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NEUROLOGY
Review Article

The blood brain barrier and the cerebral blood flow: From basics to the bedside

Bhumir Chauhan[1]* and Grishma Thaker[2]

[1]*Department of Neurology, Narayana Health City, Bangalore, Karnataka, India*
[2]*Department of Basic Sciences, AMC-MET Medical College, Ahmedabad, Gujarat, India*

***Corresponding Author:** Dr. Bhumir Chauhan, Department of Neurology, Ground floor, MSH building, Narayana Health City, Hosur main road, Bommasandra Industrial Area, Bangalore, Karnataka, Bangalore, India.

Received: February 11, 2016; **Published:** February 25, 2016

Abstract

Human brain has certain unique characteristics in terms of blood flow and its regulation. Blood brain barrier has been known to exist since long, however the understanding regarding its structure and functions has recently evolved. It forms an anatomical and a physiological entity, composed of astrocytes, blood capillaries and pericytes. Its functions and role in cerebral blood flow control is intriguing and complex. Also, the components of blood brain barrier take part in other non-vascular functions such as immune functions, enzymatic activity and interstitial fluid formation. The complex interplay of numerous variables ensure precise blood flow control in the central nervous system. It has been realized that cerebral blood flow is dependent on chemical, physical, metabolic, synaptic and neurogenic factors. With ongoing research in this field, the blood brain barrier and cerebral blood flow dysregulation have been documented to have important role in wide range of neurological disorders that include stroke, infections, autoimmune diseases, etc. Their role in neurodegenerative disorders is under research and has received significant attention in last few years. This review highlights the basic anatomy and physiology of these vital entities and also draws focus to the spectrum of disorders associated with them. The discussion in this review is just the beginning of the thousands of pages that await to be written in this field. Understanding the physiology is an essential step towards further research. The structure and functions of blood brain barrier and cerebral blood flow have many investigational and therapeutic implications.

Keywords: *Blood Brain Barrier; Astrocytes; Endothelium; Cerebral blood flow; Clinical implications*

Abbreviations: BBB: Blood Brain Barrier; BM: Basement Membrane; BOLD: Blood Oxygen Level Dependent; CBF: Cerebral Blood Flow; CNS: Central Nervous System; COX: Cyclooxygenase; CPP: Cerebral Perfusion Pressure; CSF: Cerebrospinal Fluid; EDHF: Endothelium Derived Hyperpolarization Factor; EPOX: Epoxygenase; Fmri: Functional Magnetic Resonance Imaging: ICP: Intracranial Pressure; LOX: Lipoxygenase; MAP: Mean Arterial Pressure; NOS: Nitric Oxide Synthase; TJ: Tight Junctions

Introduction

The human brain is a specialized vascular organ. The neurons are exquisitely sensitive to minute changes in the internal milieu. Hence, as a protective mechanism, the pressure and rate of flow of blood is regulated by inherent protective mechanisms. The cerebral blood flow (CBF) and the blood brain barrier (BBB) constitute an essential and one of the most researched physiological entities of the human brain. As the research continues, newer and newer implications have been hypothesized linking them to various neurological disorders. The anatomical structure and their physiological roles are complex, consisting of multiple overlapping paradigms with key regulatory components.

Knowing the basics forms the first step in understanding any complex mechanism and helps further research in the field. This review will attempt to enlighten the basic sciences related to these vital neurophysiological functions and also discuss the spectrum of neurological disorders linked with dysfunction of BBB and CBF.

Building the Blood Brain Barrier

The BBB is an anatomical as well as a physiological entity, which prevents free flow of substances from systemic circulation to the brain or cerebrospinal fluid (CSF) and vice versa. This limited exchange of substances, regulated through specific mechanisms, is known as the Blood Brain Barrier (between capillaries and neurons) and the Blood CSF Barrier (between capillaries and choroid plexus). The chief constituents of the BBB are as under [Figure 1]:

Endothelial Cells

In central nervous system (CNS), the capillaries have specialized endothelial cells that differ from those in the systemic circulation. The unique features of CNS endothelial cells make them a very important component of the BBB and regulation of the CBF [1].

1. Lack of fenestrations and presence of tight junctions (TJ)
2. Presence of mitochondria for ATP generation during active transport
3. Presence of glucose (GLUT) and amino-acid transporters
4. Presence of astrocytic foot processes
5. Presence of specialized cells surrounding the endothelium, known as pericytes
6. Presence of ATPase channels
7. Capacity to secrete various vasoregulatory substances
8. Presence of specialized receptors such as endothelin receptors

The TJs are the connections between adjacent endothelial cells. The site of connection is known as the 'Zona Occludens'. The TJ consist of three integral membrane proteins, namely, Claudin, Occludinand junction adhesion molecules [2]. The claudin molecules from adjacent endothelial cells assemble to form a 'zip-lock' junction [3]. The TJ help to create a physical barrier as well as provide electrical resistance to regulate the transport of macro and micro molecules.

The presence of glucose, amino acids, ATPase and other specialized transporters also control the movement of specialized molecules and maintain the internal microenvironment [1].

Capillary basement membrane

The basement membrane (BM) of CNS capillaries in composed of type IV collagen, fibronectin, heparansulfate, laminin and entactin. It encircles the abluminal surface of the endothelial cells and generates a physical barrier for molecular transport.

Astrocytes

These are the glial cells of the CNS and one of the most important constituent of the BBB. The foot processes of the astrocytes are attached to the BM. Over the years, it has been realized that the most important function of astrocytes is the induction of formation of tight junction and differentiation of the developing endothelial cells [4]. It has been proposed that an astrocyte induced soluble factor may be responsible for the induction of BBB characteristics in the endothelial cells [5]. The role of astrocytes in the BBB is of great interest to the current research world and may have therapeutic importance in the future.

Pericytes

These are special cells that are a combination of smooth muscles and macrophages, attached on the BM [6]. Currently, the exact role of these cells is not clear, although they have been designated with various functions such as [2]:

A. Providing structural integrity
B. Vasodynamic control and autoregulatory functions
C. Promote angiogenesis and repair of BBB
D. Phagocytic and neuroimmunological functions

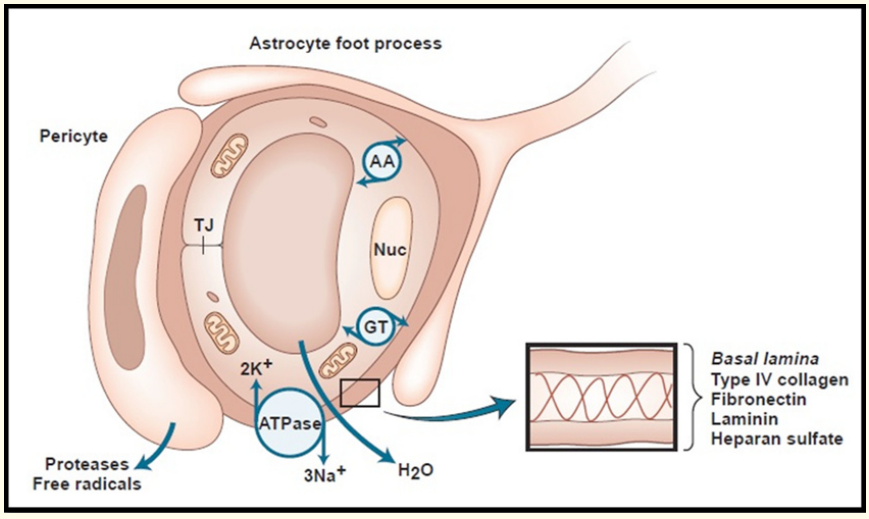

Figure 1: *The Blood Brain Barrier.*

The constituents of blood brain barrier are capillary endothelium, capillary basement membrane, astrocytes (foot processes) and pericytes. The special properties of the central nervous system capillaries are presence of tight junctions (TJ), ATPase pumps, glucose (GT) and amino acid (AA) carrier channels, presence of mitochondria and unique composition of the basement membrane. The astrocytic foot process surround the capillary whereas the pericytes are believed to have phagocytic and vasoregulatory functions.

Functioning of the Blood Brain Barrier

The blood brain barrier lacks passive transport. Under physiological conditions, only the water, carbon dioxide, oxygen and the lipid soluble molecules are allowed to move freely across the BBB. The rest of the transport is carried out through active mode, using the ATP generated by the mitochondria. The presence of specific transporters such as ATP binding cassette are responsible for the active transport [7]. Channels for glucose (GLUT), amino acids, Na/K/2Cl transporter and aquaporin channels allow finely regulated movement of substrates as per the requirements of the CNS.

The lipid composition of the BBB has been studied widely over the past few years. The brain capillary endothelium was demonstrated to be consisting of complex lipids such as cholesterol, phosphatidylcholine, sphingomyelin and glucosylceramide [8-10]. As demonstrated by Bénistant et al, the unique lipid composition of the brain endothelial cells seems to be influenced by the presence of astrocytes during the stages of neural development and angiogenesis [11]. The possible functions of lipid molecules in BBB are generation of a suitable lipid environment for the membrane proteins and synthesis of plasma membrane domains with different biophysical properties and permeabilities.Moreover, the endothelium contains the Multidrug Resistance proteins and its associated proteins, which form active transport channels to extrude the substances against the concentration gradient across the BBB [7]. One of the earliest identified transporter protein, the P-glycoprotein, has been implicated for lipid, steroid and peptide transport across the BBB. Additionally, its wide binding specificity allows the transport of xenobiotics, thereby limiting the entry of therapeutic molecules in the brain [12]. Hence, the

presence of suchcomplex lipid and protein molecules in the BBB create a major impediment for the transfer of drugs into the brain. Only the lipid soluble molecules have been demonstrated to enter the CNS freely. Chemotherapeutic agents, when given through parenteral or oral route, have limited access to brain tumors. Thus, to circumvent this, intrathecal or intraventricular route of administration has been employed for drug delivery.

The brain endothelium has also been shown to possess metabolic functions. The metabolism of fatty acids and proteins is regulated at the level of BBB. The endothelium also has enzymatic activity with the presence of important enzymes such as cytochrome P450 system, monoamine oxidase and dopamine decarboxylase [7]. One of the well-studied example of enzymatic function of BBB is that of dopamine regulation. The lipid soluble compound of dopamine L-DOPA enters the brain easily, thereby has therapeutic utility in Parkinson's disease. However, its efflux into the parenchyma is regulated at the level of BBB through the decarboxylase and monoamine oxidase enzymes present in the endothelium [13].

The CNS endothelium regulates the entry of peripheral cells into the brain parenchyma. During infection or inflammation, the cytokines and chemokines released in the circulation activate the endothelial cells. This results in increased expression of selectins and integrins over the capillary surfaces, which assist the entry of immune cells inside the parenchyma [14]. Apart from infectious and inflammatory disorders, the recent research has extrapolated the role of immune cells in neurodegenerative disorders as well (see below).

From the physiological point of view, the components of BBB contribute to specific functions at different interfaces. The BBB therefore consists of the physical barrier (TJ), immune barrier (astrocytes, pericytes), enzymatic barrier and transport barrier. Apart from these, BBB also contributes in formation of CNS interstitial fluid, autoregulation of CNS capillaries and prevent the escape of essential neurotransmitters into the systemic circulation.

The Physiology of Cerebral Blood Flow and Autoregulation

The process whereby the cerebral arterioles maintain a constant cerebral blood flow in the face of a changing cerebral perfusion pressure (CPP) is referred to as Cerebral Pressure Autoregulation. Human brain is an extremely vascular and sensitive organ, with high susceptibility to hypoxemia and lack of nutrients. Fluctuations in the systemic blood pressures are prevented from being transmitted to the CNS via this immaculate and efficient system of autoregulation. The CBF is maintained at a constant rate within the CPP range of 50-150 mm Hg [Figure 2]; above and below which CBF varies according to the CPP [15].

The normal CBF is 50-70 ml / 100 grams brain tissue / minute. Values below 20 ml have been associated with cerebral ischemia and neuronal damage. While the CBF is dependent on the CPP, the CPP in turn is regulated by the mean arterial pressure (MAP) and the intracranial pressure (ICP). The relationship of CPP, MAP and ICP has been formulated as

$$CPP = MAP - ICP$$

The systemic blood pressure depends on physical exertion, hormones, cardiac functions, circadian rhythm and changing requirements of blood flow in visceral organs. The autoregulatory control of CBF ensures consistent supply of nutrients to the sensitive neurons and provides protection against the systemic fluctuations in blood pressure.

Control of the Cerebral Blood Flow

With passing years, it has been realized that the CBF is not under regulation of any single system. A wide array of variables work in harmony for precise control of the CBF [Table 1].

Cerebral Capillaries

The endothelium has been a dynamic source of vasoregulatory molecules, which regulate the vascular tone in the CNS and thereby the cerebral blood flow. In addition, the endothelium contains the 'mechanoreceptors' which respond to the increased flow velocities and transmural pressures so as to induce vasoconstriction.

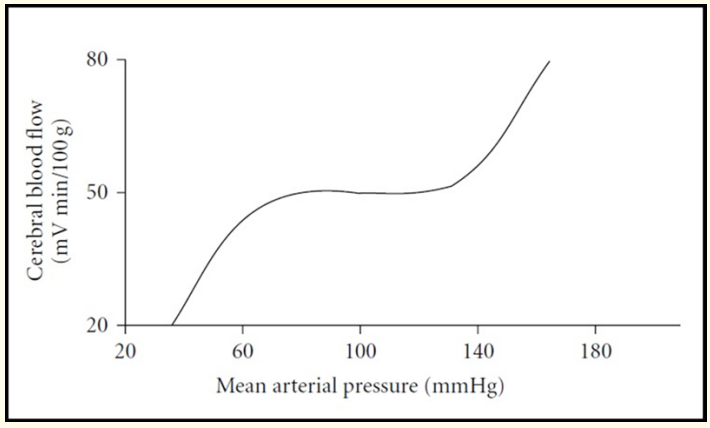

Figure 2: *Relationship between cerebral blood flow and mean arterial pressure.*
The cerebral blood flow stays constant in the mean arterial pressure range of 50 to 150mm Hg, thereby providing a protective mechanism for the central nervous system against the systemic fluctuations in blood pressure. This is known as autoregulation of cerebral blood flow. Changes in mean arterial pressure beyond this range fails the autoregulation mechanism and is associated with several neurological disorders.

Variable	Control
Cerebral Capillaries	Endothelium, Smooth muscles
Physical factors	Vessel radius, Vessel length, Tensile strength of vessel wall, Blood viscosity
Neurogenic factors	Sympathetic and parasympathetic nerves, local interneurons
Systemic factors	Oxygen, Carbon dioxide, Potassium, Hydrogen, Acid-base balance
Astrocytes	Potassium and calcium mediated
Endothelium	Nitric oxide, Endothelium derived hyperpolarization factor, Endothelins, Eicosanoids
Synaptic activity	Flow-metabolism coupling
Microvascular communication	Connexins

Table 1: *Control of the cerebral blood flow.*

The smooth muscles in the capillaries also contribute to its functions of autoregulation. The 'myogenic theory' suggested that smooth muscles themselves act as mechanoreceptors and respond to the variations in blood flow and pressures via the voltage gated calcium channels [16].

Physical factors

As per the law of fluid motion, the cerebral blood flow is also dependent on the tensile strength of the vessel wall, radius of the blood vessel, blood viscosity and vessel length.

Neurogenic factors

The functional unit formed by the endothelial cells, astrocytes and the perivascular nerves has been increasingly recognized as a complex network, referred to as the 'neurovascular unit'. The neuronal regulation of blood flow is basically classified as extrinsic and intrinsic mechanisms.

The extrinsic mechanism comprise of the perivascular innervation outside the brain parenchyma. The chief sources are trigeminal nerve, sphenopalatine ganglion and the superior cervical ganglion which carry the sensory, parasympathetic and sympathetic nerves respectively.

The intrinsic mechanism refers to the perivascular innervation arising from distant pathways [17,18]. and local interneurons [19]. Most of these nerves abut on the foot processes of the astrocytes. The nucleus basalis (cholinergic), locus coeruleus (nor-adrenergic) and raphe nucleus (serotonergic) have been implicated to play a role in blood flow regulation.

Systemic factors

Hypoxia causes vasodilation and increase in CBF. The mechanism involved in this phenomenon are reduced ATP causing reduced potassium concentrations, activation of nitrous oxide synthase enzymes and production of adenosine [20].

Hypocapnia results in vasoconstriction and reduced CBF. Systemic alkalosis due to hypocapnia causes excess H+ ion formation which causes smooth muscle contraction. On the other hand, hypercapnia causes induction of prostanoid and nitric oxide, causing vasodilation and increase in CBF.

The cerebral blood flow increases in a focal area after neuronal activity. This has been confirmed by advanced neuroimaging techniques like functional magnetic resonance imaging (fMRI). Potassium and hydrogen ions are generated during the synaptic activity and they have been shown to stimulate vasodilatation [21,22].

Role of Astrocytes

The astrocytes are the glial cells linked directly to the cerebral capillaries and the BBB via the foot processes. Beyond the role in formation and maintenance of BBB, astrocytes have now been implicated in vasoregulatory functions at the synapses.

The astrocytes are known to uptake the excess potassium ions generated during the synaptic signalling. This excess potassium may be responsible for the focal vasodilatation around the neuronal activity [22].

Moreover, electric stimulation of astrocytes was associated with increase in the intracellular calcium, causing capillary vasodilation [23]. The astrocytic stimulation during synaptic activity is thought to occur by glutamate. This phenomenon again explains the focal increase in the cerebral blood flow following synaptic transmission.

Chemical Control through Endothelium

As noted previously, endothelium forms an epicentre in the CBF control. It is appreciated as a dynamic organ that has physical, neuronal and chemical influences. The chief chemical systems linked to CNS endothelium are nitric oxide (NO), endothelium derived hyperpolarization factor (EDHF), eicosanoids and the endothelins.

NO is a second messenger that is found in smooth muscles. It relaxes the smooth muscles via the cyclic GMP pathways. Induction of NO synthesis is mediated by nitric oxide synthase enzyme (NOS), which has three isoforms, namely endothelial NOS (eNOS), neuronal NOS (nNOS) and inducible NOS (iNOS). Of these, the eNOS and nNOS are active under physiological conditions whereas the iNOSis found under pathological conditions such as hypertension or sepsis [24].

Eicosanoids are derived from the arachidonic acid. The three main enzyme systems that have been identified in the endothelium are cyclooxygenase (COX), lipoxygenase (LOX) and epoxygenase (EPOX) [25]. These enzymes are also active in a variety of tissues, especially platelets. The metabolites such as thromboxane, prostacyclins, leukotrienes, etc. produced by these enzyme systems regulate the vascular tone under physiological and pathological conditions.

The endothelin system has two receptors (ET-A, ET-B) and three ligands (ET1, ET2, ET3). Again, the interplay of these ligands with their receptors alters the vessel tone; ET1 being the most important of them all [26]. ET-A receptors when stimulated by ET1 and ET2 cause vasoconstriction, whereas ET-B receptors result in vasodilation.

In spite of NO and eicosanoid pathways being dominant, another separate pathway has been proposed that includes a diffusible molecule known as endothelium derived hyperpolarization factor (EDHF). It is a vasodilatory pathway that causes hyperpolarization of the smooth muscles and involves potassium channel activation [27].

Synaptic activity

Activation of certain neuronal population results in increased blood flow surrounding that area. This phenomenon is known as 'Flow-Metabolism coupling' and is a basis of newer investigation modalities [28]. A synaptic activity occurs via release of neurotransmitters and interaction of ions or molecules. Substances such as potassium, hydrogen, adenosine, lactate, glutamate, etc. are released in variable amounts during a synaptic activity and have direct or indirect impact over the local vasculature and blood flow as mentioned above.

Microvascular communication

Several lines of evidence have been proposed over the years to support certain kind of communication between and amongst the micro as well as macro circulation channels in the CNS [29-32]. The small vessels communicate with each other and transmit signals for alterations in the vessel tone. Such communication is proposed to be carried out by the Connexin molecules in the endothelial junctions [33]. In response to ischemic insult, changes in the expression of connexins results in alterations in the vasomotor activity.

Clinical Implications

Unlike earlier assumptions, recently the BBB and CBF have been implicated in a wide spectrum of pathological conditions. They have been proven to be of a significant importance in the pathophysiological, investigational and therapeutic aspects of many neurological disorders.

1. Endothelial dysfunction and impaired vasoregulatory functions form the basis of vasogenicedema in cerebral hyperperfusion syndrome that comprise of diseases like hypertensive encephalopathy, posterior reversible encephalopathy syndrome, reversible cerebral vasoconstriction syndrome and eclampsia.
2. The relationship of CBF and ICP (CPP = MAP - ICP) explains the management of blood pressure during acute ischemic stroke. In case of a large vessel infarction, local reduction in CPP compromises the CBF in that area. Simultaneously, the ICP increases due to edema surrounding the infarcted region. This rise in ICP further reduces the CPP and CBF, worsening the ischemia. Hence, it becomes prudent to maintain the MAP at a higher level, so as to compensate for the increase in ICP and sustain the CPP at near normal level.
3. Ischemic insult results in BBB dysfunction, causing loss of autoregulation of blood flow. This concept is important during the blood pressure management in stroke. Even minor fluctuations in systemic blood pressure may cause worsening of ischemia (in case of hypotension) or hyperperfusion intracranial haemorrhage (in case of hypertension).
4. Inflammation induced breach in the BBB results into disease maintenance and propagation in autoimmune neurological diseases, CNS infections and multiple sclerosis [34]. The mechanism of BBB mediated immune cell entry into the brain has been well studied. The cytokine and chemokine mediated upregulation of integrins and selectins causes excess entry of lymphocytes and monocytes in the CNS. This understanding can be extended to therapeutic use of substances that can inhibit these adhesion molecules. One such example is the use of Natalizumab, anα4β1 integrin inhibitor, which prevents the entry of immune cells against CNS myelin in multiple sclerosis.

5. Cerebral amyloid angiopathy and arteriosclerosis are chronic disorders of cerebral vasculature. These diseases result in altered CBF control and endothelial function, resulting into susceptibility for micro-haemorrhages and lobar haemorrhages.
6. BBB dysfunction has been implicated as one of the pathophysiological mechanisms for Alzheimer's disease [35]. Excess accumulation of amyloid and impaired clearance through capillary endothelium results in progressive accumulation of amyloid in the parenchyma. Specific transporters have been identified in the CNS endothelium, responsible for the amyloid transport, which are upregulated in Alzheimer's disease [36]. With increasing load of amyloid, microglial activation and reactive oxygen species mediated damage perpetuates the disease process [37].
7. In amyotrophic lateral sclerosis, dysfunction of the BBB allows the leakage of immunoglobulins and immune cells from the circulation into the parenchyma. Interaction with CNS antigens leads to immune reaction and reactive oxygen species formation, causing motor neuron dysfunction [38].
8. More recently, the role of BBB in pathogenesis of HIV dementia has also been speculated. The gp120 receptor of HIV surface has been shown to alter the BBB endothelial integrity, causing immune reaction in brain parenchyma and resultant neuronal degeneration [39].
9. Medical treatment of CNS disorders such as cancer is hampered by the limitation to the transport of drugs inside the CNS. The BBB forms a major barrier for free entry of drug molecules inside the CNS, with the help of specific transport proteins. Molecules that can inhibit these multidrug transporter proteins may be an option to enhance the drug delivery inside the brain parenchyma.
10. Dysfunction of BBB results in leakage of the contrast dye administered parenterally. This forms the basis for contrast based imaging investigations in various infective and inflammatory conditions.
11. The mechanism of flow-metabolism coupling, mediated by BBB and CBF dynamics, has been utilized to analyse the functional aspects of the brain. The blood oxygen level dependent (BOLD) mechanism forms the basis of functional MRI that is one of the advanced mode of neuroimaging, allowing the functional mapping of brain areas.

Conclusions

The concept of BBB, autoregulation and CBF is one of the most basic fundamentals in understanding the vast spectrum of neurological disorders. Endothelial cells are the orchestrators of the neural vascular system. Together with the astrocytes and neurons, forming the neurovascular unit, they play a central role in CBF regulation. The future lies in the ongoing and upcoming research which involves investigational and therapeutic usefulness of these anatomical and physiological entities. This review was an attempt to provide an overview on these complex mechanisms. The discussion provided here forms just a few drops of an entire ocean of information in the field of cerebral circulation. The genetic, microstructural and environmental factors influencing the cerebral circulation may be exceedingly complex and only beginning to be elucidated.

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Volume 2 issue 6 February 2016