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Central nervous system diseases and the role of the blood-brain barrier in their treatment

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Abstract

The Neurodegenerative diseases, cancer and infections of the brain are becoming more prevalent in society as population become older. Nowadays, these diseases represent a major medical challenge, so neuroprotective therapeutics have the potential to play a key role in managing this growing global burden of long-term neurological care. Despite major advances in neuroscience, treatment for these diseases is still a challenging area due to the presence of the blood-brain barrier. Conventional therapeutics remain critically below levels of optimum therapeutic efficacy, since the blood-brain barrier ensures that many potential therapeutics cannot reach the central nervous system. Hence, the current challenge is to develop drug-delivery systems which ensure that drugs cross the blood brain barrier in a safe and effective manner. Robust methods to assess Central Nervous System permeation are therefore essential for drug discovery. Drug candidates can be successfully designed to cross the blood-brain barrier, but for those that can't cross it, a delivery system that facilitates the movement of drug candidate across the barrier may possibly enable this entry. In order to assess the drug capacity to cross the brain, animal models of neurological disorders are increasingly employed. This review focuses on the properties of the blood-brain barrier that restrict drug delivery to the brain as well as on some of the most hopeful strategies developed to study and enhance drug delivery across the blood-brain barrier.

Keywords: Brain diseases, blood-brain barrier, drug delivery systems, animal diseases models

Introduction

The human central nervous system (CNS) is the most complex organ. It determines our most unique human function, namely, consciousness. Its activity underlies all aspects of our behavior from basic requirements such as breathing to supporting our thoughts and feelings [1]. Brain diseases can result directly from intrinsic dysfunction of the brain or from complex interactions between the brain and the physical environment [2]. Brain and mind disorders include a wide range of common neurological and psychiatric illnesses. They afflict a very significant portion of the population, right across the life span, and are prevalent in both developed and developing countries. Likewise, these diseases pose the largest health, economic and social capital burden worldwide of any disease group [3].

While the mental and neurological disorders are responsible for about 1% of deaths, they account for almost 11% of disease burden all over the world. The extension of life expectancy and the ageing of the general populations in both developed and developing countries are likely to increase the prevalence of many chronic and progressive physical and mental conditions including neurological disorders [4] (**Table 1**). Brain and mind disorders actually affect as many as 1.5 billion people worldwide, and the number is expected to increase. No less than 25% of the total burden of disease in the established market economies is at present attributable to brain and mind disorders [5]. Altogether, brain disorders now affect 300 million persons and their total cost is 640 billion per year in Europe [6]. Indeed, the proportionate share of the total global burden of disease due to neurologic disorders is projected to rise to 14.7% by 2020 [7], highlighting an urgent need for more drugs to treat CNS disorders.

Ageing population, brain disorders and health impact

The nature of these brain disorders changes across the human lifespan. The young have a higher incidence of psychiatric disorders, including depression, anxiety, schizophrenia and substance abuse. In contrast, the elderly suffer particularly from neurodegenerative conditions such as dementia or stroke [8]. More widely appreciated is that the elderly suffer neurodegenerative disorders, like Parkinson (PD) and Alzheimer's disease (AD), which are increasing because of an ageing population [9].

The neurodegenerative CNS disorders, such as PD and AD, are among the leading causes of disability and death in the developed world [10]. The twentieth century saw a revolution in longevity. Between 1950 and 2010 life expectancy rose worldwide from 46 to 68 years and is expected to extend a further 10 years by 2050. This demographic triumph and the fast growth of the population in the first half of the twenty-first century

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Table 1. Age and sex specific prevalence rates (%) of dementia and Parkinson in Europe. The extension of life expectancy and the ageing of the populations are likely to increase the prevalence of neurological disorders.

	Dementia		Parkinson	
Age group (Year)	Men	Women	Men	Women
65-69	1,8	1,4	0,7	0,6
70-74	3,2	3,8	1	1
75-79	7	7,6	2,7	2,8
80-84	14,5	16,4	4,3	3,1
85-89	20,9	28,5	3,8	3,4
>90	32,4	48,8	2,2	2,6

mean that the number of people over sixty will increase from about 600 million in 2000 to almost 2 billion in 2050 [11] and the proportion of people defined as older is projected to increase globally from 10 per cent in 1998 to 15 per cent in 2025 [12].

Thus, age-related diseases such as AD and PD disease will also increase. The neurodegenerative diseases are characterized by inexorably progressive deterioration in cognitive ability and capacity for independent living [13]. Constituting around the 80% of the neurologic disorders, they have drawn a lot of attention due to their irreversibility, to their lack of effective treatment, and because they accompany social and economical burdens [14]. The neurodegeneration produces a clinical syndrome called dementia, which describes a set of symptoms including loss of memory, mood changes, and problems with communication and reasoning. AD is the leading cause of dementia, causing about half of all cases. This disease is characterized by a progressive decline in brain function, which typically begins with deterioration in memory [15].

AD neuropathology shows two types of lesions, senile plaques and neurofibrillary tangles composed of β-amyloid. Although plaques and neurofibrillary tangles appear to be the most prevailing features of AD pathology, they alone are not sufficient to generate the significant and profound neuronal loss during disease [16]. People with AD also have a shortage of the chemical acetylcholine in their brains. This chemical is involved with the transmission of messages within the brain [17]. Age is the greatest risk factor for dementia. However, dementia is not restricted to older people [18]. Since the elderly population is growing worldwide, AD is quickly becoming one of the major universal healthcare problems. Today, there are neither precise diagnostic approaches nor curative therapeutic agents available for AD. However, drug treatments that can temporarily alleviate some symptoms or slow down their progression in some people are available [19]. PD is the second most common neurodegenerative disease, affecting 1% of the population over 55 years of age. This disease is characterized by the loss of ~50–70% of the dopaminergic neurons in the substantia nigra pars compacta, a profound loss of dopamine in the striatum, and the presence of intracytoplasmic inclusions called Lewy bodies, which are mainly composed of α-synuclein and ubiquitin [20].

Like in AD, PD symptoms appear gradually but are unique and dependent on the affected brain subregion. They include difficulties in maintaining balance and in ambulation; tremors; inflexibility/stiffness of the limbs and trunk; and bradykinesia (slowness of movement) [21]. Neuronal damage caused by neurotoxic factors initiated from inflammatory responses by immune activated glia are linked to cognitive and motor deterioration, which contribute to the breakdown of the blood-brain barrier (BBB). This allows leukocytes to enter into the brain serving to speed a neuroinflammatory cascade. Although the causes of both AD and PD remain unknown, patterns of familial inheritance suggest a possible connection involving abnormal protein processing (Aβ for AD and alpha synuclein for PD) and accumulation [22].

As neurodegenerative diseases, brain tumors are also included in CNS disorders. Brain tumors have a great significance between the CNS diseases and have one of the higher costs per habitant of the neurological disorders (**Figure 1**). Difference between men and women are reflected in the different statistics for brain tumors (**Table 2**). Primary brain tumors represent 2% of all cancers [23] and are a diverse group of tumors with marked differences in etiology, treatment and prognosis [24]. The term ''brain tumours'' refers to a mixed group of neoplasms originating in intracranial tissues and the meninges with degrees of malignancy ranging from benign to aggressive [25]. Primary brain tumors can be classified into gliomas, the most common adult brain tumors occurring in the brain parenchyma above the tentorium, and medulloblastomas, child or young adult cerebellar tumors occurring below the tentorium [26]. Most of these brain tumors have an unknown etiology and they represent the most devastating and difficult cancer to treat.

Currently, a majority of modern pharmacological therapies provide symptomatic relief to patients with CNS diseases, but are commonly associated with adverse side effects and often do not halt disease progression. Moreover, patients afflicted with complex CNS diseases typically require life-long medication with a marginal improvement in the quality of life [27]. On the one hand, a major limitation for the development of efficacious CNS treatments is the lack of knowledge on the mechanism of neurological diseases. And on the other hand, the currently available therapeutics for these disorders only act to lower its symptoms [28].

Animal models of neurological disorders

Actually, *in vivo* techniques are the most reliable techniques for studying and understanding the neurological disease progression as they use living tissue and they examine

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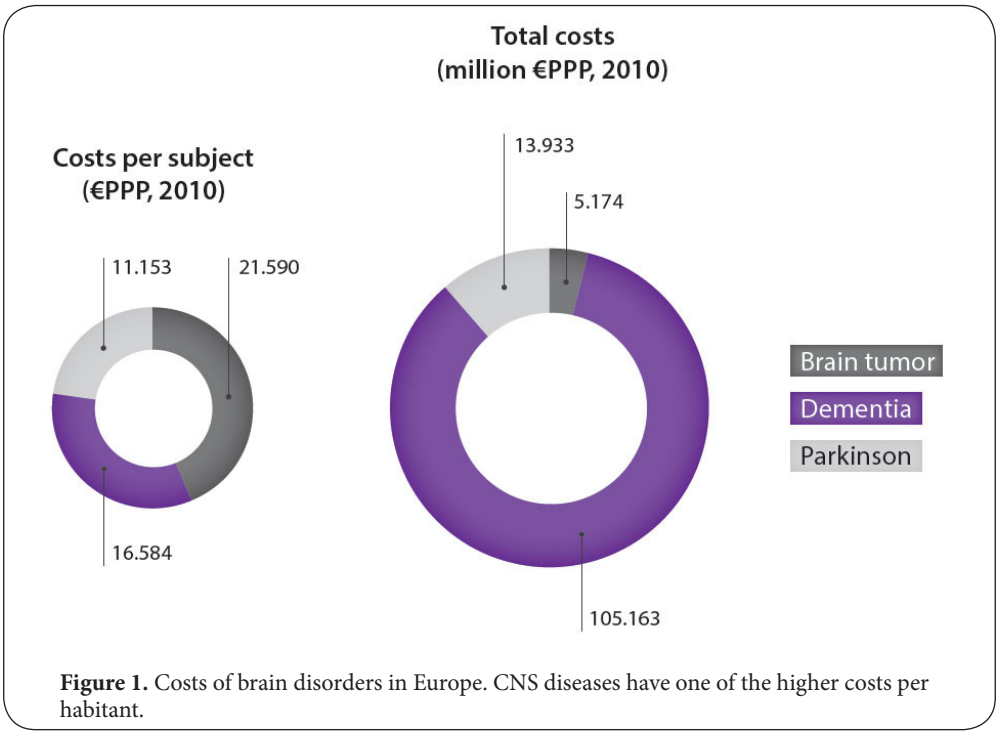

Figure 1. Costs of brain disorders in Europe. CNS diseases have one of the higher costs per habitant.

Table 2. Brain and other central nervous system tumors statistics in Europe. Difference between men and women are reflected in these statistics for brain tumors.

	Incidence			Mortality			5-years prevalence		
	Number	%	ASR(w)	Number	%	ASR(w)	Number	%	PROP
Men	28.942	1,7	6,2	23.312	2,4	4,6	32.846	0,8	11,2
Women	25.863	1,7	4,6	19.641	2,6	3,1	27.165	0,6	8,4
Both	54.805	1,7	5,3	42.953	2,5	3,8	60.011	0,7	9,7

the overall effect of the whole body on an experiment. However, drawbacks include the requirement of large numbers of live animals, low throughput, the need for expensive equipment and experimental expertise as well as the highly invasive nature of the studies [29].

Ideally, animal models of neurodegenerative diseases should reproduce the clinical manifestation of the disease, a selective neuronal loss [30]. There are two approaches to produce mouse models of human disease. On the one hand, the genotype-driven approach depends on knowing the gene of interest, and then manipulating this gene in the mouse to create the appropriate model. On the other hand, the phenotype-driven approach, is not gene dependent, but uses standard gene-mapping and cloning techniques to identify the causal genetic change in an interesting phenotype [31].

In AD have been described many experimental models. For example, there are animal models based on the metabolism of the amyloid precursor protein, and other models based on Presenilin or on tau protein [32]. According to PD, animal models of PD can be divided into those using environmental or synthetic neurotoxins and those utilizing the *in vivo* expression of PD-related mutations [33]. Toxic models represent the classic experimental PD models; they aim to reproduce the pathological and behavioural changes of this human disease in rodents or primates by using pharmacological agents (neurotoxins) that induce the selective degeneration of nigrostriatal neurons [34].

Brain tumor models have been developed in a variety of forms, which can be classified as chemically induced models, xenograft tumor models or models of spontaneous tumor formation in genetically engineered mice and help address issues of utmost importance in drug development: toxicity and *in vivo* antitumor effectiveness [35]. The establishment of tumors in animals by xenografting tumor material has been highly valuable in the search for mechanisms that determine tumor formation, growth, and progression. In particular, with the advent of immunodeficient animals, important insights have been obtained relating to the growth of human tumors within the CNS [36]. Xenograft

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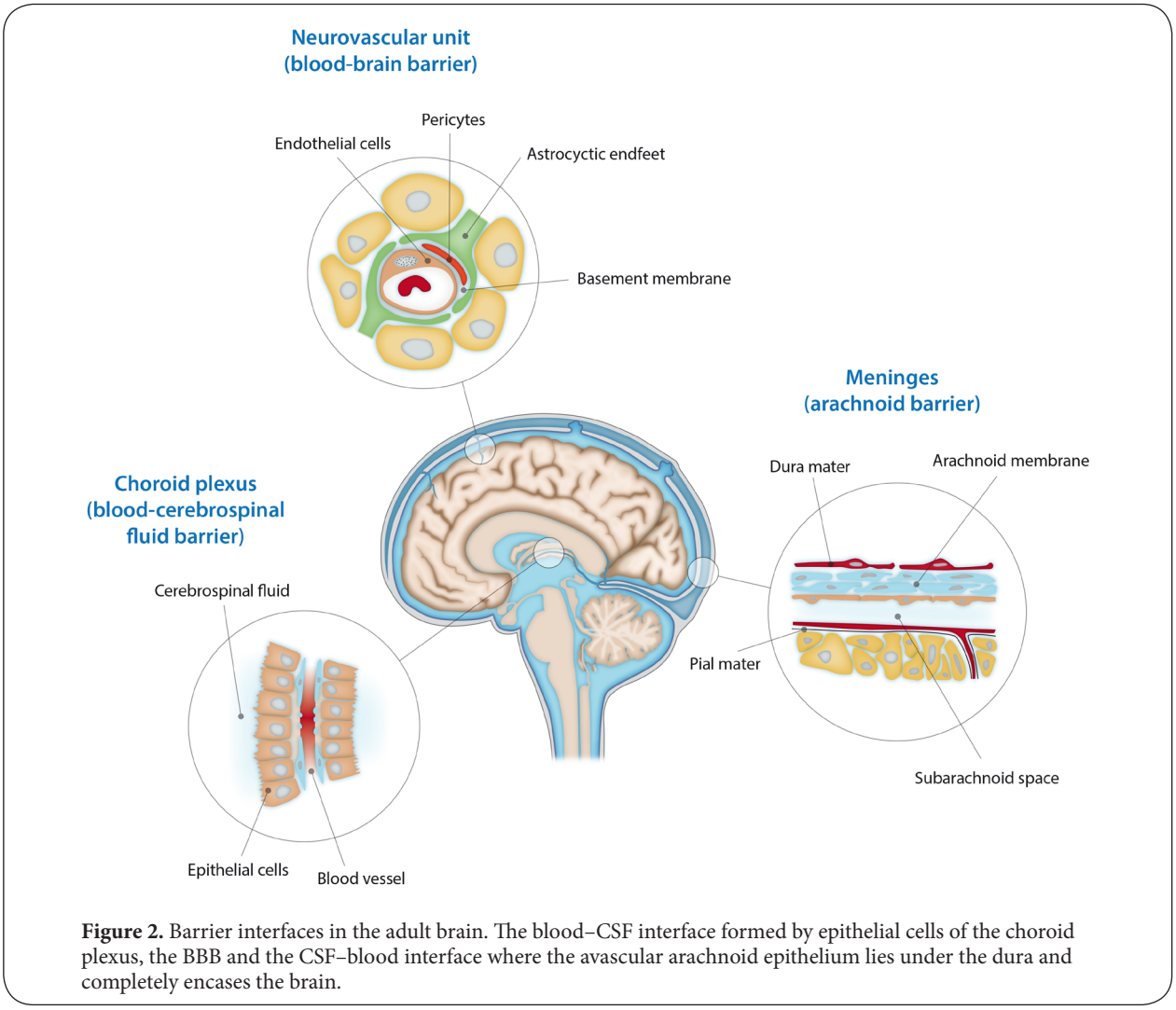

Figure 2. Barrier interfaces in the adult brain. The blood–CSF interface formed by epithelial cells of the choroid plexus, the BBB and the CSF–blood interface where the avascular arachnoid epithelium lies under the dura and completely encases the brain.

tumors are characterized by synchrony and reproducibility of tumor formation, rapid tumor development, easy tumor visualization and high penetrance [37]. Increased understanding of genomic alterations in primary brain tumors has led to the development of highly characterized genetically engineered mouse models of glioma based on specific genetic alterations observed in human tumors [38]. These mouse models of human cancers are generated by somatic or germline genetic modification strategies [39]. At least in brain tumor modeling, the use of mouse models forming spontaneous tumors is complicated by poor reproducibility, low tumor penetrance, prolonged tumor formation latency, and a need for advanced *in vivo* imaging techniques.

Preferably animal models of CNS disorders should reproduce all the specific changes to a given disease. Unluckily, most of the models reproduce only certain aspects of the diseases. For this reason they are poorly indicative of the efficacy of neuroprotective substances in humans.

Blood-brain barrier

Not only understanding the neurological diseases progression, but also discovery and development of CNS drugs is a substantial challenge in the neuropharmaceutical industry, due to the persistent difficulty of delivering drug molecules across the BBB [40].

There are three main interfaces in the brain that protect neurons from blood-borne substances and help to maintain water homeostasis and an appropriate milieu for neuronal function (**Figure 2**). The blood–CSF interface formed by epithelial cells of the choroid plexus, the BBB and the CSF–blood interface where the avascular arachnoid epithelium lies under the dura and completely encases the brain [41]. The BBB has the largest surface area of all three interfaces, creating an extremely high density capillary network throughout the brain parenchyma with a total length of 600-650 km and a surface area of 20 m^2 [42] providing almost every neuron with an individual blood supply [43]. Hence, the BBB is considered to be the primary interface of the brain.

The CNS requires a perfectly regulated environment and homeostasis with characteristics far different from those in the rest of the organism. The main factor maintaining the homeostasis of the CNS is the proper function of the BBB. Under both physiological and pathological conditions, the BBB isolates and protects nervous tissue of the brain and spinal cord from fluctuations in nutrients, hormones, metabolites, and other blood constituents. It also protects this tissue from the direct influences of many endo- or exogenous compounds circulating in the blood [44]. Therefore, the BBB forms the anatomical and physiological interface separating the brain from the blood and protecting the microenvironment of the CNS via controlling the passage of endogenous substances and xenobiotics into and out of the CNS [45].

Structural components of BBB: neurovascular unit

The BBB is composed of a microvascular endothelium, astrocytes, basement membrane, pericytes and neurons that are in physical proximity to the endothelium. All these elements are part of the functional neurovascular unit.

Brain microvascular endothelial cells (BMECs) perform essential biological functions, including barrier, transport of micronutrients and macronutrients, receptor-mediated signaling, leukocyte trafficking and osmoregulation [46]. BMECs form a very thin but very effective barrier between blood and brain parenchyma. Brain micro-vessels are phenotypically unique compared to vessels in the periphery. They have somewhat smaller diameter, thinner wall and higher mitochondrial density than vessels in other organs [47]. BMECs possess also an enzymatic function, capable of metabolizing drug and nutrients. These enzymes include γ-glutamyl transpeptidase and alkaline phosphatase present at the luminal endothelium. Furthermore, BMECs express several drug efflux transporters mainly present on the luminal membrane surface, including P-gp, multidrug resistance-associated proteins, GluT1 and LAT1 [48]. The basement membrane of the BBB endothelial cells is common with that of the perivascular astrocytic endfeet and that of the pericytes, which are completely surrounded by a basement membrane, making the endothelial cells tightly integrated into the brain parenchyma [49].

Astrocytes, like neurons, derive from the ectoderm of the neural tube. BMECs are enveloped by astrocytes endfeet specialized processes sent by astrocytes, where they form rosette-like structures [50]. Astrocytes and endothelial cells influence each other's structure; their interactions induce and modulate the development of the BBB and unique endothelial cell phenotype. Interaction of astrocytes with BMECs greatly enhances endothelial cell tight junctions (TJs) and reduces gap junctional area. This interaction increases the number of astrocytic membrane particle assemblies and astrocyte density [51].

In an identical manner as capillaries, venules, and arterioles that wrap around the endothelial cells, pericytes are cells of microvessels. They are separated from BMECs by the basement membrane, but gap junctions provide contact spots. There is evidence that pericytes are able to mimic astrocyte ability to induce BBB "tightness." These evidences support the hypothesis that pericytes play an important role in maintaining the structural integrity of the BBB [52].

Structural integrity of BBB: junctional complexes

The most important factors responsible for BBB impermeability are the junctional complexes existing between the ECs of brain microvessels. TJs exist between the ECs and encircle the cells like a continuous belt. The TJs consist of three integral membrane proteins (occludin, claudin and junctional adhesion molecules (JAM)), which are linked to different cytoplasmic accessory proteins, including the zonula occludens (ZO) proteins ZO-1, ZO- 2, ZO-3 and cingulin. Cytoplasmic proteins link membrane proteins to actin, which is the primary cytoskeleton protein for the maintenance of structural and functional integrity of the endothelium [53].

Functionally, TJs work in several ways. They constitute the frontier for protein and lipid diffusion across the membranes and confer to the ECs polarity, which is manifested by a non-uniform distribution of a number of transporters between the luminal and abluminal membranes. Due to complete fusion, they also seal the paracellular way to force transport of substances through the membranes and cytosol [54]. TJs are characterized by high electrical resistance. The integrity of the TJs assembly determines the paracellular permeability of water-soluble molecules across the BBB.

The first integral membrane protein to be discovered was the occludin. The cytoplasmic domains of occludin are directly associated with ZO proteins. It seems that occludin function is regulatory and may influence paracellular transport [55]. Occludin content is much lower in endothelial cells of non–CNS origin, suggesting that occludin is actively involved in BBB function. It has been shown that high levels of occludin ensure high electrical resistance (tightness) of the epithelial cell monolayers [56].

The major components of TJs are claudins. The claudin from one endothelial cell connects with an analogous claudin from an adjacent endothelial cell to create the "primary closure" of the TJs, and the carboxylic end of each protein links it to cytoplasmic ZO-1, ZO-2, or ZO-3. At the BBB, claudin-3 and claudin-5 appear to be responsible for the low paracellular [57].

The JAMs are transmembrane proteins belong to the immunoglobulin superfamily [58]. It mediates the early attachment of adjacent cell membranes via homophilic interactions of a single membrane-spanning chain with a large extracellular domain [59]. Their function in the mature BBB is still largely unknown [60]. The expression of JAMs at the human BBB remains to be explored.

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Regulation of Paracellular Permeability

The mechanisms affecting the brain uptake of drugs include passive diffusion, carrier-mediated transport, receptor-mediated transport and active efflux transport.

The independent movement and energy of drug molecules along a concentration gradient are involved by passive diffusion. The rate of diffusion is directly proportional to the concentration gradient of the solutes across the membrane. Passive diffusion can occur either between the cells (paracellular) or through the cells (transcellular), depending on the physicochemical properties of the solutes. Since tight junctions block the paracellular route across the BBB, only solutes which are able to penetrate through the endothelial cell membrane are able to cross the BBB via passive diffusion [61]. Therefore, only a few drug molecules can efficiently cross the BBB by passive diffusion.

Carrier-mediated transport proteins move small hydrophilic molecules such as amino acids, nucleosides or glucose. These transporters systems are expressed on both the luminal and abluminal membranes of the capillary endothelium, catalysing the bidirectional movement between blood and brain transporting solutes solutes either from brain to blood or from blood to brain. All of these molecules access different specialized transporter proteins, which are stereospecific and mediate solute transport in the order of milliseconds. All of them use chemical and/or electrical gradients to move molecules across cell membranes. Examples include the GLUT1 glucose transporters, MCT1 lactate transporters, LAT1 large neutral amino-acid transporters or CNT2 adenosine transporters [62].

Brain uptake of large molecules such as peptides and proteins is limited due to the BBB. The endocytotic activity of BMECs is lower than in the peripheral endothelial cells [63]. However, the brain uptake of some large molecular weight molecules is necessary to ensure the normal function of the brain. Therefore, some peptides and proteins gain their access into the CNS via receptor-mediated transport, such as the insulin receptor, the transferrin receptor or the leptin receptor.

Active efflux transporters have a major impact on the drug systemic pharmacokinetics. The lower brain uptake of lipophilic solutes is often due to active efflux proteins [64]. The efflux transporters have a broad range of substrates, and strong substrates of BBB efflux transporters do not pass the BBB to a functionally relevant extent, which restricts their therapeutic effects to the periphery. ABC transporters comprise one of the largest protein families, and they are crucial for a number of biomedical aspects like drug transport and resistance to cancer and xenobiotics. These transporters are membrane proteins consisting of many domains that use ATP-bound energy for the transport of solutes across the cell membrane in all mammals [65]. Members of this family include P-gp, ABCC family and breast cancer resistance protein (BCRP). These proteins have a broad substrate specificity including organic cations, weak organic bases, some organic anions and some uncharged compounds which compromise a wide variety of drugs, such as anticancer drugs, anti-HIV drug and glutathione, glucuronide, carcinogens and dietary toxins [66-69].

Due to the BBB composition and its specific regulation of paracellular integrity described above, the BBB is now recognized as the major obstacle to the treatment of most neurological disorders, as it hinders the delivery of many potentially important therapeutic and diagnostic substances to the CNS [70].

A successful CNS drug disposition is hindered by the high degree of protection afforded to the brain via the BBB [71], CNS drug penetration is modulated by BBB permeability and active transport at the BBB. Analysis of currently approved therapies shows that all products depend on the molecular properties of the drug to penetrate the BBB [72]. To facilitate drug delivery, several approaches to overcome the BBB have been investigated [73].

Delivery systems across the bbb to treat brain diseases

Generally, only low molecular weight, lipid-soluble molecules and a few peptides and nutrients can cross this barrier to any significant extent, either by passive diffusion or using specific transport mechanisms [74]. To overcome the BBB restricting CNS drug delivery of potential therapeutic agents and in response to the insufficiency in conventional delivery mechanisms, extensive research efforts have recently focused on the development of new drug delivery strategies to more effectively deliver drug molecules to the CNS [75].

To bypass the BBB and to deliver therapeutics into the brain, two different approaches are currently used; invasive and non-invasive methods including BBB disruption, nasal delivery or colloidal drug carriers.

Invasive methods

The drugs can be administered directly into the brain tissue. There are some physical based techniques that include intracerebroventricular injection into the cerebrospinal fluid, intraparenchymal infusion by convection-enhanced delivery, intracerebral implantation and the BBB integrity disruption.

Disruption of the BBB can open access of the brain to components in the blood by making the tight junction between the endothelial cells of the brain capillaries leaky [76]. The idea behind this approach was to break down the barrier temporarily by an osmotic disruption [77]. The disruption could also be broken down by MRI-guided focused ultrasound BBB disruption technique [78]. These methods allow the delivery of therapeutic agents in patients with CNS disorders. However, this approach also causes several undesirable side effects in humans, including physiological stress, transient increase in intracranial pressure, and unwanted delivery of therapeutic agents

to normal brain tissue [79].

Other strategies to overcome the BBB that have been used extensively in clinical trials are the direct administration of drugs by intraventricular and intracerebral routes. CNS local delivery includes intracerebroventricular injection (ICV) into the cerebrospinal fluid, where the drug enters the brain parenchyma following transport across the BBB and the convection enhanced delivery (CED), an intraparenchymal infusion of the drug solution into the brain parenchyma by a catheter. This method involves the stereotactically guided insertion of a small-caliber catheter into the brain parenchyma. Through this catheter, infusate is actively pumped into the brain parenchyma and penetrates in the interstitial space [80]. The infusion is continued for several days before catheters remove. Both neurosurgical based delivery approaches have limitations. For example, the diffusion of the drug by ICV delivery in the brain parenchyma is very low. Besides, an insufficient concentration of drug may reach the target site, secreted interstitial fluid flow works against diffusive drug penetration and the high turnover rate of the CSF continuously clears injected drug back into the blood apart from the surgical intervention required [81]. Likewise, in the CED strategy, some areas of the brain are difficult to saturate fully with infusate, particularly infiltrated tissues surrounding a cavity. Proper drug delivery depends on the placement of catheters based on knowledge of these factors [82].

CNS local delivery also includes intracerebral implants. The advantages of implantable polymer systems have recently prompted several teams to study their use in CNS pathologies. Different CNS diseases principally brain tumours and neurodegenerative disorders such as PD and Huntington's diseases can be treated with intracranially administered controlled drug delivery systems [83]. The efficiency of various devices has been investigated in animal models and some systems have also been subjected to clinical trials [84]. But the efficacy of this method is still unclear, since the injection site has to be very precisely mapped in order to get efficacy and overcome the problem associated with diffusion of drugs in the brain parenchyma.

The approaches above described are relatively costly, requiring anesthesia and hospitalization. Likewise, these neurosurgical based delivery approaches have several limitations in the drug administration and diffusion into the brain. The distribution in the brain by diffusion decreases exponentially with distance and these methods have to be very precisely mapped to get efficacy. So, although invasive methods of administration have been used to overcome the BBB, these methods are not really practical for use due to several reasons, including convenience, safety and cost.

Non-invasive methods

A variety of non-invasive brain drug delivery methods have been investigated, these methods make use of the brain blood vessel network to gain widespread drug distribution. Noninvasive 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 [85].

Intranasal administration

The use of intranasal administration (IN) to target therapeutics to the CNS has many benefits in the treatment of neurologic disorders. IN drug delivery has been investigated due to the direct access from the nasal cavity to the CNS via the olfactory epithelium and/or the trigeminal nerve system [86]. It offers rapid absorption to the systemic blood avoiding first pass metabolism in the gut wall and the liver. This route of administration has been shown to present a safe and acceptable alternative to parenteral administration of specific drugs [87].

Taking into account that drugs absorbed via the olfactory route do not have to cross the BBB, substances could possibly be delivered to the CNS directly. This can be advantageous for delivery of CNS therapeutics, including those that can cross the BBB upon systemic administration. CNS therapeutics do not necessarily need to be modified for IN delivery, and delivery of therapeutics to the CNS is rapid, occurring within minutes [88].

Systemic delivery / Transported mediated delivery

Peptides and small molecules may use specific transporters expressed on the luminal and basolateral side of the endothelial cells forming the BBB to cross into the brain [89]. Carrier transporters are stereospecific and small, therefore, only a limited number of substances can potentially be delivered via these transporters. As mentioned previously, the BBB contains several efflux transporters (ATP-binding cassette, ABC), which expel a multiplicity of drugs from the CNS. Various strategies have emerged in order to avoid the activity of these efflux transporters: either by developing specific inhibitors for the efflux transporters, thus giving their substrates a greater access to the CNS or by attempting to design analogues of drugs with known efficacy but with poor BBB penetration due to ABC transporter activity, which will no longer have a reactivity with the efflux transporters [90]. P-glycoprotein (P-gp) is one of the most studied active efflux transporters. Inhibition of the P-gp functions may improve brain permeation as many chemotherapeutic drugs were reported to P-gp substrates.

Large molecules which are necessary for the normal function of the brain are also delivered by specific receptors, via receptor-mediated transcytosis. These receptors are highly expressed on the endothelial cells forming the BBB. These include the insulin receptor, transferrin receptor, LDL

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receptor and its related protein, and others [91]. Over the last decade, there have been significant developments in the area of receptor transporters. The carriers should be conjugated with a ligand able to target a receptor transporter [92].

Finally, another systematic delivery is the use of cell-penetrating peptides which are able to translocate across biological membranes, and to assist the transport of various substances across these biological barriers. Peptide mediated BBB penetration has thus been widely exploited. A number of peptides (*eg.,* TAT, angiopep-2) were tested to identify a more effective BBB penetrating peptide [93]. Several cell-penetrating peptides, which appear to enter cells with alacrity, have been developed recently. At present, little is known about the mechanism by which these peptides can cross the cell membrane.

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 [94].

Liposomes and nanoparticles are large and complex constructs which can be made from a variety of chemical constituents and may range up to 200 nm in diameter. Relatively large amounts of drug or agent can be incorporated into these structures, providing the possibility for significant delivery to the CNS. The surface of the liposome or nanoparticle can be modified and groups can be attached so that the construct can be targeted to the CNS via specific BBB mechanisms [95].

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. Moreover, the colloidal systems allow access of non-transportable drugs across the BBB by masking their physicochemical characteristics through their encapsulation in these systems [86].

Polymeric micelles as drug delivery systems are formed by amphiphilic copolymers having an A-B diblock structure with A, the hydrophilic (shell) and B, the hydrophobic (core) polymers. The polymeric micelles are thermodynamically and kinetically stable in aqueous media. The narrow size range is similar to that of viruses and lipoproteins [97]. It has also been suggested that liposomes can enhance drug delivery to the brain across the BBB. Liposomes are small artificial vesicles that form a globular shape that consists of two major components: an aqueous core and a surrounding phospholipid bilayer membrane. The aqueous core provides an inner compartment in which a cargo, such as a water-soluble drug, can be carried. The phospholipid bilayer membrane provides a protective coating that insulates the contents of the inner core from release of contents at unintended sites as well as from degradation [98].

Other colloidal drug carriers are the polymeric nanoparticles. Nanoparticles (NPs) are solid colloidal matrix-like particles made of polymers or lipids. Compared with other colloidal carriers, polymeric NPs present a higher stability in contact with the biological fluids. At the same time, their polymeric nature permits the attainment of the desired properties such as controlled and sustained drug release [99] Their main advantages over liposomes are the low number of excipients used in their formulations, the simple procedures for preparation, a high physical stability, and the possibility of sustained drug release that may be suitable in the treatment of chronic diseases [100].

Polymeric NPs were the first polymeric nanocarrier studied for drug delivery devices; they were prepared from a block of polymeric material giving the material an increased blood circulation time and a reduced phagocytic uptake [101]. Biodegradable polymers were then incorporated to maximise the tissue compatibility and minimise the toxicity of the material [102]. Another important type of nanoparticle is the nanotube, which is a hollow cylindrical molecule usually made of a single element. Carbon nanotubes are essentially grapheme sheets which are rolled up to produce perfect cylinders. Chemically, this kind of nanotubes is the most interesting option among all the materials considered for the use as nanocarriers, since they give you a degree of control that is not possible with other materials as almost every carbon atom can be functionalized [103].

Improving new NPs like iron oxide nanoparticles, gold nanoparticles or quantum dots (nanocrystals). The main uses of NPs are therapy and imaging for diagnosis. Imaging is a relatively new discipline that uses probes known as biomarkers to measure biological processes at a molecular level, allowing visualization of events in a living system without causing any damage. This technique is useful in the diagnosis of cancer, as well as other neurological and cardiovascular diseases. The targeting ability of nanoparticles provides them with a number of advantages compared with conventional contrast agents and may provide them the ability to more sensitively detect a number of disease entities [104].

Conclusions

In summary, brain disorders are currently the core health challenge. The treatment of CNS diseases is particularly difficult since the BBB restricts the access of many compounds to their CNS targets. Accordingly, identifying brain delivery strategies for new therapeutics has become essential. For this reason, efforts are underway to develop strategies increasing the BBB permeability of CNS drugs. In order to assess the drug ability for entering the brain, BBB models that mimic human CNS diseases conditions have been developed. However, there is a need for further optimization of drug design and development of CNS

therapeutics with enhanced activity and improved BBB permeability.

List of abbreviations

ABC: ATP-binding cassette
AD: Alzheimer's disease
BBB: Blood-brain barrier
BCRP: Breast cancer resistance protein
BMECs: Brain microvascular endothelial cells
cAMP: cyclic Adenosine monophosphate
CED: Convection enhanced delivery
CNS: Central nervous system
ICV: Intracerebroventricular injection
IN: intranasal administration
JAM: Junctional adhesion molecules
MDR: multidrug resistance
MRPs: Multidrug resistance-associated proteins
NPs: Nanoparticles
PD: Parkinson's disease
P-gp: P-glycoprotein
TEER: Transendothelial electrical resistance
TJs: Tight junctions
ZO: Zonula occludens

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Alazne Domínguez participated in the design of the work and performed the draft of the manuscript; Antonia Alvarez and Enrique Hilario retrieved conceptual information; Blanca Suarez-Merino carried out a critical revision to structure the content intellectually and Felipe Goñi-de-Cerio took part in the concept of the work and approved the final version in order to be published. All authors read and approved the final manuscript.

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