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The Blood-Brain Barrier and Epilepsy

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1. Introduction

The blood-brain barrier (BBB) is a dynamic interface between the blood and the central nervous system (CNS), that controls the exchanges between the blood and brain compartments. Therefore, the functional and structural integrity of the BBB is vital to maintain the homeostasis of the brain microenvironment and it provides protection against many toxic compounds and pathogens (Cardosa et al., 2010; Cucullo et al., 2011).

Anatomically, the BBB consists of microvascular endothelial cells (ECs) lining the brain microvessels together with the perivascular elements such as astrocytes, pericytes, neurons, and the extracellular matrix. The microcapillary endothelium is characterized by the presence of tight junctions (TJs), lack of fenestrations, and minimal pinocytotic vesicles. TJs between the cerebral ECs form a diffusion barrier, which selectively excludes most blood-borne substances from entering the brain, protecting it from systemic influences. Brain ECs also express plasma membrane transport protein and receptors, both of which provide selective routes of entry for polar nutrients such as glucose transport (GLUT-1), ions (Na, K-ATPase and Na, K) and some macromolecules (insulin and transferring receptors) and routes of exit for potentially toxic metabolic waste and macromolecules (ATP-binding cassette (ABC) transporters). Through restrictive barrier properties and polarized expression of selective transport proteins, the BBB effectively regulates solute and fluid exchange between the blood and brain parenchyma (Marchi et al., 2011a; Paolinelli et al., 2011).

The BBB is a dynamic system, capable of responding to local changes and requirements, and is regulated by a number of mechanisms and cell types, in both physiological and pathological conditions. Such regulation includes changes in tight junction function, and in expression and activity of many transporters and enzymes (Abbott et al., 2010). BBB breakdown has often been documented in the epileptic brains (Ilbay et al., 2003; Uzüm et al., 2006). Recently, as within many CNS diseases, also in epilepsy, BBB dysfunction have been described not only as a late event, but more interestingly as putatively involved in the early steps of disease progression. It is well acknowledged that epileptic seizures are the result of

instant abnormal hypersynchronous electrical activity of neuronal network, originating from discharges of local brain tissue that caused by an imbalance between excitation and inhibition. However, in a substantial number of epilepsies, the etiology is almost unknown. The complex and multifactorial nature of epileptogenesis (occurrence of spontaneous epileptic seizures) has highlighted the fact that limited therapeutic solutions in clinical practice are left to a proportion of epilepsy patients that are refractory to all anti-epileptic drugs (AEDs). During the past several years, increasing interest has arisen in the role of the BBB in epilepsy. Recent advances in understanding nature of epileptogenesis have made it possible to realize the role of the BBB disruption in epileptogenesis (David et al., 2009; de Boer et al., 2008; Vezzani et al., 2008; Weis et al., 2009; You et al., 2011).

2. Blood- Brain Barrier: Structure and function

The BBB is localized at the interface between the blood and the cerebral tissue and, formed by the ECs of cerebral blood vessels which are characterized by the absence of fenestration correlating with the presence of intercellular TJs, the low level of non specific transcytosis and paracellular diffusion of hydrophilic compounds. ECs have a high number of mitochondria, associated with a strong metabolic activity and the polarized expression of membrane receptors and transporters, which are responsible for the active transport of blood-borne nutrients to the brain or the efflux of potentially toxic compounds from the neural tissues to the vascular compartment (Weis et al., 2009).

BBB properties are primarily determined by junctional complexes between the cerebral ECs. These complexes are comprised of TJs and adherens junctions (AJs). Such restrictive angioarchitecture at the BBB reduces paracellular diffusion, while minimal vesicle transport activity in brain ECs limits transcellular transport. Under normal conditions, this largely prevents the extravasation of macromolecules and most polar solutes (unless specific transporters are present) and prevents migration of any type of blood-borne cell. In AJs, cadherin proteins span the intercellular cleft and are linked into the cell cytoplasm by the scaffolding proteins alpha, beta and gamma catenin. The AJs hold the cells together giving the tissue structural support. They are essential for formation of TJs, and disruption of AJs leads to barrier disruption. The TJs consist of a complex of proteins spanning the intercellular cleft (occludin, nectin, claudins), and junctional adhesion molecules A, B and C (JAMs). TJs adhesion proteins are linked to a specific network of cytoskeletal and signaling proteins which include ZOs (zonula occludens proteins 1, 2, 3 and zonula occludens-1 associated nucleic-acid-binding protein (ZONAB), cingulin and others). The TJs are responsible for the severe restriction of the paracellular diffusional pathway between the ECs to ions and other polar solutes, and effectively block penetration of macromolecules by this route. The impediment to ion movement results in the high in vivo electrical resistance of the BBB, of $\sim$1800 Ω cm². This high electrical resistance or low conductance of the potential paracellular pathway emphasises the extreme effectiveness of the TJs in occluding this pathway by effectively reducing the movement of ions (Abbott et al., 2010; Paolinelli et al., 2011; Stamatovic et al., 2008). However, the BBB is a dynamic structure capable of rapid modulation in response to physiological or pathological signals. The permeability can be controlled by a variety of signaling pathways that regulate TJs organization. Numerous substances and signaling tracks, such as Ca2+, protein kinase C, G protein, calmodulin, cAMP, phospholipase C, and tyrosine kinases, are believed to play a role in this regulation. Several cytoplasmic signaling molecules are concentrated at TJs complexes and are involved

in signaling cascades that control assembly and disassembly of TJs. ZOs proteins link claudins and occludin via cingulin to intracellular actin cytoskeleton. Importantly, it has been shown that ZO-1 and ZONAB are a substrate of a serine kinase and protein kinase C, respectively, which are crucial for the formation and regulation of TJs. Failure to maintain the integrity of brain EC junctions can have profound effects on permeability control. (Paolinelli et al., 2011). In addition, the BBB is structurally associated with brain parenchymal cells. Pericytes, glial cells (especially astrocytes), neurons, together with the basal lamina (also called lamina basalis) ensheathing cerebral blood vessels, are indirectly involved in the establishment and maintenance of the BBB (Figure 1). These various cell types and basal lamina collectively constitute the neurovascular unit (NVU), a concept recently proposed to highlight the functional interactions that control the BBB integrity. The basal lamina of the cerebral endothelium is constituted by 3 apposed layers, one produced by ECs and containing laminin -4 and -5, one being astrocyte-derived, containing laminin -1 and -2 and the collagen IV-containing the middle one, contributed by both cell types. All three layers are also made of various types of collagen, glycoproteins and proteoglycans. The basal lamina of the cerebral endothelium shows strong labeling with cationic colloidal gold indicating that it forms a negatively charged screen or filter controlling the movement of charged solutes between blood and the brain interstitial fluid. Therefore large, charged molecules such as ferritin do not cross the basal lamina. Multiple basal lamina proteins, matrix metalloproteases and their inhibitors are involved in the dynamic regulation of the BBB in physiological as well as pathological conditions. (Cardosa et al., 2010; Marchi et al., 2011a; Nag, 2003a; Weis et al., 2009).
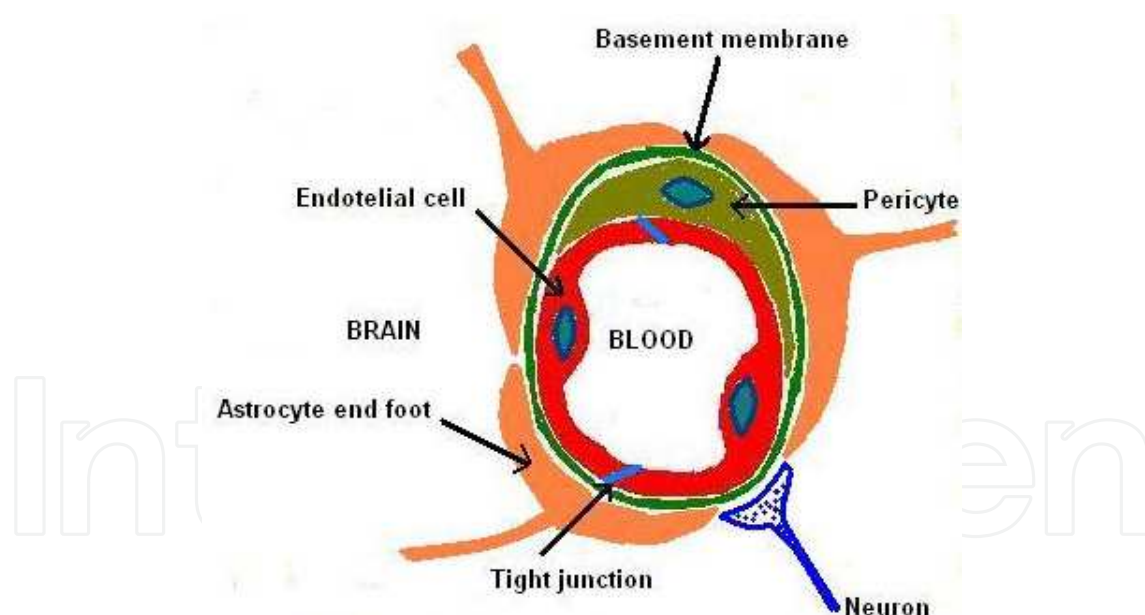

Fig. 1. Schematic representation of the BBB structure.

Induction and maintenance of many BBB properties depends on a close association with astrocytes. Astrocytes are one of the important components of NVU. Astrocytes are glial cells whose end feet form a lacework of fine lamellae closely apposed to the outer surface of the BBB endothelium and respective basement membrane (Figure 2). They play a major role in promoting proteoglycan synthesis with a resultant increase in brain microvascular ECs charge selectivity. On the other hand, a number of astrocyte-released and more generally

glial-released factors have been suggested to contribute to BBB integrity, including glial-derived neurotrophic factor, angiopoietin-1 and more recently angiotensin II. Another important cell that contributes to the NVU is the pericytes. Pericytes are cells that are present along brain and non-brain microvessels, within the basal lamina surrounding ECs; interestingly, brain microvessels are notably rich in pericytes and the pericytes/ECs ratio has been correlated with the barrier capacity of the endothelium. Pericytes are actively involved in maintenance of the integrity of the vessel, vasoregulation and restricted BBB permeability. ECs, astrocytes and pericytes are in close contact with neuronal projections, allowing neuronal mediators to affect cerebral blood flow and vessel dynamics. However, the precise physiological or pathophysiological consequences of neuronal input onto the BBB remain largely unknown (Cardosa et al., 2010; Marchi et al., 2011a; Weis et al., 2009).
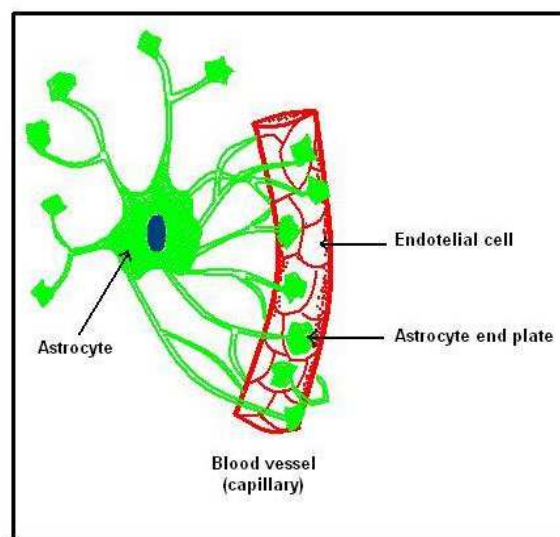

Fig. 2. Note that astrocytes's endfeet are in contact with the endothelial surface.

As mentioned above, BBB properties are primarily determined by junctional complexes between the cerebral ECs and NVU. However, it is necessary to put those junctions into the context of other BBB properties. These include the general paucity of vesicular transport at the BBB, the presence of enzymes that by degradation prevent the entry of a variety of compunds, and the presence of a wide range of transport systems. Because non-lipid soluble compounds only diffuse slowly across the BBB, the latter are necessary for both the entrance of nutrients into brain and the clearance of waste products from brain (Stamatovic et al., 2008).

In general, the brain ECs has a very low number of vesicles under normal conditions compared to other types of ECs. However, during some disease states the number of vesicles can increase. Fusion between vesicles may eventually lead to the formation of transendothelial channels and/or vesicle/vacuolar organelles (VVO). Transendothelial channels correspond to chains of two or more fused vesicles that are open simultaneously on the luminal and abluminal side of ECs. Besides that, channels made by one of the vesicle open on the both sides of ECs can occur. VVO on the other hand are large collection of interconnected vesicles and vacuoles. The fusion of vesicles, vacuole with luminal and

abluminal plasma membranes creates transcellular pathways confirmed in the several ultrastructural studies (Stamatovic et al., 2008).

The BBB can also act as an enzymatic barrier, capable of metabolizing drug and nutrients. The ECs particularly in the BBB contain elevated concentrations of enzymes that are involved in metabolizing neuroactive blood-borne solutes. Such enzymes are γ-glutamyl transpeptidase, alkaline phosphatase, aromatic acid decarboxylase, and monoamine oxidases. These enzymes are often polarized between the luminal and abluminal membrane surface of brain ECs. We know that, the barrier to paracellular diffusion potentially isolates the brain from many essential polar nutrients such as glucose and amino acids. However, the BBB endothelium must contain a number of specific solute transporters to supply the CNS with these substances. The brain ECs forming the BBB expresses transport proteins for a wide variety of solutes and nutrients, mediating flux into and out of the brain. For example, the BBB has very high levels of the glucose transporter 1, GLUT1, and the large neutral amino acid transporter, LAT1, that facilitate movement of those nutrients from blood to brain. Other transporters are involved in ion homeostasis and the transport of signaling molecules between blood and brain. Ions or small molecules are mostly transferred through the brain ECs by transporters/carriers/channels present on the plasma membrane. Most macromolecules move across brain capillary endothelium by bulk phase non-receptor mediated endocytosis. For example, cationic macromolecules prefer uptake by clathrin coated membranes and pits and are subsequently delivered to and degraded in lysosomes. There are also efflux transporters that move compounds from brain to blood. Efflux transporters of the ATP Binding Cassette (ABC) family transport a large panel of lipophilic molecules, in particular xenobiotics, against a concentration gradient by ATP hydrolysis. The most active ABC-transporters at the BBB are P-glycoprotein (P-gp) encoded by the multidrug resistance gene (MDR1 or ABCB1), multidrug resistance proteins (MRPs, or ABCC proteins) and the breast cancer resistance protein (BCRP or ABCG2). The major role of the ABC transporters in the BBB is to function as active efflux pumps consuming ATP and transporting a diverse range of lipid-soluble compounds out of the brain capillary endothelium and the CNS. In this role, they are removing from the brain potentially neurotoxic endogenous or xenobiotic molecules and they are carrying out a vital neuroprotective and detoxifying function. In addition, many drugs are substrates for these ABC efflux transporters and their brain penetration is significantly reduced (Abbott et al., 2010; Stamatovic et al., 2008; Weiss et al., 2009).

3. Blood- Brain Barrier dysfunction in epilepsy: Experimental and clinical studies

The BBB breakdown has been recognized long ago in experimental and human epilepsy. There have been numerous reports indicating that seizures may produce an increase in cerebral capillary permeability (Ruth et al., 1984; Ilbay et al., 2003; Sheen et al., 2011). On the other hand, epileptogenic process may also be triggered by impaired function of BBB (Oby and Janigro, 2006). Generally, the duration of seizure activity is correlated with reduced BBB functions. However, with increased arterial blood pressure, the BBB becomes permeable to macromolecules under induced epileptiform seizures (Öztas et al., 1991; Sheen et al., 2011). Studies reveal that an acute increase in blood pressure or epileptic activity causes an increase in pinocytosis at the level of the cerebral endothelium (Ilbay et al., 2003;

Oby and Janigro, 2006). There is also information from earlier experiments indicating that this BBB alteration is reversible and confined to anatomically limited brain areas. BBB openings have been mapped for a variety of convulsive agents with different mechanisms of action (i.e., impairment of GABA transmission, increased glutamate neurotransmission, direct excitatory action) (Oby and Janigro, 2006; Vezzani et al., 2008). A direct link between the mechanism of action and the region where BBB breakdown was observed is not obvious. However, a few brain regions are easily affected by seizure activity irrespective of the means of induction. Other regions of the brain show BBB breakdown only under the influence of specific convulsants. It is shown that seizures induced by pentylenetetrazole primarily affect thalamus, hypothalamus, midbrain and cerebellum (Sahin et., 2003; Uzüm et al., 2006) (Figure 3). Also, the GABA-receptor blocker bicuculline induces loss of barrier in hippocampus whereas kainic acid induces alterations in capillaries of the neocortical brain areas (Nitsch et al., 1983). The results of our previous study demonstrated that generalised tonic-clonic convulsions, together with elevated blood pressure resulted in BBB opening in multiple areas (Ilbay et al., 2003; Sahin et al., 2003), (Figures 4). Unfortunately, while several models are available to study the BBB in animal models, a suitable (i.e., microscopic, quantitative, and minimally invasive) technique for evaluating BBB integrity in humans does not exist. However, studies on human epileptic tissue show clear BBB abnormalities, including increased micropinocytosis and fewer mitochondria in ECs, a thickening of the basal membrane, and the presence of abnormal Tjs. Finally, it can be stated that opening of BBB is present before, during or after epileptic seizures, is a hallmark of vascular injury in the brain and there are multiple factors involved in etiology of BBB breakdown in epilepsy (Oby and Janigro., 2006; Stamatovic et al., 2008; Vezzani et al., 2008;).

It has been demonstrated that, seizures and epilepsy often develop after traumatic, ischemic, or infectious brain injury. After injury, local compromise of BBB integrity is common (Abbott et al., 2010; Cacheaux et al 2009; Oby and Janigro, 2006), as revealed by ultrastructural studies of animal and human epileptic tissue in multiple forms of epilepsy. (Cacheaux et al 2009; Marchi et al., 2007a; van Vliet et al., 2007), and BBB opening may specifically serve as a trigger event leading to epilepsy. However, the research field has recently considered the fact that damage to the cerebral vasculature could be involved in the pathogenesis of seizures (Oby & Janigro, 2006).

While large amount of published data support a correlation between occurrence of spontaneous epileptic seizures, seizures and abnormal BBB, direct evidence for the involvement of BBB breakdown in epileptogenesis has been only recently confirmed by the studies, in which opening of the BBB was sufficient to induce delayed epileptiform activity (Cacheaux et al., 2009; Seiffert et al., 2004).

Epileptogenesis in the BBB-disrupted brain seems to be mediated by exposure of the brain cortex to serum albumin, mediated via its action on brain astrocytes. The possible involvement of albumin in astrocytic activation and proliferation is supported by previous studies. Based on the studies, it was concluded that there is a specific glial receptor (TGF-β) and signaling pathway for the action of albumin. Thus, it seems plausible that damage to the microvasculature during brain insults leads to the extravasation of serum proteins, leading to the transformation of the neighboring astrocytes as the primary step in the epileptogenic process. In addition, it is notable that in many cases of epilepsy, as well as in most animal models, neuronal damage is observed. In this respect it is interesting to point

out that BBB breakdown has been associated with early or delayed neuronal damage to what extent this damage contributes to epileptogenesis, a result of abnormal activity or not related, is not as yet clear (David et al., 2009; Friedman et al., 2011; vanVliet et al., 2007).
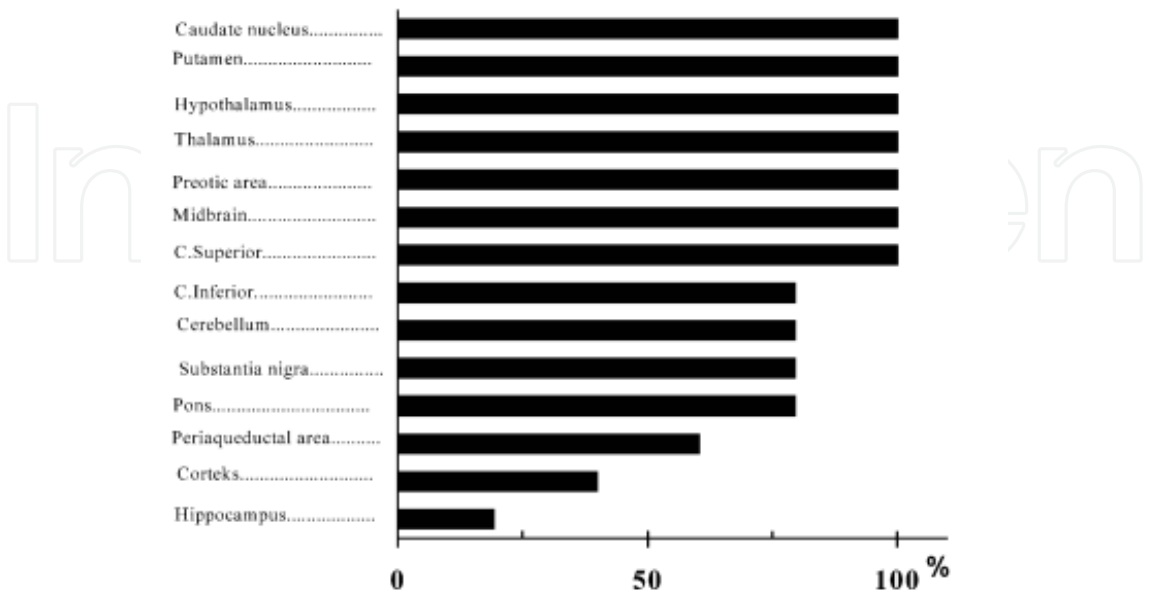
Fig. 3. Patern of BBB opening after PTZ-induced seizures is demonstrated. Regional distribution indicated as percent of total number of animal exhibiting EB leakage. BBB opening is most pronounced and frequently observed in the deep brain areas (Sahin et al., 2003).
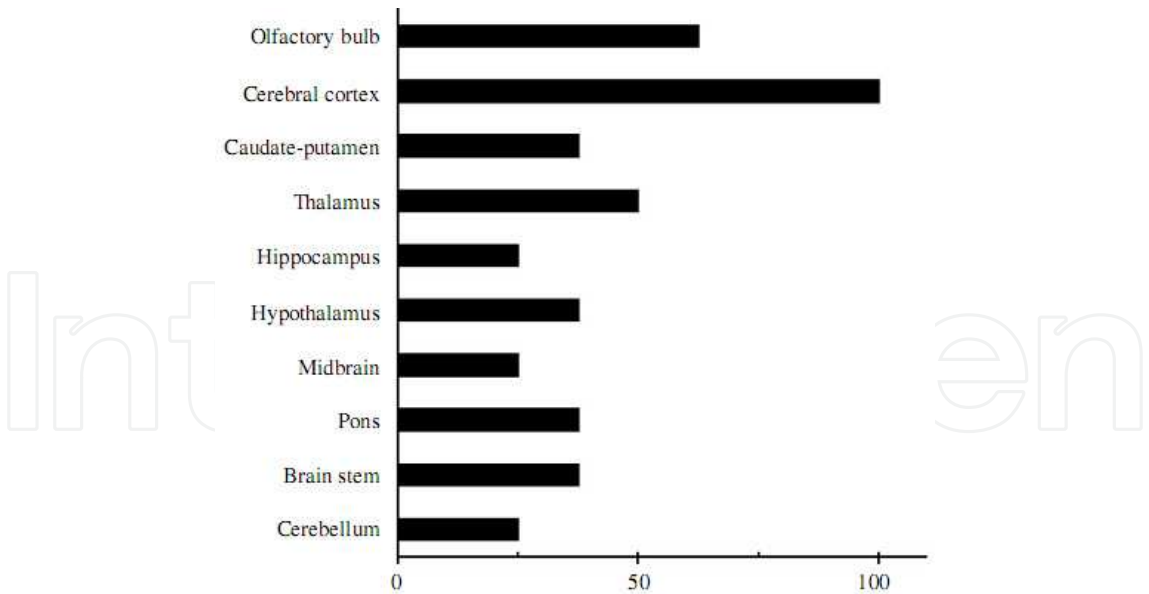
Fig. 4. Pattern of BBB opening after hot water-induced epilepsy is demonstrated. Regional distribution indicated as percent of total number of animal exhibiting EB leakage. BBB opening is most pronounced in cortical areas (Ilbay et al., 2003).

Experimental evidence also supports a role of intravascular inflammation, often associated with BBB damage, in seizure disorders (Marchi et al., 2007a; Marchi et al., 2009; Seiffert et

al., 2004; van Vliet et al., 2007). Recently, the association between circulating immune cells, their interaction with the BBB, and seizure propensity was proposed; leukocyte adhesion was shown to directly support ictogenesis in the pilocarpine model of seizures (Fabene et al., 2008). A recent study conducted on patients affected by temporal lobe epilepsy demonstrated an increase in circulating natural killer cells and cytotoxic T lymphocytes (Bauer et al., 2008). The results were limited by blood analysis at one single time point, making the relationship of these findings to seizures uncertain. These results are, however, comparable to what was reported in the pilocarpine model of epilepsy (Marchi et al., 2007b), where an increase in circulating CD8+ cytotoxic T lymphocytes was measured. In general, concordant data have been obtained using either models of peripheral inflammation, regardless of the initiating trigger; activation of white blood cells was observed prior to development of seizures. Moreover, when kainic acid was used to induce seizures, a contribution of the immune response was demonstrated, suggesting the influence of the adaptive immune response on kainic acid induced hippocampal neurodegeneration (Chen et al., 2004; Silverberg et al., 2010). Taken together, these findings support a link between seizures and immunity in both animal models and in a clinical scenario. The molecular players linking white blood cells activation to BBB damage and seizures are, however, still unknown (Marchi et al., 2011b; Marchi et al., 2009).

BBB dysfunction is a major etiological event of seizure disorder in GLUT-1 deficiency syndrome. Glucose is the principal energy source for the brain and a continuous supply of this substrate is essential to maintain normal cerebral function. GLUT-1 ensures nutrient delivery, supplying glucose for the brain, which is its main energy source. GLUT-1 is highly restricted to the capillary ECs in the brain. The GLUT-1 deficiency syndrome is attributed to a defect of GLUT1 causing impaired transport of glucose across the BBB, interfering with cerebral energy metabolism and brain function, ultimately leading to seizures. GLUT1 deficiency syndrome has led to the investigation of the properties of GLUT1 in epilepsy. Many clinical studies showed that by using fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) of patients with complex partial seizures yielded interictal scans that exhibit hypometabolic regions including the epileptic focus as identified by electroencephalography (EEG). In contrast, ictal scans showed focal, multifocal and generalized increases in the metabolic rate. However, ictal hypermetabolism did not always correspond to regions of interictal hypometabolism. Recent studies concluded that in epileptogenic temporal cortex both the physiology of blood flow and glucose metabolism are altered (Oby & Janigro, 2006). It is hypothesized that the interictal zone of hypometabolism coincides with altered BBB transporter activity and demonstrated that the zone of reduced metabolism according to a FDG-PET corresponds to a region of decreased BBB glucose transporter activity (Cardoso et al., 2010; Cornford et., 1999; Oby & Janigro, 2006). Moreover, human and animal epilepsy studies suggest that, a ketogenik diet leads to anticonvulsant consequences (Masino et al., 2011). The findings of these studies underline that BBB-related hypometabolism may be a common feature of focal epilepsy and not only limited to molecular changes in GLUT1 transporter expression.

Another important aspect of BBB function is its control of drug transport to brain. Permeability of the BBB determines the bioavailability of therapeutic drugs and resistance to chemically different AEDs. ABC efflux transporters at the BBB influence the brain uptake of a variety of therapeutic agents, including many AEDs. The permeability of the BBB becomes

particularly relevant in drug resistant patients. Also effective concentrations of the AEDs are not attained in the brain, because of aberrant functioning of multidrug transporters and changes in drug efflux transporters include the overexpression of P-gp (MDR1), MRP1 and MRP2 (Oby & Janigro, 2006). The ABC transporter P-gp or MDR1 recognizes a wide range of substrates, including a number of AEDs, and is thought to play a major role in drug extrusion. MDR1 overexpression has been demonstrated in a variety of cells in both the BBB and the parenchyma in patients with intractable epilepsy. Many researchers have shown that, there is an overexpression of P-gp in ECs, astrocytes and neurons in a variety of animal models of epilepsy. Seizures have been shown to induce overexpression of other transporters as well. In many cases the overexpression of efflux drug transporters contributes to reduced efficacy of AEDs (Bartmann et al., 2010; Oby & Janigro, 2006; Seegers et al., 2002).

4. Detection of Blood- Brain Barrier dysfunction in epilepsy

As addressed above, epileptic activity influences the BBB and can result in disturbances of its integrity and functionality. From the visible and fluorescence to electron microscope, microscopy constitutes as a widely used tool to study the permeability properties of cerebral vessels in epilepsy. Conventional visible microscopy is used in detecting focal changes in BBB permeability such as in the detection of exogenous tracers or plasma proteins immunoreactivity around blood vessels in brain sections. BBB related proteins can therefore, be detected by immunocytochemical analysis using a flourescent microscope.

Transcellular permeability to exogenous tracers can yield valuable information regarding barrier integrity. Tracers such as horseradish peroxidase (HRP) and Evans blue were used extensively in epilepsy studies (Nag, 2003b). Horseradish peroxidase (HRP) is a plant enzyme having a molecular weight of 40,000 daltons and a diameter of 5 nm. When HRP is reacted with the oxidizable substrate 3 -3′ diaminobenzidine, an insoluble brown reaction product is produced that is easily visualized by light microscopy, and after exposure to osmium ions, and is easily detected by electron microscopy. Multifocal areas of HRP extravasation from cerebral vessel has been observed in rat brains after epileptic seizures (Nag, 2003c).

Evans blue, a dye with high affinity to serum albumin that is not expected to permeate through the BBB, has been used as an indicator of BBB breakdown in epilepsy. Following EB injection in an animal, the staining of the brain is evaluated macroscopically against an arbitrary staining scale, providing a qualitative evaluation of the BBB permeability (Figures 5 and 6). Although this approach has several pitfalls as evaluation is inherently subjective, it is still used nowadays, at least as a first approach to assess BBB permeability in vivo. Such assessment can be improved by semiquantitative analysis of brain slices by fluorescence microscopy or by quantitative determination of the dye in brain homogenates (Ahishali et al., 2010; Cardosa et al., 2010; Uzüm et al., 2006; Ilbay et al., 2003; You et al 2011). Most tracers are labeled by a fluorescent dye or radioactive label that helps the quantification of the molecule (Marchi & Teng, 2010). To determine the limiting size for permeability, different molecular weight tracers can be used, such as fluorescent conjugated dextran (20-,10- and 4-kDa FITC-dextran), propidiumiodide (668 Da), and sodium fluorescein (376 Da). (Cardosa et al., 2010). The main features of the BBB are the presence of tight intercellular junctions, which strictly limit the diffusion of blood-

borne solutes and cells into the brain. Several studies have been performed regarding these junctions, based on commonly used methodologies such as Western blot and PCR, as well as several types of microscopy, as addressed above. Using such approaches, increased BBB permeability associated with a loss of TJ integrity was also demonstrated in models of epilepsy (Ahishali et al., 2010; Rigau et al., 2007).

Membrane transporters and vesicular mechanisms protect the healthy brain, shielding it from toxic substances and allowing the entrance of others that are necessary. Some of the most recent studies regarding this barrier include the regulation of major efflux transporters in epileptic brains (Bartmann et al., 2010). Immunohistochemical methods are used in evaluating P-gp expression induced by seizure in post mortem. Positron emission tomography and Single-photon emission computed tomography (SPECT) studies are currently describing to asses changes in P-gp expression and functionality in vivo (Bartmann et al., 2010; Seegers et al., 2002). The impermeable properties of the BBB constitute an obstacle to AEDs delivery to the CNS, essential to treat brain epilepsy. Therefore, transport of therapeutic agents across the BBB is an area of intensive research. In addition, qualitative evaluation of BBB disruption in humans is available using imaging modalities (magnetic resonance imaging, computerized tomography, and SPECT) following the peripheral administration of non-permeable contrast agents. Although MRI imaging, due to its' high spatial resolution, is considered the best available method for studying anatomical lesions, it is regarded as relatively insensitive for detecting small changes in contrast agent accumulation as compared with SPECT. A quantitative evaluation of BBB permeability functioning in patients may be obtained using analysis of the cerebro-spinal fluid for serum proteins or brain constitutes (e.g. S100β) in the peripheral blood. Opening of the BBB provides molecules normally present in blood with open passage into the CNS. Proteins normally present in the blood freely diffuse into the CNS, and in turn, molecules and protein normally present in high concentrations in the CNS freely diffuse into the blood. Such markers of BBB opening can be detected in the blood in order to evaluate the permeability characteristics of the BBB. However, these methods do not offer spatial information, are invasive, may give false positive results in the presence of intracerebral hemorrhage and S100 levels may depend on the extent of injury or activation of brain astrocytes (Friedman et al., 2009; Marchi et al., 2010; Marchi et al., 2011a).
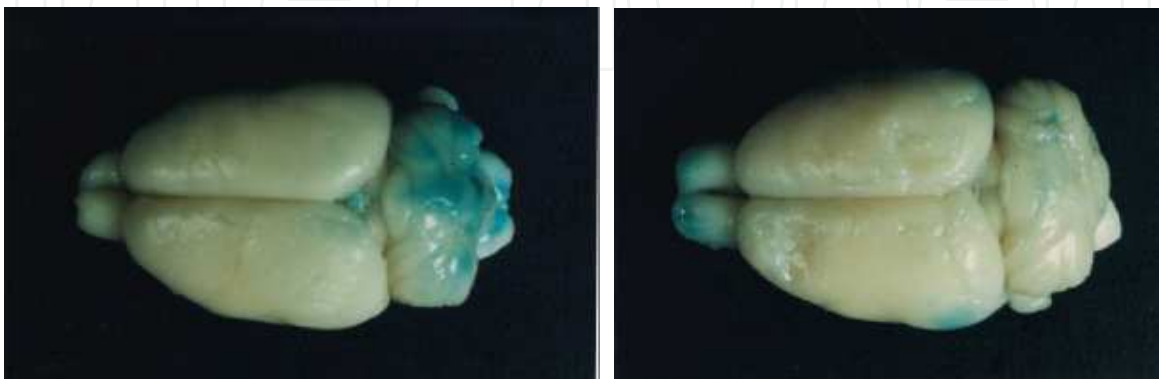

Fig. 5. Gross evaluation of BBB opening in rat brains. Evan's blue staining is noticable by visual inspection in cerebellum (left), temporal cortex and olfactory bulbs (right).

On the other hand, there are studies suggest that a correlation between disrupted BBB and abnormal neural activity. Quantitative EEG analysis may offer spatial information of cortical dysfunction due to BBB disruption. Spectral EEG analysis reveals slow (delta band) activity in regions showing BBB disruption. The usage of quantitative EEG analysis and the detection of abnormal BBB permeability may give information not only about the identification of the epilectic region, but also for targeting population at risk to develop epilepsy (Friedman et al., 2009; Mairinger et al., 2011; Marchi et al., 2010; Tomkins et al., 2007)
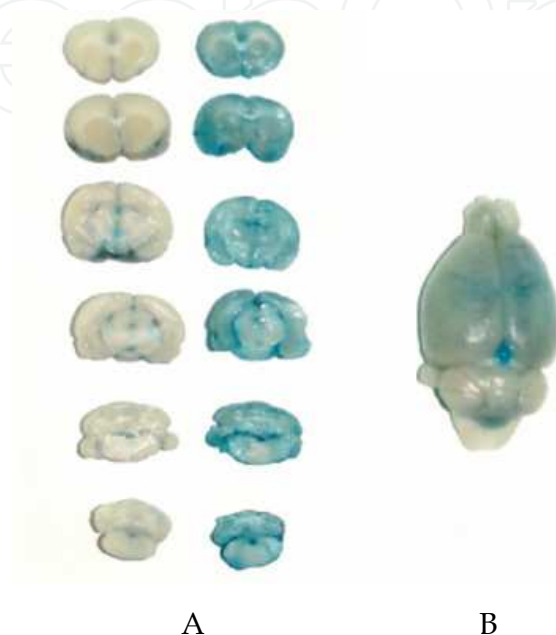

A   B

Fig. 6. Photographs of rat brains are depicted. Evan's blue staining is seen in the whole brain and corresponding slices (B) whereas no stain is present in the other brain slices (A).

5. Spectral nalysis of EEG signals

Spectral analysis methods are used for determining the spectral content (distribution of power over frequency) of a time series from a finite set of measurements (Kay & Marple, 1981; Kay, 1988; Proakis & Manolakis, 1996; Stoica & Moses, 1997; Akay, 1998; Akay et al., 1990). The power spectrum is showing abnormal neural activity caused by BBB disruption in the frequency bands.

The power spectral density (PSD) of the signal is estimated by applying spectral analysis methods. The PSD estimates represent the changes in frequency with respect to time. The classical methods (nonparametric or fast Fourier transform-based methods), model-based methods (autoregressive, moving average, and autoregressive moving average methods), time-frequency methods (short-time Fourier transform, wavelet transform), eigenvector methods (Pisarenko, multiple signal classification, Minimum-Norm) can be used to obtain PSD estimates of the signals (Kay & Marple, 1981; Kay, 1988; Proakis & Manolakis, 1996; Stoica & Moses, 1997; Akay, 1998; Akay et al., 1990; Übeyli, 2009a; Übeyli, 2009b; Übeyli, 2010). The obtained PSD estimates provide the features which are well defining the signals. Therefore, spectral analyses of the signals are important in representing, interpreting and discriminating the signals (normal and abnormal signals).

The frequency resolutions of the fast Fourier transform based (FFT-based) methods are limited by the data record duration, independent of the characteristics of the data. The spectral leakage occurs due to windowing that are seen in finite-length data records. The effect of windowing processing with the FFT-based methods is obtaining smear or smooth estimated spectrum (Kay & Marple, 1981; Kay, 1988; Proakis & Manolakis, 1996; Stoica & Moses, 1997). The modelling approach for the model-based methods eliminates the need for window functions. The statistical stability and spectral resolution properties of the model-based methods are better and the resolution is less dependent on the length of the record. The disadvantages of the model-based methods compared to the FFT-based methods are: the FFT-based methods are more widely available and are more widely used approach in spectrum analysis; the model-based spectra are slower to compute; the model-based methods are not reversible; the model-based methods are slightly more complicated to code; the model-based methods are more sensitive to round-off errors, and the orders of the model-based methods depend on the characteristics of the signal and the methods for model order determination are not sufficient (Kay & Marple, 1981; Kay, 1988; Proakis & Manolakis, 1996; Stoica & Moses, 1997). The results of the studies existing in the literature are indicating high performance of the model-based methods for the time-varying biomedical signals such as EEG signals (Übeyli, 2010).

The time-frequency analysis methods show better performance in spectral analysis of nonstationary signals by comparing with the classical and model-based methods. Time and frequency resolutions of the short-time Fourier transform (STFT) are fixed over the entire time-frequency plane. The STFT assumes that the data are quasistationary for the duration of each analyzed segment. The computation of the FFT of a short segment of the signals is forming a spectral estimate distortion and leakage of signal energy into spurious side lobes due to the sharp truncation of the signal. In order to reduce this distortion, a window function is used which reduces the amplitude of the analyzed signal toward the beginning and end of the data segment. Using short data windows lead to the distortion and poor spectral resolution and using longer data windows lead to the spectral broadening that arises from nonstationary characteristics of the signal. In order to solve this problem, a scalable window, which is more flexible approach, can be used (Akay, 1998). The WT solves the problem of fixed resolution by using base functions that can be scaled. The wavelets are better suited to analyzing nonstationary signals, since they are well localized in time and frequency. The property of time and frequency localization is one of the most important features of the WT. The WT has a varying window size, being broad at low frequencies and narrow at high frequencies, and therefore leading to an optimal time-frequency resolution in all frequency ranges. The windows are adapted to the transients of each scale and then the wavelets do not require stationarity. The EEG signals are time-varying and random and therefore, the WT has become a powerful alternative to the STFT in analysis of the time-varying biomedical signals (Akay, 1998; Übeyli 2009a).

The estimation of frequencies and powers of signals from noise-corrupted measurements can be performed by the eigenvector methods. Eigen-decomposition of the correlation matrix of the noise–corrupted signal is the basic process of the eigenvector methods. The resolution of the PSD estimates obtained by these methods is high for the signals having low signal-to-noise ratio (SNR). These methods have a good performance for obtaining PSD estimates of the signals that can be assumed to be composed of several specific sinusoids buried in noise (Akay et al., 1990; Übeyli, 2009b). Therefore, the eigenvector methods have good performance in spectral analysis of the EEG signals.

6. Conclusion

BBB is present at the interface between the blood and the CNS. It controls the exchanges between the blood and brain compartments, by actively transporting nutrients to the brain, and protecting CNS from many toxic compounds and pathogens. Its extremely low permeability is due to the endothelial tight junctions and the activity of multiple efflux transport systems. BBB dysfunction or BBB opening has long been known in seizure disorders and epilepsy. Data from experimental and clinical studies indicates that epileptic seizures produce significant alterations in BBB permeability. These BBB alterations are reversible and confined to anatomically limited brain areas. Epileptic seizure induced disturbances in cerebrovascular permeability involve an interaction between global systemic factors and more localised molecular phenomena occuring in the microenvironment of recruited neurones. However, cerebrovascular dysfunction has been recently proposed to have an etiological role in epilepsy. It is suggested that astrocytic activation, inflammation and neuronal damage contribute to epileptogenesis in the BBB- disrupted brain. There are several applications used to understand BBB dysfunction in the epileptic brains. The exogenous tracers have been used to detect BBB permeability. The endogeneous protein extravasations caused by BBB disruption have been detected by immunohistochemistry. Magnetic resonance imaging, positron emission tomography, computerized tomography, and SPECT studies are currently described to assess changes in BBB permeability. In addition, evaluation of BBB disruption is available using EEG analysis. Spectral analyses of the signals are important in representing, interpreting and discriminating the signals (normal and abnormal signals). Finally, spectral analysis methods can be used for obtaining the power spectrum those showing abnormal neural activity caused by BBB disruption in the frequency bands.
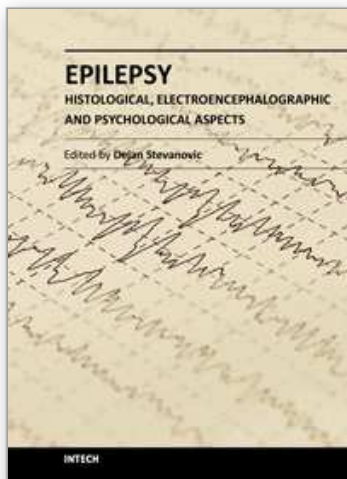
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With the vision of including authors from different parts of the world, different educational backgrounds, and offering open-access to their published work, InTech proudly presents the latest edited book in epilepsy research, Epilepsy: Histological, electroencephalographic, and psychological aspects. Here are twelve interesting and inspiring chapters dealing with basic molecular and cellular mechanisms underlying epileptic seizures, electroencephalographic findings, and neuropsychological, psychological, and psychiatric aspects of epileptic seizures, but non-epileptic as well.

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