brain in-situ |
| | Blood brain distribution |

Biological activity is a general measure of brain uptake. The hypnotic
activity of a number of congenic series of CNS depressants reached a
maximum when log octanol water partition coefficient (log Po/w)
was near to 2. Various researchers confirmed this finding and the
"rule of 2"became generally accepted. But the difficulty here is that
the biological activity will depend on at least two factors:

- Rate of transport from blood to brain, or distribution between blood
and brain; and
- Interaction between drug and some receptors in the brain.

If these two factors cannot be distinguished, then it is impossible to
use biological activity as a measure of either rate or equilibrium
transfer. The log Po/w probably still represents the most
informative physicochemical parameter used in medicinal chemistry
and countless examples where it proved as useful descriptors are
available in the literature. On the other hand, increasing lipophilicity
with the intent to improve membrane permeability might not only
make chemical handling difficult, but also increase the volume of
distribution in particular plasma protein binding and tends to affect
all other pharmacokinetic parameters 86. Furthermore, increasing
lipophilicity tends to increase the rate of oxidative metabolism by
cytochromes P450 and other enzymes86. Hence, to improve
bioavailability, the effects of lipophilicity on membrane permeability
and first pass metabolism have to be balanced. The brain uptake
index is a more rigorous measure of brain uptake in which there is a
relative measure of brain uptake by intra-carotid injection of a
mixture of 14C-labeled compound and 3H-labeled water (i.e. a saline
solution in 3H-labeled water). The radioactivity in brain tissue is
recorded 15 seconds after administration, and a brain uptake index
(BUI) for water is defined in equation-1:

\[ BUI = \frac{100 \times M_{CPU}/M_{H}}{PS \times \text{saline}} \]  

Where, the BUI for water is 100. Although, the BUI is useful as a rank
order index of brain uptake, it is not easily amenable to analysis by
physicochemical methods. A more well-defined measure of rapid
brain uptake is the permeability, expressed either as a permeability-
surface area product (PS) or as a permeability coefficient (PC),
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the phase of unidirectional uptake, the following equation-2 holds:

\[ C_{tissue} (T) = PS \times AUC \times T \]  

Where PS is the brain capillary permeability surface is a product, an
expression equivalent to the organ clearance and AUC is the area
under the plasma concentration time curve. It should be mentioned
that this equation does not take into account efflux of either intact
including physiological stress, transient increase in intracranial pressure, and unwanted delivery of anticancer agents to normal brain tissue. In addition, this technique requires considerable expertise for administration. However, disrupting the BBB even for brief periods leaves the brain vulnerable to infection and damage from toxins. Even substances that circulate harmlessly through the peripheral bloodstream, such as albumin, can have deleterious effects if they enter the brain 53.

Non-Invasive Approaches

A variety of non-invasive brain drug delivery methods have been investigated, that make use of the brain blood vessel network to gain widespread drug distribution. Non-invasive techniques of delivery may be of a chemical or biological nature. Such methods usually rely upon drug manipulations which may include alterations as prodrugs, lipophilic analogues, chemical drug delivery, carrier-mediated drug delivery, receptor/mediator mediated drug delivery etc. Intranasal drug delivery which primarily exploits the olfactory and trigeminal neuronal pathways has also gained a recent reappraisal as a potential non-invasive approach.

Chemical Methods

The main premise for the chemical methods remains the use of prodrugs. An extension of the concept uses the chemical transformation of drugs by changing the various functionalities. Such chemical change is usually designed to improve some deficient physicochemical property such as membrane permeability or solubility. For example, esterification or amidation of hydroxy-, amino-, or carboxylic acid containing drugs may greatly enhance the lipid solubility and hence, entry into the brain. Generally, conversion to the active form is realized via an enzymatic cleavage. Going to the extremes of the lipophilic precursor scale, a possible choice for CNS prodrugs is to link the drug to a lipid moiety, such as a fatty acid, a glyceride or a phospholipid. Such prodrug approaches were explored for a variety of acid containing drugs, like levodopa54. Problems associated with prodrugs are: the poor selectivity and poor tissue retention of some of these molecules.

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 55. The antibody-drug conjugate is directed towards an antigen residing on or within the target tissues. Antibodies are particularly well suited for targeting BBB receptor-mediated transcytosis systems given their high affinity and specificity for their ligands 56.

Colloidal Drug Carriers

In general, colloidal drug carriers include micelles, emulsions, liposomes and nanoparticles (nanospheres and nanocapsules). It is noteworthy that only liposomes and nanoparticles have been largely exploited for brain drug delivery because the methods of preparation are generally simple and easy to scale-up 57. The aim of using colloidal carriers is generally to increase the specificity towards cells or tissues, to improve the bioavailability of drugs by increasing their diffusion through biological membranes and/or to protect them against enzyme inactivation. Colloidal particles that are small and hydrophilic enough can escape, at least partially, from the opsonization process and consequently, remain in the circulation for a relatively longer period of time 58.

Nanoparticles

Nanoparticles are solid colloidal particles ranging 1 to 1000 nm in size 59-60. They consist of macromolecular materials in which the active principle is dissolved, entrapped or encapsulated or to which the active principle is adsorbed or attached. Polymeric nanoparticles have been proposed as interesting colloidal systems that allow the enhancement of therapeutic efficacy and reduction of toxicity of large variety of drugs. Nanoparticles were found to be helpful for the treatment of the disseminated and very aggressive brain tumors. Valproic acid-loaded nanoparticles showed reduced toxic side effects of valporate therapy, not by reducing the therapeutically necessary dosage but by inhibition of formation of toxic metabolites. In conclusion, the capacity of the biodegradable polymer delivery methodology to deliver drugs directly to the brain interstitium is vast.

Liposomes

Liposomes are lipid vesicles first characterized by Bangham 61. Liposomes were initially developed as models of biological membranes. Liposomes are well defined lipid vesicles that offer an immense advantage of targeting the drug to selected tissues via appropriate modifications mediated by either passive or active mechanisms. Liposomes are biocompatible, non-toxic, and biodegradable carrier constructs, which offer the possibility of carrying hydrophobic, hydrophilic or amphoretic molecules. They can act as carrier for drugs, enzymes proteins, anticancer substances and other macromolecules.

CURRENT & FUTURE DEVELOPMENTS

A number of concrete examples where successful delivery and sustained activity have been achieved were provided. They clearly prove that, with adequate design, the approach can provide substantially increased and prolonged brain exposure of the drugs. From the discussion it was found that many delivery systems like polymeric Nanoparticles and liposomes are the promising carriers to deliver drugs beyond the BBB for the scrutiny of the central nervous system. This is even more evident in light of the fact that most of the potentially available drugs for CNS therapies are large hydrophilic molecules, e.g., peptides, proteins and oligonucleotides that do not cross the BBB. Among the several strategies attempted in order to overcome this problem, properly tailored NPs may have a great potential. The large amount of evidence regarding brain drug delivery by means of P80-coated NPs cannot be ignored or considered as single evidence even though its action mechanism is not completely understood. Lipid NPs, e.g. SLN, NLC, LDC NPs, may represent, in fact, promising carriers since their prevalence over other formulations in terms of toxicity, production feasibility and scalability is widely documented in the literature. The ability of engineered liposomes to enter into brain tumours makes them potential delivery systems for brain targeting. Biodegradable polymers are also making their place in the area of matrix type sustained-release of neuro therapeutics. Every delivery system has some potential advantages over each other along with some limitations but it's a need of the hour to design a developmental programme in such a way that the delivery of the drugs across the BBB should be looked simultaneously along with the discovery programmes. Patient compliance and risk-benefit ratio suggest the use of non-invasive methods of drug delivery over invasive methods.

A technology of chimeric peptides which are potential BBB transport vectors and have been applied to several peptide pharmaceuticals, nucleic acid therapeutics, and small molecules to make them CNS transportable. It is estimated that the global CNS pharmaceutical market would have to grow by more than 500% just to equal the cardiovascular market. If BBB delivery solutions were in place for either small or large molecules, then almost any pharmaceutical could enter clinical drug development programs and therapies could be developed for most CNS disorders. A sound review of the patents dealing with CNS drug delivery approaches has shown that scientific interest in the field has risen but a lot needs to be done. The poor status of patent molecules available in customized formats produces a dismal picture for a vast population waiting to be treated.

REFERENCES


