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Central Nervous System: A Review

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Abstract

The current review gives detail insight about central nervous system various barriers like Blood Cerebrospinal fluid barrier, Blood tumor barrier and efflux mechanisms in drug transportation to brain chemical factors affecting inputs to brain and distribution strategy like Invasive strategies, Physiological strategies, Pharmacological strategies which gives a detail idea abour brain transport and central nervous system.

Key Words: CNS, CNS Transport, CNS Drug Delivery, Barriers for drug transport, Distribution of drug in Brain

1. INTRODUCTION

Despite dramatic improvements in brain research, disorders of the brain and central nervous system continue to be the leading cause of disability worldwide, accounting for hospitalizations and long-term care. term more than most other comorbidities. The presence of BBB is a major obstacle to drug delivery to the brain. BBB must be overcome by drugs effective against central nervous system diseases and reach the brain via the hematoma. Understanding the mechanisms involved in uptake and efflux from the brain is essential for the development of drugs that successfully cross the BBB and display the expected therapeutic effects on the CNS. The function of the BBB is dynamically regulated by many cells present at the level of the BBB.

This discovery requires a deeper understanding of the relationship between the drug's structure and the physico-chemical and transport properties of BBB. Although there are good examples of central nervous system delivery of drugs, only a few have developed to the extent that they can be used safely and effectively in humans. Invasive techniques for the treatment of CNS diseases will become less necessary as

pharmaceutical strategies improve. Intravascular administration and invasive neurosurgery procedures to deliver drug chemotherapy to the brain have made significant progress. (1)

2. BARRIERS TO THE DELIVERY OF CNS DRUGS

The inability of systemic drugs to adequately treat many CNS diseases can be explained by considering the various barriers that prevent drugs from reaching the CNS. Cerebral vascular occlusion.

The BBB is now widely recognized as a unique membrane barrier that protects the brain from blood flow. The CNS is composed of blood capillaries that have a unique structure compared to those found in other tissues, creating a permeable barrier between the blood in the brain capillaries and the extracellular fluid in the brain tissue. (2-3)

The capillaries of the brain and spinal cord are lined with a single layer of endothelial cells with no stroma and sealed by tight junctions, allowing rapid transport of solutes from the circulation to the muscles other officials. Other organs (skin, bladder, colon and lungs) have a tight epithelium similar to this natural barrier (4). The BBB is an osmotic barrier composed of the endothelium of the cerebral capillaries. The ventricles are lined by three types of basal cells and glial cells. Astrocytes provide the structural framework of neurons and also maintain their metabolic environment. BBB is produced by the process of astrocytes, or limbs, which extend and enclose and surround capillaries, which are closely related to blood vessels.

Oligodendrocytes generate and maintain the myelin sheath, which surrounds the axon and is necessary for the rapid transmission of action potentials via salutary conduction. Blood-derived mononuclear macrophages are called microglia. Because the endothelial cells are tightly interconnected, there is a very high endothelial resistance of 1500–2000 cm2 compared with 333 cm2 in other tissues, which prevents the water-based intracellular diffusion seen in the endothelial cells. other agencies (5, 6).

Microvessels make up more than 95% of the BBB`s total surface area and are the main route for medicines to enter the brain. The brain's vessels are smaller in diameter and have a thinner wall than those in other organs. Furthermore, brain microvessel mitochondrial density was shown to be higher than in other capillaries, not because of more or larger mitochondria, but because of the brain microvessels' small diameters and, as a result, lesser cytoplasmic area. Because brain capillaries lack intercellular clefts, pinocytosis, and fenestrae, exchange must take place transcellularly. Only lipid soluble solutes that may easily diffuse across the capillary endothelial membrane are permitted to passively flow across the BBB. Other nonspecific exchanges in capillaries from other parts of the body overshadow this exchange. Despite the fact that the human brain's capillaries have a total length of 650 km and a total surface area of 12 m2, this barrier is extremely effective, rendering the brain almost inaccessible to lipidinsoluble substances including polar compounds and small ions. As a result, many promising medications' therapeutic value has been reduced, and cerebral disorders have proven to be the most resistant to treatment. Given the prevalence of brain disorders alone, this is a big issue. (7)

Almost all drugs used to treat brain illnesses today are lipidsoluble and can easily cross the BBB when given orally. Antibacterial blactam antibiotics cause severe convulsions when injected intracerebroventricularly, but due to their poor transport through the blood–brain barrier, they do not cause similar CNS side effects when given intravenously or orally (BBB). Furthermore, grepafloxacin, a lipophilic new quinolone antimicrobial agent, is unable to enter the brain despite being widely distributed in various tissues, avoiding CNS side effects such as headache and dizziness caused by the displacement of gaminobutyric acid (GABA) from GABA receptor binding sites. Because benzodiazepines, such as diazepam, are lipophilic and easily cross the BBB, they have been used as sedative hypnotic drugs. However, cyclosporin A, an immunosuppressive medication that is more lipophilic than diazepam, has a difficult time crossing the BBB. Similarly, almost all lipophilic anticancer medicines, such as doxorubicin, epipodophylotoxin, and Vinca alkaloids (e.g., vincristine and vinblastine), barely permeate the brain, making treatment of brain tumours difficult. Despite its hydrophilicity, levodopa, which is used to treat Parkinson's disease, can easily pass across the BBB. What mechanism underlies the different BBB transport features of apparently structurally and pharmacologically unrelated drugs? Small molecule drugs are transported across the BBB via transporters, while peptide pharmaceuticals are transported via adsorption mediated, to avoid overlap with this fraction. Although some areas of the CNS lack BBB capillary endothelial cells, they contain microvasculature identical to those found in the peripheral nervous system.

Ventricular organs are regions of the brain located near the ventricles (CVOs). CVOs include the choroid plexus, mediastinal gland, neuroarrhythmia, pineal gland, lamina terminalis vascular organ, subchondral organ, subchondral organ, and posterior region. Although capillaries in the CVO brain region are more permeable to solutes, epithelial cells in the choroid plexus and tanycytes in other regions form tight junctions that prevent fluid movement. extracorporeal spinal cord (ECF) to brain ECF. The choroid plexus may be involved when considering peptide drug transfer because it is a major site of CSF production and CSF and ECF can be readily exchanged. In addition, BBB contains an enzyme component. Degrading enzymes are abundant inside endothelial cells, including a large number of mitochondria, which are metabolically active organelles, and solutes that cross the cell membrane then pass through the cell membrane. Contact them. BBB enzymes recognize and destroy most peptides, including naturally occurring neuropeptides. Finally, a high concentration of P-glycoprotein (Pgp), an active drug transport protein, in the cell membranes of the cerebral capillary endothelium enhances BBB. This flow transporter forcefully removes drug molecules from the cytoplasm of endothelial cells before they can enter the brain parenchyma. (8-9)

2.1 Blood Cerebrospinal fluid barrier

The second barrier that injectable drugs must overcome before entering the CNS is the blood-brain barrier (BCB). Because CSF can exchange molecules with the interstitial fluid of the brain parenchyma, BCB regulates the reception of molecules from the blood into the CSF. BCBs, found in the epithelium of the choroid plexus, are built to block molecules and cells from entering the CSF. The second barrier that injectable drugs must overcome before entering the CNS is the blood-brain barrier (BCB). Because CSF can exchange molecules with the interstitial fluid of the brain parenchyma, BCB regulates the reception of molecules from the blood into the CSF. BCBs, found in the epithelium of the choroid plexus, are built to block molecules and cells from entering the CSF. (10)

The choroid plexus, which actively regulates the concentration of chemicals in the cerebrospinal fluid, produces it. The choroid plexus is made up of cauliflower-like masses located in stromal vesicles and is highly vascular. The choroid plexus is mainly present in the fourth ventricle near the base of the brain, as well as in the lateral ventricles of the right and left cerebral hemispheres. The cells of the choroidal epithelium have been modified to have epithelial features. Multiple mitochondria, cerebrospinal fluid lateral microvilli and basal interphase can be found in these ependymal cells. (11)

A continuous membrane of square cells surrounds the choroid plexus, which separates the ventricles. While the choroid plexus capillaries are compressed, discontinuous, and there are spaces between the capillary endothelial cells that allow small molecules to move freely, the choroidal epithelial cells establish. The tight junction prevents most macromolecules from entering the cerebrospinal fluid. However, these epithelial-like cells have modest resistance compared with brain endothelial cells, which have a resistance of about 200 cm2 between blood and cerebrospinal fluid. An active organic acid transport system in the choroid plexus supports the BCB by transporting CSF-transmitted organic acids into the circulation. (12)

As a result, medical organic acids such as penicillin, methotrexate and zidovudine are actively removed from the cerebrospinal fluid, preventing them from diffusing into the brain parenchyma. In addition, there are often significant differences in the composition of cerebrospinal fluid and parenchymal interstitial fluid, confirming the presence of a CSF barrier. This barrier is due to the insurmountable diffusion distance required for the balance between the cerebrospinal fluid and the interstitial fluid. Therefore, just because a drug goes into the CSF does not mean it will reach the brain. (13)

2.2 Blood tumor barrier

Intracranial drug delivery becomes much more complicated when the target is a CNS tumor. The presence of BBB in the microvasculature of CNS tumors has therapeutic implications. When primary and secondary systemic malignancies respond to chemotherapy drugs delivered by the circulatory system, intracranial metastases often continue to develop. If the BBB is significantly compromised, the various physiological barriers common to all solid tumors impede systemic drug delivery in CNS malignancies. Drug delivery to cancer cells is influenced by the diverse distribution of microvasculature across the tumor's interstitium, resulting in spatially uneven drug delivery. In addition, as the tumor grows, the surface area of

the blood vessels decreases, reducing the amount of chemicals in the blood that are exchanged through the blood vessels. Due to elevated tumor interstitial pressure and associated peritoneal edema, the intracapillary distance is increased, resulting in a higher need for drug diffusion to neoplastic cells and increased hydrostatic pressure in the brain parenchyma. Normal next to the tumor. As a result, brain microvasculature in normal brain regions adjacent to the tumor may be even less permeable than in normal brain endothelium, resulting in extremely low drug concentrations in the pericardial interstitium. Brain tumors can interfere with BBB, however these disorders are localized and heterogeneous. Finally, some formidable barriers, such as BBB, BCB and BTB, frequently prevent drugs from reaching the CNS through the systemic circulation. (14,15)

3. EFFLUX MECHANISMS IN DRUG TRANSPORTATION TO BRAIN

Understanding the mechanism of BBB absorption and excretion would be extremely helpful in directing drugs to the brain to achieve desired pharmacological effects on the central nervous system or limiting BBB entry to reduce effects dependent on the central nervous system. Any central nervous system activity is automatically included in most in vivo experimental methods for characterizing drug absorption in the brain. The CNS has several conduction mechanisms that influence drug concentrations in the brain. Some people are inactive, while others are actively involved

Drug penetration at the BBB is often limited by the CNS efflux of activity through specific transporters, less than expected based on the physical properties of the drug, such as potency. lipid solubility. The activity of different flow systems affects the concentrations of free drugs accessible to interact with drug receptor sites in the extracellular fluid of the brain. Transporter protein members of the ABC cassette (ATPbinding cassette) family, such as multidrug resistance protein (MRP), P-glycoprotein (Pgp), and multispecific organic anion transporter (MOAT), have recently been obtained attract a lot of attention. (16, 17). There appear to be five unique isoforms of human MRP, each with varying degrees of expression in different tissues. Pgp is induced in humans by the MDR gene, which actively releases a variety of fat-soluble substrates from cells expressing the gene product. In the choroid plexus, the substrate preference of MOAT is similar to that of MRP. Notably, enhanced brain exposure can be achieved by decreasing the outflow through the BBB as well as increasing the inflow. Thus, increasing brain uptake of drugs that are substrates for specific flow mechanisms requires engineering responses to transporters out of the drug molecule or seeking to inhibit their activity. flow mechanism by concurrent administration of a competitive or non-competitive flow-pump inhibitor with the desired drug. . (18,19,20). For example, when Pgp inhibitors are used with specific Pgp substrates, not only is oral absorption possible, but also the permeability of BBB can be increased. Concomitant administration of Pgp-blocking valspodar to rats not only improved paclitaxel levels in the brain, but also enhanced its therapeutic effect on tumors. Chemical drug delivery systems (CDDS), on the other hand, are the only brain drug delivery techniques that attempt to increase and decrease flow. This is achieved by using a stepwise metabolism that increases inflow through passive diffusion due to increased lipophilicity and then restricts outflow through a "lock-in" mechanism. (20)

4. CHEMICALS FACTORS AFFECTING INPUT

Concepts such as brain penetration, brain absorption, and BBB crossing capacity need to be appropriately explained in order to understand them. Biological activity is a general indicator of brain uptake. The hypnotic activity of several series of fellow CNS depressants peaks when the log octanol-water division (log Po/w) approaches 2. Other investigators subsequently determined accept this finding, and the "rule of two" has become widely accepted. The problem, however, is that biological activity is influenced by at least two factors: (21)

- The rate of transmission from the blood to the brain, or the distribution between the blood and the brain; and
- Drug interactions with certain brain receptors.

If these two components cannot be distinguished, biological activity cannot be used as a measure of transfer velocity or equilibrium. Log Po/w remains the most informative physicochemical metric used in pharmaceutical chemistry and has proven to be valuable descriptors in a variety of situations in the literature. On the other hand, increasing lipophilicity to increase membrane permeability can complicate chemical manipulation while increasing the volume of distribution, including binding to plasma proteins, and affects all pharmacological parameters (22-24). In addition, as lipophilicity increases, the oxidative metabolism of cytochromes P450 and other enzymes accelerates. Therefore, to optimize bioavailability, the effect of lipophilicity on membrane permeability and first-pass metabolism must be modified. (23-25)

A more rigorous measure of brain uptake is the cerebral absorptive index, which involves injecting a mixture of 14C-labelled material and 3H-labeled water into the carotid artery to produce a relative estimate of brain absorptive capacity (i.e. a salt-in-water solution labeled 3H). Radioactivity in brain tissue was examined 15 s after birth, and brain uptake index (BUI) was calculated. (26)

Permeability, expressed as the product of permeable area (PS) or permeation coefficient (PC), is a more accurate measure of the rapid brain uptake resulting from intravenous administration and profile testing. drug in arterial blood. Both PS and PC products are quantitative measures of transport rates obtained by local perfusion and can therefore be analyzed using standard physicochemical techniques. Infusion as a measure of brain uptake has the advantage of identifying PS products in a relatively short period of time, eliminating retrograde pathways and biodegradation. (27)

Despite the existence of several physicochemical studies on cerebral perfusion, no general conclusions can be reached. The following parameters will affect the absorption of a specific organ of interest from the circulation into the parenchyma following systemic administration of the drug: the area under the plasma concentration curve representing

(a) flow organ blood flow,

(b) wall micro vascular permeability, and

(c) drug availability for absorption, are inversely proportional to systemic clearance (AUC).

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), at least three groups can be identified. individual:

(a) substrates are strongly correlated,

(b) substrates with PS values substantially higher than their lipophilic properties suggest, and

(c) substrates have PS values significantly lower than their lipophilic properties suggest.

The transport mechanisms of groups (a) and (b) are passive diffusion and mediated transport, respectively. Substances of group (c) have a molecular weight greater than 400 Da, which is the absolute threshold for significant BBB bridging, regardless of lipophilicity. This molecular weight threshold theory has been proposed to explain how group therapy works (c) Lipid solubility is favorably related to brain uptake, while hydrogen bonding is involved in a negative way. 28

The ability of a chemical to form hydrogen bonds determines its ability to penetrate endothelial cell membranes. The higher the hydrogen bond potential, the lower the absorption in the brain. With each hydrogen bond pair removed, the hydrogen-bonding potential of the steroid hormone homologous sequence is reduced, resulting in a logarithmic increase in uptake. Although the correlations for log PS are not very close, correlations for the cerebral blood distribution coefficients (such as in vivo and in vitro log BB values) using hydrogen-bonding descriptors are known. arrive. (29.30)

Therefore, factors affecting cerebral blood distribution are different from those affecting quantitatively cerebral perfusion. Therefore, when it comes to brain absorptive capacity, it is important to indicate which metric is used. Many in vitro permeability tests and in silico models, as well as many other parameters, have been developed with the aim of determining and predicting the permeability of BBB and integrating this prediction into the early stages of the process. drug development. (31-35).

5. DISTRIBUTION STRATEGY (36)

Due to the variety of psychopharmaceuticals as well as transport mechanisms, drugs

5.1. Invasive strategies

(a) Disruption of the BBB

(b) Organ Transplant

5.2. Physiological strategies

(a) Fake nutrients

(b) Ligand-binding proteins

(c) Turmeric starch peptide

5.3. Pharmacological strategies

(a) Product-based brain targeting

(b) Nanoparticles

(c) Redox chemical delivery system

(d) Liposomes.

(e) Nano conjugates

(f) Vector-mediated distribution

5.1. INVESTMENT STRATEGY

5.1.1. Dispensing drugs by breaking barriers

Because it involves arterial infusion of a barrier opener, transient physicochemical degradation of the integrity of the brain endothelial barrier is considered one of the invasive drug delivery techniques. Intrathecal infusion of membrane-bound substances such as bile salts, oleic acid, the cytostatics etoposide and melphalan, and cytochalasin B is indicated to open the barrier to cancer and low-molecular-weight macromolecules. The BBB is also opened by injecting a low pH buffer solution into the ear. The delivery of low molecular weight cytostatics in brain tumors is enhanced by disrupting hypertonicity with 25% mannitol or arabinose. The underlying mechanisms include endothelial cell shrinkage, tight junction disruption, and osmotic displacement. Prostaglandins, histamine, serotonin, and bradykinin are all vasoactive substances that promote BBB permeability. For example, light microscopy reveals macromolecular and ultrastructural changes in the brain, such as swelling of astrocyte processes and severe mitochondrial damage in neurons. In addition to the development of endothelial spaces and the opening of junction complexes, injured endothelial cells show openness and transport of markers through their cytoplasm. There are additional markers of persistent cellular stress or injury in neurons and glial cells in response to disruption of the hypertonic barrier, as indicated by heat shock protein activation . Osmotic disruption has been used to deliver macromolecular drugs such as monoclonal antibodies, nanoparticles, and viruses to the brain.

5.1.2. Organ transplant

Humans with recurrent malignant gliomas and animals with transplanted gliomas live longer when chemotherapy drugs are delivered to the brain via polymeric implants. The drug is injected through an intracranial polymeric pellet implant that bypasses the BBB and slowly releases the drug molecules into the brain. Because malignant gliomas are found deep in the brain, the effectiveness of polymer-delivered drugs is determined by the ability of the drug molecule to travel a sufficient distance from the implantation site to reach the malignant glioma. count. Researchers implanted biodegradable poly anhydride tablets containing

carmustine [1, 3bis (2 chloroethyl) nitrosourea] into the brains of cynomolgus monkeys to improve the pharmacokinetic basis of macromolecular chemotherapeutic agents. in the human brain. They found that after a single dose of the polymer-encapsulated drug, lower drug concentrations could be maintained at distant sites in the brain.

5.2. PHYSICAL STRATEGIES

Previous procedures were generally geared toward short-term use in the treatment of malignant brain tumours, but chronic degenerative conditions will require long-term treatment. As a result, a non-invasive method for systemic drug delivery to the brain has been developed. **5.2.1. The pseudo-nutrition approach.**

Peptide drugs may have a chemical property that allows one or more inward nutrient transporters to transport the drug more easily. The BBB exhibits different transport systems for nutrients and endogenous substances, and modulation of drug delivery in the brain by these transport systems may be a viable option. These drugs must have a molecular structure similar to that of endogenous nutrients. Hexose and the major nutritional amino acid transporters are at maximum capacity, making them ideal for providing brain substrates.

5.2.2. Ligand-binding proteins

Protein ligands have several properties, including high affinity for receptors and specificity for targeting, which have sparked interest in using proteins to deliver drugs to the brain. Core ligand-binding components such as lectins act as ligand-binding proteins to target the brain of glucose-induced glycosylated insulin and dual-specific antibodies. Ionized albumin seems to be effective in bypassing the BBB and delivering active drugs to the brain. Biotin-binding protein, lipid-binding protein, and avidin-binding protein are examples of ligand binding proteins. Because of their ability to detect an almost unlimited number of ligand molecules, immonoglobins, such as avidin and biotin conjugates, occupy a unique place in the field of ligand-binding proteins.

5.2.3. Turmeric Peptide

Synthetic chimeric peptides are another method of delivering drugs to the brain. At the lateral membrane of brain capillary endothelial cells, a drug (without BBB transport) is bound to a vector, initiating receptor-mediated or adsorption-mediated conversion.

5.3 PHARMACOLOGY STRATEGIES

5.3.1. Product-based brain targeting

Drug absorption in the brain can be enhanced by the production of precursors. Precursors are pharmacologically inactive compounds that result from transient chemical changes in physiologically active species. Often, chemical modifications are made to improve a missing physicochemical property, such as membrane permeability or water solubility.

The precursor is brought closer to the receptor site after injection and remains there for long periods of time due to its enhancing properties. Then an activity form is created, which is usually done in a single activation step. The active molecule is released when the CNS regulator group is hydrolyzed. However,

simple precursors offer some significant limitations. Binding drugs to a lipid component, such as a fatty acid, glyceride, or phospholipid, at the other end of the lipophilic precursor ladder, may be a viable approach to CNS precursors. While greater lipophilicity may aid BBB mobility, it also enhances absorption into other tissues, increasing tissue load. Increased lipophilicity could help drugs get into the CNS and improve efflux mechanisms. This can result in poor tissue retention and a biological response that is too fast. Furthermore, while a prodrug`s only metabolism should be its conversion to the parent drug, alternative routes might occur, and the metabolites produced can contribute to the compounds' toxicity. Poor selectivity, retention, and the potential for reactive metabolites are all characteristics that could conspire to worsen the therapeutic index of medicines disguised as prodrugs, rather than improve it. Prodrug techniques targeting specific membrane transporters, such as amino acids, peptides, and glucose transporters, have recently been investigated by (chemically) modifying the drug to be classified. so that it can become the target of specific membrane transporters, such as amino acids, peptides, or glucose transporters.

5.3.2. Nanoparticles

Solid colloidal particles between 1 and 1000 nanometers in diameter are called nanoparticles. They are macromolecular materials whose working principle is to dissolve, retain, encapsulate, adsorb or bind to it. In many drugs, macromolecular nanoparticles have been proposed as an attractive colloidal system to improve therapeutic efficacy and minimize drug toxicity. Nanoparticles have been shown to be useful in the treatment of both widespread and aggressive brain tumors. Polysorbate-coated 80 nanoparticles containing doxorubicin injected intravenously cured 40% of glioblastoma mice that received intracranial transplantation. Another study showed that polyethylene glycol PHDCA (nexa decyl cyanoacrylate) nanoparticles generated from the amphiphilic copolymer of polyethylene glycol penetrated deeper into the brain than all other nanoparticle formulations tested. , while maintaining BBB permeability. The results also highlight two important factors in the development of an efficient brain delivery system: the long-circulatory character of the medium and the suitable surface characteristics for interactions with endothelial cells. Nanoparticles containing valproic acid reduce the harmful side effects of valproate therapy by inhibiting the synthesis of dangerous metabolites rather than reducing the required therapeutic dose. Finally, the biodegradable polymer delivery method offers a significant possibility to deliver drugs directly into the interstitium of the brain.
5.3.3 Enhancement of the drug transport across the BBB by means of nanoparticles

1) Nanoparticles are absorbed on the inner surface of brain blood arteries, avoiding transport across the endothelium.
2) The surface activity of the surfactant polysorbate 80 improves drug transport through the brain by fluidizing the endothelium.
3) Another possibility to improve drug delivery across the BBB is the opening of tight junctions between the endothelial cells of the brain.

4) Currently, the most plausible mechanism for drug delivery into the brain is intracellular uptake by endothelial cells lining the blood vessels of the brain. These cells are part of the traditional reticuloendothelial system and are responsible for granulomatous endocytosis. Following endocytosis, drug delivery to brain cells can occur by desorption of the drug from the nanoparticle with or without nanoparticle destruction.
5) Cell transfer through brain endothelial cells is another method of delivering drugs to the brain. Through nanoparticle cell transfer, the adsorbed nanoparticles and drugs can be transported to other brain cells after being taken up by endothelial cells.
6) Inactivation of the p-glycoprotein flux pump may enhance the transport of nanoparticles in the brain. Dalargin, loperamide and tubocurarine are some of the drugs that have been successfully delivered across this barrier by nanoparticles.

5.3.4. Redox chemical delivery system

Chemical delivery (CD) systems are novel, systematic methods for delivering biologically active materials to specific target organs based on predictable enzyme activation and need to be controlled. included in every drug targeting system, including chemoresistance. At least one chemical bond must be broken to release the active ingredient. Two types of bioavailable fragments are used to convert the drug to an inactive precursor form. [F1 - Fn] regulatory functions act as lipolysis, protecting specific processes, or fine-tuning the molecular features needed to avoid premature metabolic switching. [F1 - Fn] regulatory functions act as lipophilic functions, protecting certain functions or modulating molecular properties necessary to prevent premature undesired metabolic conversions . A target fragment [T] is responsible for targeting, site specificity, and locking, while adjuvant [F1 - Fn] functions act as lipophilic, protecting certain functions or modulate the molecular properties required to prevent premature metabolic changes. A precursor is distinguished from a DC by the absence of T fragments. DCs based on the redox conversion of lipophilic dihydropyridine to the lipid-insoluble pyridinium ion salt have been developed to improve CNS access to therapeutic drugs. CDS dihydropyridinium or its redox analogue is lipophilic enough to enter the brain by passive transport, where it is then oxidized by enzymes to the pyridinium ion compound, which enhances CNS retention central and can be considered "locked". The fact that the same transition occurs in the rest of the body accelerates peripheral elimination, facilitating brain targeting, aiding in target identification.

5.3.5. Liposomes

Bangham was the first to describe liposomes, which are lipid vesicles. Liposomes were created as a model for biofilms. Liposomes are well-defined lipid vesicles that have the advantage of allowing drugs to be targeted to specific tissues through transformations mediated by either passive or active mechanisms.

Liposomes are biocompatible, nontoxic and biodegradable carrier structures that can transport hydrophobic, hydrophilic or amphoteric compounds. Drugs, enzymes, proteins, anticancer compounds and other macromolecules may be carried by them. Reduced systemic toxicity and targeted drug delivery to the tumor are two advantages of liposome-based cancer therapy. According to recent studies, a novel formulation of small (less than 100 nm) long circulating liposomes seems to offer selective tumor localization. This localization is most likely due to the long circulation time of the liposomes, which increases the likelihood of tumor vascular endothelial spread. In several systemic models, tumor-specific localization of doxorubicin encapsulated in stealthy liposomes (SLs) has also been shown to be associated with enhanced therapeutic effects on free drug activity.

5.3.6. Nanoconjugates

They are low molecular weight conjugates of a small drug or toxin that target ligands and are linked together by a separable bond group. They have three functional domains: the targeting region, the linker, and the addictive/active agent. Convection and diffusion are used to transport and deliver drugs in the interstitium.

5.3.7. Vector-mediated distribution

In vector-mediated drug delivery to the brain, chimeric peptide technology is used to combine a drug that cannot be delivered with the BBB transporter vector. The latter is a receptor-specific monoclonal antibody or modified protein that crosses BBB in vivo through receptor-mediated cell transfer. Drug carrier conjugation can be facilitated by chemical binders, avidinbiotin technology, polyethylene glycol and liposome binders. Peptide pharmaceuticals as an active peptide analog and neurons as brain-derived neurotrophic factor, antisense drugs such as peptide nucleic acids (PNA) and small molecules are encapsulated packages in liposomes were delivered to the brain at the same time using chimeric peptide technology. Alternatively, the drug can be attached to the transport vector by an indivisible connection, such as an amide bond. Cleavage refers to the reduction of disulfide bonds in this case since all bonds including the amide bond are hydrolyzed in the lysosome compartment. For some peptide treatments, polyethylene glycolation technology is used with a longer buffer arm consisting of a polyethylene glycol base with molecular weight 20003400 if a disulfide linker and inactive drug are not desired. After conjugation via the amide linker.

5.3.8. Lung birth

This procedure involves the introduction of a drug into the patient's airway to deliver it to the pulmonary system, such as the alveoli or deep lung particles that contain the drug. The preferred grain density is 0.4 g/cm3. Other ingredients, such as phospholipids, amino acids, or combinations thereof, may be included in the ingredients along with the drug. The drug is administered at a dose that is at least twice the dose required for oral administration.

Conclusion

This review throws light on all the aspects of Central nervous system and brain transport mechanism and gives idea about the barriers and factors affecting distribution.

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