The blood-brain barrier and drug delivery in the central nervous system

Gecioni Loch-Neckel, Janice Koepp

Aim. To provide an updated view of the difficulties due to barriers and strategies used to allow the release of drugs in the central nervous system.

Introduction. The difficulty for the treatment of many diseases of the central nervous system, through the use of intravenous drugs, is due to the presence of barriers that prevent the release of the same: the blood-brain barrier, blood-cerebrospinal fluid barrier and the blood-arachnoid barrier.

Development. The blood-brain barrier is the main barrier for the transport of drugs in the brain that also acts as a immunologic and metabolic barrier. The endothelial cells of the blood-brain barrier are connected to a junction complex through the interaction of transmembrane proteins that protrude from de inside to the outside, forming a connection between the endothelial cells. The transport of substances to the brain depends on the mechanisms of transport present in the barrier and the diffusion of these compounds also depends on the physicochemical characteristics of the molecule. Some diseases alter the permeability of the blood-brain barrier and thus the passage of drugs. Strategies such as the use of methods for drug delivery in the brain have been investigated.

Conclusions. Further details regarding the mechanisms of transport across the blood-brain barrier and the changes in neuropathology would provide important information about the etiology of diseases and lead to better therapeutic strategies.

Key words. Blood-brain barrier. Central nervous system. Drug delivery. Tight junctions.

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Introduction

The blood-brain barrier (BBB) is a structural, biochemical and transport barrier, highly specialized, consisting of vessels formed by endothelial cells, connected by tight junctions and surrounded by astrocyte foot processes. The BBB selectively prevents the passage of certain substances to the brain interstitium. Many drugs are useful in the treatment of systemic disorders but are ineffective concerning similar disturbances of the central nervous system (CNS) due to their inability to cross the barrier: neuropeptides, proteins and chemotherapeutic agents are important examples of the therapeutic, where lays the difficulty in transposing this barrier. The BBB and its cellular components and molecular changes observed in diseases that affect the CNS and the difficulties and strategies used for drug delivery to the CNS are presented in this review.

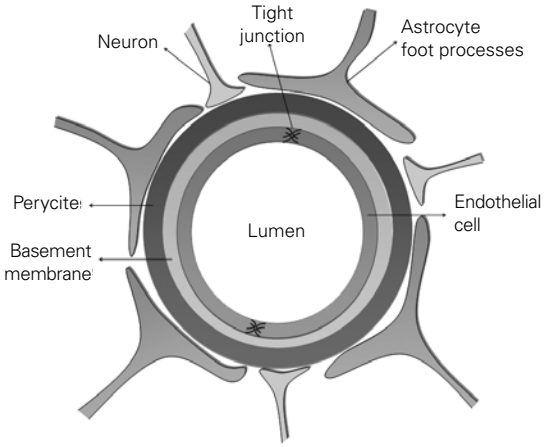
Barriers to drug delivery in the CNS

There are three barriers that limit the transport of drugs to the brain parenchyma: the blood-brain barrier (BBB), formed at the interfaces of blood vessels; the blood-cerebrospinal fluid barrier (BCSFB), localized in the choroid plexus and a third barrier, the blood-arachnoid barrier, that is the arachnoid layer of the meninges [1].

Blood-brain barrier

The BBB is a unique membranous barrier that separates the brain tissue from the circulating blood. In the CNS the blood capillaries are structurally different from the capillaries of other tissues, they are covered by special endothelial cells, without pores and sealed with tight junctions. This obstacle to permeability that is the brain capillary endothelium is known as the BBB [2,3].

Figure 1. Schematic drawing of the blood-brain barrier in transverse section showing endothelium, basement membrane, pericytes, astrocytes, and tight junctions.



Blood-cerebrospinal fluid barrier and the blood-arachnoid barrier

The BCSFB is located in the epithelium of the choroid plexus, consisting of the arachnoidal epithelium and choroid, which allows access to ventricular cerebrospinal fluid and subarachnoidal, respectively. Due to its location and direction of cerebrospinal fluid flow (CSF), the choroid epithelium in the choroid plexus is considered the most important part of BCSFB. The permeability of drugs in the choroid plexus seems to be higher than that of the endothelium tight junctions of the BBB [4,5]. The blood-arachnoid barrier is a single layer of epithelial cells strategically located as 'intermediate cells' between the CSF and the brain, preventing most macromolecules to pass from blood to CSF [6].

Anatomy and physiology of the BBB

Properties of the BBB

As the surface area of the BBB is about 1000 times larger than the area of BCSFB, it can be considered the most important barrier for the transport of drugs in the brain, which also acts as a metabolic and immunological barrier to the brain. Its functionality is affected by physiological and pathological processes, which can also affect the transcellular and paracellular transport of drugs [7,8]. In addition, the BBB prevents changes due to an exchange of molecules and ions between the blood and extracellular space and allows isolation of extracellular space in relation to blood [9].

Cellular components of the BBB

The BBB consists of capillary endothelial cells, although other cells such as pericytes, astrocytes and neuronal cells also play an important role in differentiation and maintenance of function of the BBB. The endothelial cells of the brain capillaries are distinguished from those in the periphery due to the presence of continuous tight junctions, no fenestrations, virtually lack of pinocytosis and are composed of two plasma membranes in series, forming a continuous endothelium [10]. They are also covered by a basement membrane and extracellular matrix, pericytes, as well as by neuronal endings and astrocytes end-feet that cover more than 90% of the endothelial cell surface and that mediate the permeability of the BBB (Fig. 1). Moreover, endothelial cells have a negative surface charge that repulse negatively charged compounds. These cells also have many mitochondrias, enzymes and various systems for selective active transport of nutrients and other substances to the inside and outside of the brain [7,11].

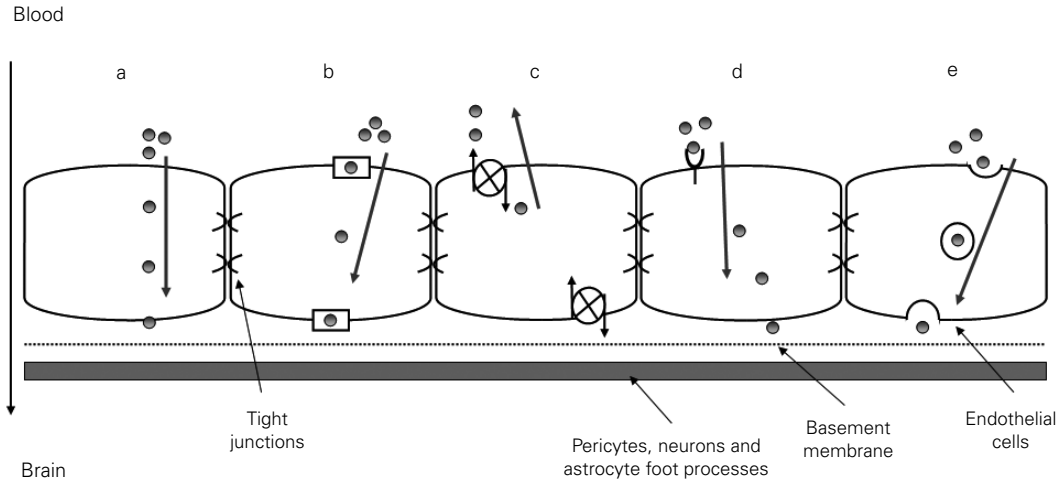
Components of structural integrity of the BBB

The tight junctions and adherents junctions form a complex integration between adjacent endothelial cells (Fig. 2). The endothelial cells of the BBB are connected to a junction complex in the most apical section of the plasma membrane of adjacent cells, produced by the interaction of several transmembrane proteins that protrude from the cytoplasm, by proteins associated with cytoplasmic actin, forming a connection between the endothelial cells [5,12,13].

Transmembrane proteins

Tight junctions are fundamentally consisted of three transmembrane proteins: occludin, claudins and junctional adhesion molecules (JAMs). Occludin is a protein of 60 to 65 kDa containing four transmembrane domains linked to two extracellular portions rich in tyrosine in the cytoplasmic amino and carboxy-terminal domain [14]. It has been shown that the cytoplasmic domain of occludin is highly phosphorylated and is associated with high electrical resistance and decreased cell permeability [15].

Figure 2. The various transport systems that may occur in the BBB: a) Passive permeability; b) Carrier-mediated transport; c) Active efflux transport; d) Receptor-mediated transport; e) Adsorption-mediated transport.



The claudins (20-24 kDa) share with occludins very similar positions in the membrane, but do not contain any homologous sequence. These proteins have four transmembrane domains, two highly charged extracellular portions with amino acids side chains and cytoplasmic tail with an important role in signal transduction. They form dimers and bind to other molecules of claudin in adjacent endothelial cells, forming the primary connection of the tight junction and seem to determine barrier function [12]. The JAMs (40 kDa) belong to the immunoglobulin superfamily, which link the membranes of adjacent cells through homophilic interactions of a single transmembrane chain with a large extracellular domain [16]. The JAMs are involved in the union and maintenance of tight junctions and are very important in the functional changes in the junctions, as the increase in electrical resistance and reductions in paracellular permeability [17]. Tight junctions represent a series of diffusion barriers that contain fluctuating channels, which could explain the relationship between the number of intramembrane strands and the high electrical resistance across the BBB [12].

Cytoplasmic accessory proteins

The intracellular transducers are also important for the formation of tight junctions and many intracellular proteins contribute to such composition. Examples include well-characterized three protein complexes known as zonula occludens (ZO), the ZO-1, ZO-2 and ZO-3. These proteins are members of a family of membrane-associated guanylate kinases (MAGUK) and serve as support, connecting multiple intracellular components and cell surfaces at the tight junction. ZO-1 connects the transmembrane proteins of the junction with actin cytoskeleton and is associated with an increased permeability of the barrier. ZO-2 is homologous to ZO-1 and binds to transmembrane proteins of tight junction and transcription factors [16,17].

Passage of drugs through the BBB

Although the cells in the microvasculature of the brain contribute to the physical barrier of the BBB, the permeability properties of the BBB are only controlled by the capillary endothelial cells. The movement of solute through the capillary endothelial barrier occurs through the two membranes, the luminal and aluminal endothelial cells, which are separated by cytoplasm with only 200 nm [18].

There are several transport systems involved in the uptake of compounds by the brain through the BBB (Fig. 2) and include the passive transport (simple diffusion of lipophilic molecules) and active transport (transport mediated by carriers, receptors, and adsorption and active efflux transport) [19].

Passive permeability

In order to drug freely permeate through the cerebral endothelium, an important requirement is the hydrophobicity of the molecule [6,20]. However, lipophilic molecules must have molecular weight below 600 Da to passively enter the membrane [21]. Moreover, predictions about the permeability also include the potential of the molecule to bind to hydrogen ions. Thus, the replacement of hydrogen binding groups by groups that do not have affinity for these ions, increases the lipophilicity of the molecule [22]. However, these two factors could reduce the retention time in the plasma due to the rapid elimination of highly lipophilic molecules and the poor solubility of these substances in body fluids [23].

Carrier-mediated transport

The carriers are transporters restricted to the membrane and transport relatively small molecules across the endothelial cell membrane, used to facilitate the passage of nutrients such as hexose, nucleoside, purine base, amino acids to the brain. At least eight different systems of nutrients carriers were identified, each carrying a group of identical structures [1]. This type of transport is substrate selective and the rate of transport is dependent on the degree of occupation of the carrier, and may be influenced by competitive and non-competitive inhibitors [24].

Active efflux transport

Functional transporters of organic anions are also present in the BBB and restrict the capture of certain drugs and molecules into the brain. These systems are known as efflux transport and include P-glycoprotein (P-gp) that is a cell surface-expressed glycosylated member of the ATP-binding cassette (ABC) transporters superfamily. P-gp is also known as multidrug resistance protein (MRP) and is involved in the clearance of drugs from the brain parenchyma, examples of which include chemotherapeutics, antibiotics, ion channel modulators, and immunosuppressants. Some MRPs are expressed in the microvessels of the brain, including breast cancer resistance protein (BCRP) and members of the organic anion transporter polypeptide (OATP) family, which mainly regulate the efflux of anionic compounds. All these carriers are able to work together, reducing the penetration of many drugs into the brain as well as increasing their efflux from the brain [13,17,25].

Receptor-mediated transport

The receptor-mediated transport is a process initiated by the endocytosis of ligand-receptor complex. Then, it is involved in an endosomal compartment that can be transported to lysosomes or along the cytoplasm for exocytosis. This type of transport is energy- and temperature dependent and saturable. The receptors are capable of transporting large molecules such as proteins and small particles. To date, several receptors have been shown to reside at the BBB, including insulin, transferrin, insulin-like growth factors (IGF), leptin and low density lipoprotein [26].

Adsorption-mediated transport

The plasma membrane surface of the brain capillaries is negatively charged at physiological pH due to the presence of proteoglycans, mucopolysaccharides, and sulphate- and sialic acid-containing glycoproteins and glycolipids. Transport by adsorption occurs as a result of an electrostatic interaction between the positively charged moiety of the peptide and negatively charged region of the plasma membrane surface region. This type of transport is saturable and non-specific and occurs at very low level under physiological conditions. Because of these properties, adsorption-mediated transport have been extensively studied as approaches to enhance the delivery of peptides and proteins into the brain [1,20]. The molecules that penetrate the BBB by adsorption include various cationic proteins such as protamine, polylysine, glycated albumin, histone and avidin [19].

Alterations in the integrity of the BBB in some conditions and implications for the passage of drugs

Changes in function of the BBB have been described in several neurological disorders, including inflammatory, infectious, and brain tumors, not only as one of the last events, but are believed to be involved in the early stages of progression of some diseases [14,27].

Brain tumors

The passage of drugs through the BBB is not the unique limitation in the treatment of brain tumors. Other factors such as resistance to anticancer agents and poor perfusion of the tumor vessels

interfere in reaching the effective concentrations of therapeutic agents [28]. Structural changes as loss of expression of proteins such as claudin-3 and occludin were observed in some experimental models of glioma in animals as well as in human primary tumors. The level of expression of occludin proportionally decreases with the increase of the severity of the tumor [29]. There is an increase in the number and size of pinocytic vacuoles and it has also been reported a decrease in the expression of transporters in the endothelial cells forming the tumor vasculature [30]. The use of chemotherapy has been reported as being limited due to the fact that the BBB restricts the accumulation of conventional cytotoxic agents in therapeutic concentrations into the tumor and peritumoral area. Only highly lipid-soluble and low molecular-weight alkylating agents, like nitrosoureas or temozolamide, are able to penetrate into BBB to reach the affected brain tissues. The accumulation of drugs in brain tumors is limited even in the presence of the damaged BBB due to high interstitial fluid pressure, which reduces the spread of drugs in tumor tissue and also the diffusion to the external surrounding brain tissue [29-31].

Inflammation

When inflammation is primary, resulting from an infection or an autoimmune disease, or secondary, the loss of BBB integrity and increased permeability of endothelial membrane are associated with the presence of vasoactive cytokines such as TNF-α, interleukin-1β, interferon-γ and histamine, beyond growth factors. JAMs may sustain the recruitment of leukocytes and promote the movement of these cells across the junctions [32,33]. Metalloproteinases (MMP-2 and MMP-9) and adhesion molecules (ICAM-1) can attract leukocytes and thus change the permeability of the endothelial membrane [34]. In addition to disrupting the BBB, pro-inflammatory factors may also mediate the degeneration of astrocytic and neuronal death [35]. Some experimental inflammatory conditions were associated with changes in the expression of proteins such as ZO-1 and occludin [36]. In clinical practice, corticosteroids are the drugs of choice in the treatment of neuroinflammations since they decrease the opening of the BBB, while the agents capable of reducing the passage of immune cells across the barrier, such as interferon-1α, interferon-1β and glatiramer acetate, are used in the treatment of multiple sclerosis [37].

CNS infections

In the presence of the intact BBB, many microorganisms are excluded from the brain. Only a few pathogens can cross the BBB via transcellular, paracellular and/or by phagocytes infected, and thus cause infections in the CNS [38]. Studies in humans and in animal models relate the magnitude of the development of bacteremia and meningitis and it has been shown that the interaction of microorganisms with the receptor of endothelial cells of the BBB are important steps in the pathogenesis of meningitis [39]. The mechanism of entry of mycobacteria such as *Mycobacterium tuberculosis* is unclear. Bacteria induce, by means of the release of lipopolysaccharide (LPS) or toxins, the secretion of cytokines and inflammatory factors (TNF-α, IL-1β, MMPs, TGF-β1, caspases) that increase endothelial permeability [40,41]. Fungi, as *Cryptococcus neoformans*, appear to be internalized by endothelial cells of the cerebral microvasculature while not causing changes in the cells integrity. Another fungus common in meningitis, *Candida albicans*, seems to cross the endothelial cells by transcytosis, without, however, affecting the integrity of these cells [42,43]. The entry of some viruses in the CNS is through the olfactory nerves or spinal cord, although the penetration of HIV can be accomplished by infected monocytes or mechanisms of endocytosis in response to cytokine release. *Post mortem* immunohistological studies have revealed that in HIV encephalitis there was a reduction in the expression of claudin-5 and occludin in cerebral endothelium. Corticosteroids are sometimes used to decrease the inflammatory damage in infections, but can restore the integrity of the BBB, thereby decreasing the release of antibiotics and difficulting the elimination of the pathogens from the CNS [37].

Neurodegenerative diseases

Neurodegenerative diseases like Alzheimer's and Parkinson's disease may also play changes in the permeability of the BBB. It is believed that cellular components of the inflammatory response may greatly contribute to increase the area of secondary injury in acute and chronic neurodegenerative diseases [44]. The increase of permeability has been hypothesized as a potential vascular mechanism by which the β-amyloid protein accumulates in the brain parenchyma in Alzheimer's disease. The oxidative stress generated in the brain can trigger changes in the BBB, possibly cell death, gliosis and changes in signaling that were related to ageing and

increased expression of amyloid precursor protein [45,46]. Changes in this pathology seem to be due to vascular factors and cellular degeneration and abnormal signaling. Thus, the disruption of the barrier can accelerate events of the disease, resulting in a vicious cycle. Small peptides or 'breaker peptides' have been shown to cross the BBB, decreasing the presence of neurofibrillary tangles and to reverse cognitive impairments in animal models of Alzheimer's disease, preventing or reversing the oligomerization and fibrillation of amyloid β protein [4]. In Parkinson's disease, there is a transient opening of the BBB associated with the secretion of inflammatory mediators, although most of the damage occurs in the BCSFB. Several studies have shown that neurodegeneration alone can lead to disruption of the BBB. In any case, the inflammation as a pathogenic mechanism in Parkinson's disease appears to be responsible for the increased permeability of the BBB [35,46]. In addition, ageing is related to changes in the BBB, with decreased activity of P-glycoprotein (Pgp), resulting in decreased extrusion of toxins.

Acute ischemia/hypoxia

Cerebral ischemia is an insult that involves decreased blood flow and the depletion of oxygen and essential nutrients, linked to increased vascular permeability. Ischemia or hypoxia leads to changes in the integrity of the BBB after trauma and shock. The integrity of the BBB varies according to the mechanism, severity and duration of the event that causes the cerebral ischemia. During the acute phase stroke, the BBB undergoes rapid change within the first three hours. The blood-brain barrier permeability is increased after ischemia, reaching a maximum 48 hours after and reduced in the fourth day. Endothelial dysfunction is responsible for such increase in permeability during cerebral ischemia and triggers the extravasation of plasma components and edema formation. Activation of microvascular angiogenesis is the first event generated during ischemia [36,44]. In any case, the increased permeability of endothelial cells are affected by oxidative stress generated, associated with tyrosine phosphorylation of proteins in the tight junctions, especially occludin and ZO-1. However, astrogliais cells protect the BBB from ischemic conditions secreting neurotrophic factors, restoring the barrier function of the tight junctions. Endothelial dysfunction results in increased permeability during cerebral ischemia, resulting in leakage of plasma components and formation of edema [47]. Changes in permeability of the BBB may represent an opportunity for the administration of drugs to the CNS. However, the permeability of the BBB after acute injury may follow a heterogeneous pattern in time and space. Moreover, the blood flow in ischemic regions is reduced, which may result in a limited concentration of drug to the site.

Strategies for drug delivery in the brain

The main challenge in the treatment of diseases of the CNS is the development of efficient methods that allow the diffusion of drugs through the BBB. A wide variety of strategies have been investigated to enable the release of drugs in the brain (Fig. 3).

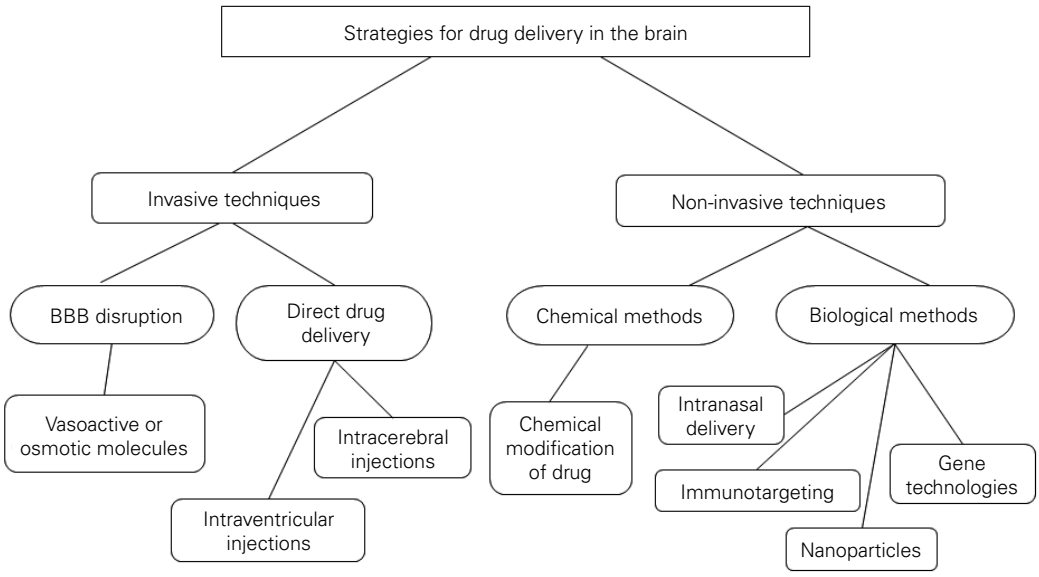
BBB disruption

The use of hyperosmotic solutions was among the first to be used in humans and it was developed by Neuwelt et al [48]. This technique is still used in the clinic for the release of chemotherapy in patients with brain tumors but this method causes more side effects and unintended release of anticancer agents on normal brain tissue [49]. Vasoactive molecules such as leukotriene C4, bradykinin, serotonin and histamine have also been employed to increase the permeability of capillaries in brain tumors. Unlike osmotic agents, bradykinin analogues are selective in human tumors compared to normal brain. However, the opening of the barrier is not a specific method to release drug as it leads to an increase of potentially toxic molecules such as albumin, and makes the brain vulnerable to infections and toxins even for brief periods [50].

Direct injection

An alternative to crossing the BBB is the introduction of drug directly to brain parenchyma. The main obstacle to this method is the limited diffusion coefficient associated with the slow movement of compounds within the brain. The diffusion of the drug in the brain depends on the concentration at the site of release, molecular weight, lipid solubility, polarity and affinity of tissues. For large molecules such as monoclonal antibodies, the rate of diffusion after the injection is often lower than the rate of local clearance. Some polymeric implants have been investigated for the use in humans and animals after surgical resection of brain tumors, releasing the drug in a controlled manner [51].

Figure 3. Schematic representation of strategies for drug delivery in the brain.



Intraventricular delivery

Recent studies have shown that the effectiveness of direct intracerebroventricular administration of drugs is limited. In addition to the required surgical intervention, there are other problems with this approach, the diffusion coefficient is highly dependent on the molecular weight of the solute and is dependent also on the rate of clearance from the CSF within the ventricles [52]. As the CSF is completely renewed in 5-6 hours, the injection of the drug would become equivalent to the slow intravenous infusion. In practice, this method would be effective for drugs where the site of action is near the surface of the parenchyma or the ventricles [53].

Chemicals methods

The chemical modification is usually designed to replace a deficiency in the physical-chemical properties, such as increase the lipophilicity and/or minimize the binding potential to hydrogen. Thus, esterification or amidation of drugs containing hydroxy groups or amino acids could increase the solubility and thus the entry to the brain. Although lipidization substantially increases the drug permeability of the BBB, it also increases its permeability in peripheral tissues, resulting in a decrease of the area under the plasma curve [19].

Immunotargeting

The use of monoclonal antibodies to receptors on endothelial cells provide an effective vectorization for the release of drugs. For this, it should recognize a specific transport mechanism of the BBB and the drug to be released must have high intrinsic activity at the receptor [51]. Unfortunately, it is difficult to find specific antigens which provide a single effect of vectorization. Another method of targeting uses sugars or lectins, which can be targeted to specific receptors found on tumor cell surfaces [54].

Intranasal delivery

An alternative route for drug delivery in the CNS is intranasal administration. The drugs released by this route are transported via olfactory sensory neurons reaching significant concentrations in the CSF and in the olfactory bulb. The release of drugs by nasal routes involves intraneuronal or extra-neuronal routes and has been demonstrated feasible in clinical studies in humans [55]. The difficulties to

be overcome include the low pH and high enzymatic activity of the nasal epithelium, the possibility of mucosal irritation or high variability caused by nasal pathology, such as a common cold. This method has as the main advantage the fact of not being invasive, and avoids first pass metabolism of the intestinal wall and liver [2,55].

Nanoparticles

Nanoparticles include nanospheres and nanocapsules and can be obtained from polymers or lipids, characterized by size which ranges from 10 to 1000 nm. Relatively large amounts of drugs or active ingredient can be incorporated in these structures, allowing the release in the CNS. The surface of nanoparticles can be modified as well as the binding to functional groups for the targeting through the specific mechanisms of the BBB and that would allow targeting of drugs to cells and tissues, improve bioavailability, increase the diffusion through biological membranes and/or protect them against enzymatic inactivation [56]. Moreover, the use of nanoparticles allows the access of drugs that usually do not penetrate the BBB, masking its physical-chemical characteristics by means of encapsulation in these systems [54].

Gene technologies

Several untreatable brain diseases by conventional therapeutic methods represent perspectives for the application of gene therapy. Progress has been achieved through the use of endogenous peptides, modified proteins or monoclonal antibodies linked to the BBB endogenous transporters, also known as chimeric peptides [18]. As these molecules are water soluble and too large to cross the BBB, it is used the so-called molecular 'Trojan horses', endogenous peptides or peptidomimetic monoclonal antibody that cross the BBB via receptor-mediated transport [29]. To allow the stability of these molecules in vivo, plasmids are incorporated into liposomes protecting its degradation by nucleases, which in turn are stabilized with polyethylene glycol (PEG) on their surface, in order to increase the detention time in the bloodstream. A small proportion of PEG molecules are produced linked to peptidomimetic monoclonal antibodies that bind to receptors on cells of the BBB, for example, there are the insulin and transferrin receptors. Other vectors used are proteins such as albumin or OX26 monoclonal antibody, which also use the transport mediated by receptors of the BBB [57].

Conclusion

The BBB is an active tissue that protects the brain from the outside, and at the same time, hinders the passage of drugs to the CNS. The treatment of CNS disorders is a challenge to the release of active molecules to the brain and is often impaired by the range of metabolic, physiological and biochemical barriers that together form the BBB. Different strategies have been used to circumvent these difficulties by using invasive and non-invasive techniques. Each one has advantages and disadvantages and their use depends on the therapeutic goal. Optimization techniques for drug delivery, combined with studies based on dynamic changes of the BBB in some conditions could improve the efficacy of substances already in use in the clinic or new drugs to treat these disorders. Overall, the changes in the brain parenchyma, as a result of damage occurred in the BBB, may affect the penetration and distribution of drugs, contributing to the phenomena of pharmacological refractoriness. Further details regarding the mechanisms of transport across the BBB and the changes in neuropathology would provide important information about the etiology of the diseases and would lead to better therapeutic strategies.

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La barrera hematoencefálica y la administración de medicamentos en el sistema nervioso central

Objetivo. Ofrecer una visión actualizada de las dificultades debido a las barreras y estrategias usadas para permitir la liberación de medicamentos en el sistema nervioso central.

Introducción. La dificultad en el tratamiento de muchas enfermedades del sistema nervioso central, mediante el uso de fármacos por vía intravenosa, se debe a la presencia de barreras que impiden la liberación de éstos: la barrera hematoencefálica, la barrera sangre-líquido cefalorraquídeo y la barrera sangre-aracnoides.

Desarrollo. La barrera hematoencefálica es la principal barrera para el transporte de medicamentos en el cerebro, que actúa también como una barrera inmunológica y metabólica. Las células endoteliales de la barrera hematoencefálica están conectadas a un complejo de uniones mediante la interacción de proteínas transmembranales que sobresalen del interior hacia el exterior, formando una conexión entre las células endoteliales. El transporte de sustancias al cerebro depende de los mecanismos de transporte presentes en la barrera y la difusión de estos compuestos depende también de las características fisicoquímicas de la molécula. Algunas enfermedades alteran la permeabilidad de la barrera hematoencefálica y, por lo tanto, el paso de los medicamentos. Se han investigado diferentes estrategias como métodos para la administración de medicamentos.

Conclusiones. La obtención de un conocimiento más profundo de los mecanismos de transporte a través de la barrera hematoencefálica y los cambios en la neuropatología proporcionarían una información importante sobre la etiología de algunas enfermedades y conduciría a mejores estrategias terapéuticas.

Palabras clave. Administración de medicamentos. Barrera hematoencefálica. Sistema nervioso central. Uniones estrechas.