Academic Sciences International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 4, Issue 3, 2012

Research Article

TARGETED DRUG DELIVERY FOR CENTRAL NERVOUS SYSTEM: A REVIEW

JINAL PRAJAPATI*, HARDIK PATEL, YADVENDRA. K. AGRAWAL

Institute of Research & Development, Gujarat Forensic Sciences University, Sec-18/A, DFS Headquaters, Gandhinagar (382007), Gujarat, Institute of pharmaceutical sciences, Birla institute of Technology, Mesra, Ranchi (835215), Jharkhand, Institute of Research & Development, Gujarat Forensic Sciences University, Gandhinagar (382007), Gujarat, India. Email: jinalprajapati@yahoo.co.in

Received: 10 Mar 2012, Revised and Accepted: 19 Apr 2012

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 to 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[1]. 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 interstitialfluid (ISF) and the cerebrospinalfluid (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[2]. 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

junctions. Tight epithelium, similar in nature to this barrier, is also found in other organs (skin, bladder, colon, and lung) [3]. This permeability barrier, comprising, the brain capillary endothelium, is known as the BBB. Micro-vessels make up an estimated 95% of the total surface area of the BBB, and represent the principal route by which chemicals enter the brain. Vessels in brain were found to have somewhat smaller diameter and thinner wall than vessels in other organs. Also, the mitochondrial density in brain micro-vessels was found to be higher than in other capillaries not because of more numerous or larger mitochondria, but because of the small dimensions of the brain micro-vessels and consequently, smaller cytoplasmic area[4]. The diffusion of drugs from the blood into the brain depends mainly upon the ability of the biologically active molecule to cross lipid membranes. Therefore, drugs of interest may not have the requisite physicochemical characteristics necessary to successfully cross the BBB. This is the reason why several strategies have been developed to overcome the BBB[5].

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 passage of blood-borne molecules into the CSF is also carefully regulated by the BCB[6]. 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 [7]. 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 [8].

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-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[9]. Brain tumors may also disrupt BBB, but these are also local and non homogeneous disruptions [10].

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[11]. 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[12]. 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[13].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[14].These techniques 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 actual transport and metabolic processes within the tissue [14].Finally, perfusion techniques, such as the in situ perfusion method, expose The brain tissue to the test substance by perfusion with a physiological buffer [15].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 104-fold range making this method100-fold more sensitive[16]. Therefore measurements of brain uptake of poorly penetrating compounds ($P= 10^{-8}$ to10^{-7}cm.s^{-1}) or Rapidly penetrating compounds($P=10^{-4}$ cm.s^{-1})can be deter-mined allowing for the characterization of carrier mediated transport at the BBB[17].The involvement of complex surgery and the requirement of mathematical models are the main disadvantages of the perfusion models[18].

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[19].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[20]. The development of tissue culture transport systems has revolutionized the drug transport field and has resulted in an explosion of research over the last 50years .Not only do cell cultures provide a level of control over the environment and various 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 phenotypic and functional characteristics of 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[21] For example ,gene expression of some drug transporters in the brain (i.e., P-gp and MRP) can be both up and down regulated in culture[22].This change in 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[23].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[24].

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 lipophilicity, molecular weight, and ionic state[25]. Generally, small, nonionic, lipid-soluble molecules penetrate easily across the BBB whereas larger, water-soluble, and/or ionic molecules will less likely exhibit passive diffusional processes [26]. 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[27]. 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, mepiperphenidol, morphine, quinine, quinidine, tetraethylammonium, verapamil, trimethoprim) and xenobiotics (i.e., paraquat), are actively transported by the OCT system primarily in the liver and kidney [28]. 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 pK_a 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 [29].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 [30] or from the blood into the bile across the hepatocyte, intestinal epithelium, and the placental syncytiotrophoblast[31]. In the brain, the physiological role of the OCT systems includes transport of cationic neurotoxins 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 [32]. 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[33].to date, seven isoforms [oatp1, oatp2, oatp3, OAT-K1, OAT-K2, OATP, prostaglandin transporter (PGT), and the liver-specific transporter-1 (LST-1)] have been identified in the oatp family [34]. In the liver, oatp1 and oatp2 are multi specific organic anion carriers that transport structurally unrelated anionic compounds in a sodium-independent manner [35]. Both are expressed in the brain. Oatp1, a bidirectional organic anion/HCO and/or organic anion/glutathione exchanger, is expressed at the apical membrane of the CP in contrast to its basolateral localization in the hepatocyte [36]. It possesses abroad substrate specificity and mediates the transport of bile salts, steroid hormones, and a variety of organic anions and cations[37]. 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 [38]. Oatp3, isolated from rat retina and expressed in kidney and retina, was shown to transport thyroid hormones and taurocholate [39].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 prostaglandin E2 [40] OATP is the cloned human liver organic anion carrier that transports bromosulfophthalein, cholate, taurocholate, glycocholate, 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 (K_m~ 330 μM) and the enkephalin analog, [d-Pen(2),d-Pen(5)]enkephalin (K_m ~202 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 [41].

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 [42]. 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[43].Most nucleosides and their analogs exert their biological activity intracellularly, but due to their hydrophilic 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 [44, 45].

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 Trans membrane domains of six α-helices each (P-gp-like core) connected to a cytoplasmic linker (L_o) region. In addition MRP1, -2, -3, and -6 contain up to six additional membrane-spanning helices (TMD_o) at the NH_2 terminus. Although this extra N-terminal domain is not required for drug transport, the linker region (Lo) 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[45]. 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 located in the apical membrane (similar to P-gp), MRP1, -3, and -5 are all routed to the basolateral membrane [46].

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.

Table 1: Measures of "Brain Uptake" [47]

Biological activity: Maximum brain concentration
The brain uptake index from single pass experiment
PS product & permeability coefficient from:
Indicator 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 congeneric 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 transfer 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 **[46].**Furthermore, increasing lipophilicity tends to increase the rate of oxidative metabolism by cytochromes P450 and other enzymes**[48].**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) is defined in equation-1:

$$BUI = \frac{100 \times (^{34}C/^{3}H)_{tissue}}{(^{34}C/^{3}H)_{saline}} \quad \textbf{(equation - 1)}$$

Where, the BUI for water is 100. Although, the BUI is useful as a rank order index of brain uptake, 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 PC are 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_{brain}) at time T during the phase of unidirectional uptake, the following equation-2 holds:

$$C_{brain}(T) = PS^{*} AUC_{plt} \quad \textbf{(Equation-2)}$$

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 **[49].**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 **[50].** Drug added to polymer pellet implants intra cranially bypass 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 intreventricular 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 meningitis or for spinal anesthesia/analgesia **[51].**

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 **[52].**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,

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/vector 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. The 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 levodopa[54]. 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 colloid 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 amphoteric 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 potent molecules available in customized formats produces a dismal picture for a vast population waiting to be treated.

REFERENCES

1. Pardridge W.M., Peptide drug delivery to the brain. Raven Press, New York, U.S.A., 1991.
2. Begley, D.J., The blood–brain barrier: principles for targeting peptides and drugs to the central nervous system .J Pharm Pharmacol, 48: 136–146, 1996.
3. Schlossauer, B. and Steuer, H., Comparative anatomy, physiology and in vitro models of the blood-brain and blood retina barrier. Curr Med Chem, 2: 175-186, 2002.

4. Crone, C., The blood–brain barrier: a modified tight epithelium, in Suckling AJ: Rums by MG: Bradbury MWB (eds), The Blood–Brain Barrier in Health and Disease. Ellis Harwood, Chichester, pp 17–40, 1986.
5. Begley, D.J. The blood-brain barrier: principles for targeting peptides and drugs to the central nervous system. J. Pharm. Pharmacol. 1996, 48, 136-146.
6. Begley, D.J. Delivery of therapeutic agents to the central nervous system: the problems and the possibilities. Pharmacol. Therapeut. 2004, 104, 29–45.
7. Garcia-Garcia, E.; Andrieux, K.; Gil, S.; Couvreur, P. Colloidal carriers and blood–brain barrier (BBB) translocation: A way to deliver drugs to the brain? Int. J. Pharmaceut. 2005, 298, 274–292.
8. Nabeshima, S., Reese, T.S., Landis, D.M. and Brightman, M.W., Junctions in the meninges and marginal glia. J Comp Neurol, 164: 127-169, 1975.
9. Brightman, M.W., The intracerebral movement of proteins injected into blood and cerebrospinal fluid of mice, Prog Brain Res, 29:19-40, 1968.
10. Saito, Y. and Wright, E.M., Bicarbonate transport across the frog choroid plexus and its control by cyclic nucleotides, J Physiol, 336: 635-648, 1983.
11. Pardridge, W.M., Recent advances in blood brain-barrier transport. Annu Rev Pharmacol Toxicol, 28: 25-39, 1988.
12. Cornford, E.M., Braun, L.D., Oldendorf, W.H. and Hill M.A., Comparison of lipid-mediated blood–brain barrier penetrability in neonates and adults. Am J Physiol, 243: C161–C168, 1982.
13. Siegal, T. and zylber-Katz, E., Strategies for increasing drug delivery to the brain: focus on brain lymphoma, Clin Pharmacokinet, 41: 171-186, 2002.
14. Fenstermacher J D, Blasberg R G, and Patlak C S (1981) Methods for quantifying the transport of drugs across brain barrier systems. PharmacolTher 14: 217–248.
15. Crone C (1963) Permeability of capillaries in various organs as determined by use of the indicator diffusion method. Act a Physiol Scand 58: 292–305.
16. Crone C (1965) the permeability of brain capillaries to non-electrolytes. Act a Physiol Sc and 64: 407–417.
17. Old end or f WH (1970) Measurement of radio labeled substances using a tritiated water internal standard. Brain Res 24: 372–376.
18. Raichle M E, Eichling J O, and Grubb R L (1974) Brain permeability of water. Arch Neurol 30: 319–321.
19. Raichle M E, Eichling J O, Straat mann M G, Welch M J, Larson K B ,and Ter Pogossian M M (1976)Blood-brain barrier permeability of ^{11}C-labeled alcohols and^{15}O-labeled water. AmJPhysiol 230: 543–552.
20. Enting R H, Hoetelmans R M ,Lange J M ,Burger D M , Beijnen J H , and Portegies P(1998)Anti retroviral drugs and the central nervous system. AIDS 12: 941–1955.
21. Parsons L H and Justice J B (1994) Quantitative approaches to in vivo brain micro dialysis. CritRevNeurobiol 8: 189–220.
22. Boschi G, Launay N, Rips R, and Scherrmann J M (1995) Brain micro dialysis in the mouse. J Pharmacol Toxicol Methods 33: 29–33.
23. De Lange EC, Hesse link M B, Danhof M, de Boer A G, and Breimer D D (1995) the use of intra cerebral microdialysis to determine changes in blood brain barrier transport characteristics. PharmRes 12: 129–133.
24. Van Bree J B, de Boer A G, Danhof M, and Breimer D D (1992) Drug transport across the blood brain barrier.II. Experimental techniques to study drug transport. Pharm WeekblSci 14: 338–348.
25. Takasato Y, Rapoport S I, and Smith Q R (1984) An in situ brain perfusion technique to study cerebrovascular transport in the rat. AmJPhysiol 247: H484–H493.
26. Smith Q R, Takasato Y, and Rapoport S I (1984) Kinetic analysis of L-leucine transport across the blood brain barrier. Brain Res 311: 167–170.
27. Enting R H, Hoetelmans R M, Lange J M , Burger D M ,Beijnen J H, and Portegies P(1998) Anti retro viral drugs and the central nervous system. AIDS12: 1941–1955.
28. Freshney I R (1994) Introduction to tissue culture, in Culture of Animal Cells: A Manual of Basic Technique (FreshneyIRed) 3rd ed, pp1–7, Wiley-Liss, Inc., New York, NY.
29. Harrison R G (1907) Observations on the living developing nervefiber. ProcSocExpBiolMed 4: 140–143.
30. Regina A, Koman A, Piciotti M, ElHafny B, Center M S, Bergmann R, Couraud P O, and Roux F (1998) Mrp1 multi drug resistance associated protein and P glyco protein expression in rat brain microvessel endothelial cells. JNeurochem71: 705–715.
31. Hunter J, Hirst B H, and Simmons NL (1991) Epithelial secretion of vinblastine by human intestinal adeno carcinomace ll(HCT-8andT84) layer sex pressing P-glycoprotein. BrJCancer 64: 437–444.
32. Hong M, Schlichter L, and Bendayan R(2001)A novel zidovudine uptake system in microglia. JPharmacolExpTher 296: 141–149.
33. Miller D S, Nobmann S N, Gutmann H, Toeroek M, Drewe J, and Fricker G (2000) Xenobiotic transport across isolated brain microvessels studied by confocal microscopy. MolPharmacol 58: 1357–1367.
34. Tamail and Tsuji A (2000) Transporter mediated permeation of drugs across the blood brain barrier. J Pharm Sci 89: 1371–1388.
35. Spector R (1987) Ceftriaxone transport through the blood-brain barrier. JInfectDis156: 209–211.
36. Spector R (1988) Transport of amantadine and rimantadine through the blood brain barrier. JPharmacolExpTher 244: 516–519.
37. Rennick B R (1981) renal tubule transport of organic cations. AmJPhysiol 240: F83–F89.
38. Zhang L, Brett C M, and Giacomini K M (1998) Role of organic cation transporters in Drug absorption and elimination. AnnuRevPharmacolToxicol 38: 431–460.
39. Ullrich K J (1994) Specificity of transporters for organic anions and organic cations in the kidney. BiochimBiophysActa 1197: 45–62.
40. Hsyu P and Giacomini K M (1987) The pH gradient dependent transport of organic cations in the renal brush border membrane. Studies with acridine orange. J Biol Chem 262: 3964–3968.
41. Escorbar M R, Wong L T, and Sitar D S (1994) Bicarbonate dependent amantadine transport by rat renal cortical proximal and distal tubules. J Pharma colExpTher270: 979–986
42. Ganapathy V, Ganapathy M E, Nair C N, Mahesh V B , and Leibach F H (1988)Evidence for an organic cation proton antiport system in brush border membranes isolated from the human term placenta. JBiolChem 263: 4561–4568.
43. Prasad P D , Leibach F H ,Mahesh V B , and Ganapathy V(1992) Specific interaction of 5-(N-methyl-N-isobutyl)amiloride with the organic cation proton antiporter in human placental brush border membrane vesicles. Transport and binding. JBiol Chem 267: 23632–23639.
44. Iseki K, Sugawara M, Saitoh N, and Miyazaki K (1993) the transport mechanisms of organic cations and their zwitter ionic derivatives across rat intestinal brush border membrane.II Comparison of the membrane potential effect on the uptake by membrane vesicles. BiochimBiophysActa 1152: 9–14.
45. Zevin S, Schaner M E, Illsley N P, and Giacomini K M (1997) Guanidine transport in a human chorio carcinoma cell line (JAR). PharmRes 14: 401–405.
46. Ullrich K J and Rumrich G (1993) Renal transport mechanisms for xenobiotics: chemicals and drugs. ClinInvestig 71: 843–848.
47. Misra A, Ganesh S, Shah S, Drug delivery to the central nervous system: a review; J Pharm Pharmaceut Sci (www.ualberta.ca/~csps) 6(2):252-273, 2003
48. Sekine T, Cha S H, and Endou H (2000) the multi specific organic anion transporter (OAT) family. PfluegersArch 89: 337–344.
49. Muller M and Jansen P L (1997) Molecular aspects of hepato biliary transport. AmJPhysiol 272: G1285–G1303.
50. Angeletti R H, Novikoff P M, Juvvadi S R, Fritschy J M, Meier P J , and Wolkoff A W (1997) The choroid plexus epithelium is the site of the organic anion transport protein in the brain. ProcNatlAcadSciUSA 94: 283–286.

51. Noe B, Hagen buch B, Stieger B, and Meier P J (1997) Isolation of a multi specific organic anion and cardiac glycoside transporter from rat brain. ProcNatlAcadSci USA 94: 10346–10350.
52. Abe T, Kakyo M , Sakagami H , Tokui T, Nishio T, Tanemoto M, Nomura H, Hebert S C, Matsuno S, Kondo H, and Yawo H(1998) Molecular characterization and tissue distribution of a new organic anion transporter subtype (oatp3)that transports thyroid hormones and taurocholate and comparison with oatp2. JBiolChem273: 22395–22401.
53. Masuda S K, Takeuchi A, Saito H, Hashimoto Y, and Inui K(1999) Cloning and functional characterization of a new multispecific organic anion Transporter , OAT-K2,in rat kidney. MolPharmacol 55: 743–752.
54. Kakyo M, Sakagami H, Nishio T, Nakai D, Nakagomi R, Tokui T, Naitoh T, Matsuno S, Abe T, and Yawo H(1999a) Immuno histo chemical distribution and functional Characterization of an organic anion transport in g polypeptide2(Oatp2). FEBS Lett 445: 343–346.
55. Carver J D (1999) Dietary nucleotides: effects on the immune and gastro intestinal systems. ActaPaediatrSuppl 88: 83–88.
56. Beach J W (1998) Chemo therapeutic agents for human immune deficiency virus infection: mechanism of action, pharmacokinetics, metabolism, and adverse reactions. ClinTher 20: 2–25.
57. Cass C E (1995) Nucleoside transport, in Drug Transport in Anti microbial and Anti cancer Chemotherapy(GeorgopapadakouNHed)pp 403–451,MarcelDekker,Inc., Monticello, NY.
58. Cass C E, Young J D , and Baldwin S A (1998) Recent advances in the molecular biology of nucleoside transporters of mammalian cells. BiochemCellBiol 76: 761–770.
59. Bormann, J., 1988. Electrophysiology of GABA A and GABA B receptor subtypes. Trends Neurosci, 11, 112–116.
60. Panyam, J., Dali, M.M., Sahoo, S.K., Ma, W., Chakravarthi, S.S., Amidon, G.L., Levy, R.J., Labhasetwar, V., 2003. Polymer degradation and in vitro release of a model protein from poly (d,l-lactide-co-glycolide) nano and microparticles. J. Control. Release, 92, 173-187.
61. Bangham, A.D., Standish M M, Watkins, J.C., 1965. Diffusion of univalent ions across the lamellae of swollen phospholipids. J. Mol. Biol., 13, 238-252.