Blood Supply, Dural Sinuses and Blood-Brain Barrier
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OBJECTIVES

Following a review of this material, the student should be capable of:

1. Identifying the arterial supply to the cerebrum and brain stem
2. Identifying the venous drainage of these regions and the sinuses receiving such drainage
3. Discussing the basic regions supplied by these arterial and venous systems
4. Discussing the functional characteristics of the blood-brain barrier
5. Identifying the transport systems found in the CNS endothelial cells
6. Appreciating how the blood-brain barrier can be altered in various disease or injury states

I. Introduction

Although the brain represents a small part of the body's mass, it receives a disproportionate amount of cardiac output to supply its constant high energy and substrate demands. Obviously, to deliver this large flow requirement, the brain possesses an elaborate and highly organized vascular system. Blood flow to the brain derives from the internal carotids which arise from the carotid trunk as well as from the vertebral arteries which originate from the subclavian arteries. The vertebral arteries pierce the dura at the foramen magnum to ramify throughout the brain stem. The internal carotid on the other hand travels through the carotid canal and the cavernous sinus to reach the base of the cerebrum from where branches supply virtually all the cerebral cortex. Both the vertebral and carotid systems join at the base of the brain to form a network of interlinked vessels termed the circle of Willis. The circle of Willis is formed by the first segments of the two anterior cerebral arteries joined by the anterior communicating artery, the internal carotids, the first segments of the two posterior cerebral arteries as they arise from the basilar artery, and the two posterior communicating arteries, connecting the posterior cerebral with the internal carotid arteries (see following passages for more detail). The circle of Willis provides a vascular shunting conduit for the two vascular systems that enables a continuous blood supply to the brain when one system or the other is compromised. If blood pressure drops in one part of the system, blood will flow into it from the other. Although this would appear to be the ideal mechanism for dealing with various abnormalities, whereby blood flow could always be maintained in the face of an obstruction in this system, regretfully this is not always the case, as the circle of Willis lacks perfect symmetry. One or more of the connecting vessels may be hypoplastic. Typically, the posterior communicating shows the most predilection for hypoplasia. Although we teach the circle of Willis as a consistent anatomical structure within direct functional implications because of this vascular hypoplasia, the circle may not be of functional consequence in many patients with occlusion. On an anatomical basis alone, it has been said that a well-formed circle of Willis exists in only 35% of cadavers.

* Link to Netter Image 1.50A
II. **Internal Carotid System**

As noted above, the internal carotid artery enters the cavernous sinus, and after taking an S-shaped course, it enters the subarachnoid space at the anterior clinoid process and gives off:

* Link to Netter Image 1.47A
* Link to Netter Image 1.47B
* Link to Netter Image 1.48A
* Link to Netter Image 1.48B
* Link to Netter Image 1.51A
* Link to Netter Image 1.51B
* Link to Netter Image 1.52

A. The ophthalmic artery which supplies the orbit

B. The posterior communicating cerebral artery linking the internal carotid system with the vertebral system. (See Figure 1)

C. The anterior choroidal artery passes into the inferior horn of the lateral ventricle and supplies the choroid plexus. Additionally, it supplies the hippocampal formation and the ventral part of the posterior limb of the internal capsule. (See Figure 1).

D. The anterior cerebral artery which is joined to the anterior cerebral artery of the opposite side by the anterior communicating artery proceeds around the medial aspect of the cerebral hemispheres in relation to the corpus callosum. In general, the anterior cerebral supplies the most dorsal medial portions of the cerebral cortex. Additionally, at its origin, it gives rise to the medial striate artery (recurrent artery of Heuber) which supplies the anteromedial part of the head of caudate and adjacent parts of the putamen and internal capsule. Lastly, central or ganglionic branches termed the anteromedial arteries arise from the anterior cerebral and the anterior communicating. These course medially and supply the hypothalamus. (See Figures 1, 3, 4 & 5)

E. The middle cerebral artery passes through the lateral fissure. Shortly, after its origin, it gives off perforating (ganglionic) branches termed the lateral striate arteries which supply portions of the internal capsule and the basal ganglia. After the origin of these ganglionic branches, the middle cerebral continues and forms large cortical branches which fan out over the lateral convexity of the cerebral hemisphere and supply blood to this large, functionally important, brain region. (See Figures 1, 2 & 6)

III. **The Vertebral Basilar System**

As noted, the vertebral arteries enter the cranial vault through the foramen magnum. They ascend along the anterior surface of the medulla; they give rise to the anterior spinal, the posterior spinal and the posterior inferior cerebellar (PICA) arteries which, in general, supply the CNS regions implied in their respective names. Specifically, the posterior
spinal artery supplies the dorsal column systems, while in the brain stem, the anterior spinal artery supplies the paramedian portion of the medulla. The PICA supplies the retro-olivary region of the medulla as well as portions of the inferior cerebellar peduncle and inferior cerebellum. (See Figures 1, 7, 8, 9 and 10) At the base of the pons, the vertebral arteries fuse and form the singular basilar artery which has the following branches: (See Figures 7, 8, 9, and 10)

* Link to Netter Image 1.47A
* Link to Netter Image 1.48A
* Link to Netter Image 1.50A
* Link to Netter Image 1.55
* Link to Netter Image 1.51B
* Link to Netter Image 1.52

A. The anterior inferior cerebellar artery (AICA) which, as its name implies, supplies the anterior inferior surface of the cerebellum. The AICA generally divides into medial and lateral trunks, with the lateral trunk supplying the brachium pontis, the anterolateral pontine tegmentum and the flocculus.

B. The labyrinthine or auditory artery which supplies the inner ear. This artery may also arise directly from the AICA.

C. The pontine arteries which via paramedian, short circumferential and long circumferential arteries supply the medial, anterolateral and lateral portions of the pons respectively.

D. The superior cerebellar artery which supplies that same area of cerebellum as well as portions of the midbrain. In the majority of cases, the superior cerebellar artery provides the sole supply to the superior cerebellum; however, in some cases, it is supplemented by branches from both AICA and PICA. The lateral division of the superior cerebellar artery supplies the deep cerebellar nuclei, while its medial division supplies the vermis, tectum, upper pontine tegmentum and superior cerebellar peduncle.

E. The posterior cerebral artery supplies the inferior temporal lobe as well as major portions of the occipital lobe. Additionally, ganglionic branches arise the posterior cerebral and posterior communicating arteries and these form posteromedial arteries, the most prominent of which include the thalamoperforating. Collectively, these vessels supply the tuber cinereum, mammillary bodies and portions of the thalamus. Posterolateral (thalamogeniculate) branches arise more laterally from the posterior cerebral artery. These ganglionic branches penetrate the lateral geniculate body and supply the caudal half of the thalamus including the geniculates and the pulvinar. Lastly, the posterior choroidal artery(ies) arise from the posterior cerebral artery. These give branches to the tectum, and choroid plexus of the third ventricle and the superior surface of the thalamus.
The cerebral arteries as seen from a midsagittal view of the hemisphere.

**Figure 3**
A frontal section through the forebrain, showing the general distribution of major cerebral arterial branches to deep structures. (After Haymaker, Bing's local diagnosis in neurological diseases, St. Louis, The C. V. Mosby Co., 1969).

Figure 5

Figure 6
Figures 7 and 8 depict anatomical structures of the brain and its blood supply. Figure 7 illustrates the anterior limb of the internal capsule, corpus callosum, caudate, ventricle, thalamus, globus pallidus, putamen, temporal lobe, and middle cerebral artery. Figure 8 provides a detailed view of the brainstem and cerebellum, showing the quadrigeminal plate, midline perforating branch of the basilar artery, anterolateral perforating branch of the basilar artery, labyrinthine artery, posterior spinal artery, anterior spinal artery, PCoA, PCA, SCA, superior cerebellar peduncle, middle cerebellar peduncle, inferior cerebellar peduncle, restiform body, juxtaarestiform body, AICA, and PICA. The figures are modified from Kanadel and with permission from Johnson and Christman.
Figure 9

A. Superior cerebellar artery
   Long circumferential branches (Basilar artery)
   Anterior inferior cerebellar artery
   Paramedian branches (Basilar artery)
   Short circumferential branches (Basilar artery)
   Posterior inferior cerebellar artery
   Posterior spinal artery

B. Vertebral artery
   Anterior spinal artery
   Posterior spinal artery

C. Vertebral artery
   Anterior spinal artery
IV. The Cerebral Veins and Venous Sinuses

The cerebral veins do not parallel the course of the cerebral arteries. They emerge from the substance of the brain and form large venous channels which empty into the endothelial-lined channels, the dural sinuses. The dural conduits then return the blood to the systemic circulation via the internal jugular veins.

A. The Venous Sinuses Include:
   * Link to Netter Image 1.59A
   * Link to Netter Image 1.59B

1. The superior sagittal sinus which extends from the foramen cecum to the internal occipital protuberance.
2. The inferior sagittal sinus which extends along the free border of the falx. At the tentorium, the sinus joins the great vein of Galen, draining deep brain structures, to form the straight sinus.

3. Two transverse sinuses arise from the confluence of sinuses and move laterally in a groove in the occipital bone. At the occipital-petrosal junction, each transverse sinus turns downward and backward as the sigmoid sinus.

4. The confluence sinuses is in theory formed by the union of the straight, superior and transverse sinuses. However, typically, the superior sagittal sinus courses right to become the right transverse sinus, while the straight sinus bends left to become the left transverse sinus.

5. The cavernous sinus lies on the side of the sphenoid bone lateral to the sella turcica. It receives the opthalamic veins and the small sphenoparietal sinuses. It drains via the superior and inferior petrosal sinuses into the transverse sinus and the internal jugular vein respectively.
B. The Cerebral Veins

The cerebral veins are generally divided into superficial and deep groups. The superficial veins drain blood from the cortex and subcortical regions into the superior sagittal sinus, while the deep veins drain the deep cerebral substance including the basal ganglia and dorsal thalamus into the internal and deep cerebral veins to reach the Great Vein of Galen.

1. The superficial cerebral veins include:

   a. The superior cerebral veins - which collect blood from the superior surface of the brain to drain into the superior sagittal sinus.

   b. The inferior cerebral veins - which drain the basal surface of the cerebral hemisphere.

   c. The superficial middle cerebral vein - which courses along the lateral fissure. It possesses anastomotic branches from the superior cerebral veins and two such prominent veins are the great anastomotic vein (Trolard) and the posterior anastomotic vein (Labbé).

2. The deep cerebral veins include the internal cerebral veins, the basal veins of Rosenthal and the great vein of Galen.
   * Link to Netter Image 1.60A
   * Link to Netter Image 1.60B
   * Link to Netter Image 1.61A
   * Link to Netter Image 1.62

   a. The internal cerebral veins course in the midline traveling in the roof of the third ventricle. They drain portions of the corpus callosum, thalamus, choroid plexus and caudate nucleus.

   b. The basal veins (of Rosenthal) drain the orbital surface of the frontal lobe, the insular cortex and the ventral striatum.

   c. The great cerebral vein of Galen receives the paired internal cerebral and basal veins.

V. Control of Cerebral Blood Flow

A. Autoregulation - is the ability of the brain vasculature to maintain cerebral blood flow constant over a wide range of mean arterial blood pressure. By means of arteriolar dilation or constriction, flow is kept constant over a mean arterial pressure rate of 60 to 150 mm Hg. Above or below these pressure ranges autoregulation fails. With some
disease states, the autoregulatory curve (range) is shifted to different mean arterial levels.

B. Metabolic - increased brain metabolism or changes in PaC0₂, PaO₂ or pH will influence arterial dilation or constriction. Elevated PaC0₂, lowered PaO₂ or a reduction in pH will cause vasodilation. Lowered PaC0₂ or increased pH will cause vasoconstriction.

C. Neurogenic - Sympathetic input will cause vasoconstriction. Limited parasympathetic input will cause vasodilation.

THE BLOOD-BRAIN BARRIER

I. Introduction

The term blood-brain barrier (BBB) originated in the early 1900's with the observation that trypan blue and other dyes failed to enter the brain parenchyma following intravenous injection. This exclusion from the brain was in contrast to the situation seen in the other body tissues, wherein these dyes had passed through their intrinsic vasculature to flood the tissue. Hence, it was clear that the cerebral microvasculature blocked the passage of these dyes, and thus, the concept of a "barrier" in the brain's vasculature originated.

II. Morphological Substrate of the Blood-Brain Barrier

A. When considering the BBB, it is most appropriate to focus on the brain's capillary bed. The thin capillary wall is the obvious conduit through which most metabolic exchange occurs, and therefore, it is reasonable to assume that most barrier properties reside at this site. As you are well aware, the brain's capillaries are composed of an endothelium lying on a basal lamina, against which abuts astrocytic (glial) processes. For many years, debate centered on the issue as to whether the BBB resides in either:

1. The endothelium
2. The basal lamina or
3. The astrocytic processes

Today, we are confident that the BBB lies in the capillary endothelium.

B. Unique properties of the brain's vascular endothelium

1. Unlike non-neural vascular beds, the brain's vascular endothelium lacks fenestrations and vesicles.

2. Unlike many non-neural vascular beds, the brain's vascular endothelium is joined by continuous tight junctions.
3. Thus, the brain's vasculature appears as a continuous endothelial layer bound together by tight junctions. In essence then, the BBB can be viewed as a continuous lipoprotein plasma membrane.

C. Sites of the blood-brain barrier

1. The blood-brain barrier exists throughout the brain vascular bed, with the exception of the following select sites:
   a. Choroid plexus
   b. Median eminence of the hypothalamus
   c. Subfornical organ
   d. Area postrema
   e. Pineal gland

2. Within these sites, the endothelium is fenestrated and thus is obviously different from that found in the majority of the brain's vasculature.

III. Functional Considerations

In that the cerebrovascular endothelium behaves as a continuous lipoprotein membrane, one can immediately infer many of its functional properties. Lipid soluble non-electrolytes would readily diffuse through such a membrane, whereas non-lipid soluble agents would not pass readily. This partially explains many of the properties of the blood-brain barrier; yet, it does not explain how many metabolic substrates, that are polar compounds, enter the brain. In the following passages, I will attempt to classify the functional parameters of the BBB as expressed in terms of basic physiologic mechanisms.

A. Diffusion through the blood-brain barrier

1. **Gases** such as C0₂, 0₂, Xe, N₂0 and volatile anesthetics diffuse rapidly through the brain vascular endothelium to reach the interstices of the brain parenchyma to come into equilibrium with the plasma concentration. The only limiting factor in this equilibration is the cerebral blood flow.

2. **Water** is the most important substance known to enter the brain by diffusion. Although many advocate that water is freely permeable, recent studies suggest that this view may not be entirely correct. The relatively "unrestrictive" passage of water to and from the brain is used to clinical advantage in those patients with brain edema. Edema, defined as an increase in brain water, usually is seen with trauma or disease. Due to the increased brain water, brain volume and intracranial pressure increase, and this has a devastating effect. To combat edema, plasma osmolarity is raised to "dehydrate" the brain and thereby exert a desirable influence.
3. **Lipid soluble substances**, which include psychoactive drugs, diffuse across the vascular endothelium in proportion to their lipid solubility. As you are well aware, alcohols are lipid soluble and thus readily cross the vascular endothelium. The permeability constants of agents such as thiopental and barbital also allow their passage through the vascular endothelium. Compounds such as salicylic acid also diffuse through the barrier. It is important to note that only unionized compounds cross the vascular endothelium, as ionized species as well as ions are restricted in their passage. By impeding the passage of ions such as potassium, the brain's microenvironment is always maintained constant, despite the ionic composition of the circulating blood. In terms of drugs, their ionization state is influenced by their dissociation constants and the pH of blood. These factors, by influencing the proportion of unionized compounds, ultimately influence what can or cannot enter the brain.

B. Carrier-mediated transport through the blood-brain barrier

As you are well aware, many metabolic substrates are not lipid soluble; yet, they do cross the BBB. These substrates employ a carrier system found within both the luminal (against the blood) and antiluminal (against the brain) membranes of the vascular endothelium. These carriers are stereospecific and saturatable and the carrier-substrate transport displays kinetics identical to those of enzyme-substrate complexing. To date, carriers for glucose, short-chain monocarboxylic acids, various amino acids, nucleic acid precursors and choline have been identified and several of these transport systems and their kinetic parameters are shown in Table 1.

<table>
<thead>
<tr>
<th>Transport system</th>
<th>Representative substrate</th>
<th>( K_a ) (mM)</th>
<th>( V_{\text{max}} ) (nmol/min/g)</th>
<th>( K_p ) (ml/min/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hexose</td>
<td>glucose</td>
<td>11.0</td>
<td>&quot; 1.4</td>
<td>1420 &quot; 140</td>
</tr>
<tr>
<td>Monocarboxylic acid</td>
<td>lactate</td>
<td>1.8</td>
<td>&quot; 0.6</td>
<td>91 &quot; 35</td>
</tr>
<tr>
<td>Neutral amino acid</td>
<td>phenylalanine</td>
<td>0.11</td>
<td>&quot; 0.01</td>
<td>28 &quot; 7</td>
</tr>
<tr>
<td>Basic amino acid</td>
<td>arginine</td>
<td>0.088</td>
<td>&quot; 0.011</td>
<td>7.8 &quot; 0.9</td>
</tr>
<tr>
<td>Amine</td>
<td>choline</td>
<td>0.3</td>
<td>&quot; 0.07</td>
<td>11.3 &quot; 0.7</td>
</tr>
<tr>
<td>Nucleoside</td>
<td>adenosine</td>
<td>0.025</td>
<td>&quot; 0.003</td>
<td>0.75 &quot; 0.08</td>
</tr>
<tr>
<td>Purine base</td>
<td>adenine</td>
<td>0.011</td>
<td>&quot; 0.003</td>
<td>0.50 &quot; 0.09</td>
</tr>
</tbody>
</table>

Table 1
1. Glucose - As one can see, glucose (D-glucose) readily crosses the BBB. Due to the stereospecificity of the carrier L-glucose is not readily transported. Similarly, fructose is not readily transported.

2. As one also can see, various amino acids are transported into the brain by a well-defined carrier system. Phenylalanine, leucine, tyrosine, isoleucine, tryptophan, methionine, histidine, and L-dopa enter rapidly, whereas alanine, proline, y-amino-butyric acid (GABA) and glycine are virtually excluded. In fact, carriers for these small neutral amino acids appear to be confined to the abluminal endothelial surface where they most likely participate in the removal of these amino acids. It should be noted that essential amino acids and the amino acids serving as precursors for catecholamine and indoleamine synthesis are transported readily, whereas amino acids synthesized readily from glucose metabolites, including those amino acids that act as neurotransmitters, are virtually excluded from the brain or cross the barrier at an extremely slow rate as in the case of glutamate and aspartate. There is a separate transport system involved in the movement of the basic amino acid arginine into the brain. The acetylcholine precursor, choline, enters the brain through a separate carrier mediated transport process which can be inhibited by such molecules as dimethylamino ethanol, hemicholinium or tetraethyl ammonium chloride.

C. Active transport

There is no evidence of the active transport of any solutes from the blood into the brain. However, there is evidence that various compounds can be removed from the brain at the abluminal front of the vascular endothelium and moved across the vascular endothelium against a concentration gradient to reach the circulating blood. Such transport is energy-dependent and is obviously, consistent with an active transport process. Such active transport processes have been suggested for the brain's clearance of K⁺, weak organic acids and prostaglandins and the existence of such clearance mechanisms has led to the concept of BBB polarity. Polarity implies that the luminal and abluminal fronts of the BBB may not be functionally the same.

D. Enzymatic barriers

In addition to the above, the BBB contains numerous enzymes which degrade compounds moving through the vascular endothelium. Enzymes such as MAO, COMT, alkaline and acid phosphatase, dopa decarboxylase and y-glutamyltranspeptidase area found in the brain's vascular endothelium, and these further regulate which substances can reach the brain front.

IV. Disorders of the Blood-Brain Barrier

Many diseases or insults to the brain can alter the BBB's permeability characteristics. Examples of these are shown in the following table.
Reported changes in blood-brain barrier nutrient transport in pathological conditions

<table>
<thead>
<tr>
<th>Transport System</th>
<th>Modulation</th>
<th>Condition</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hexose</td>
<td>Increased Activity</td>
<td>Seizures</td>
<td>Indirect Studies</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Insulin</td>
<td>Conflicting Reports</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fasting</td>
<td>Unconfirmed</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypocapnia</td>
<td>Unconfirmed</td>
</tr>
<tr>
<td></td>
<td>Decreased Activity</td>
<td>Pentobarbital</td>
<td>Confirmed</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mercury</td>
<td>Confirmed</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anoxia, Ischemia</td>
<td>Confirmed</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypercapnia</td>
<td>Confirmed</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hyperglycemia</td>
<td>Confirmed</td>
</tr>
<tr>
<td>Neutral Amino Acid</td>
<td>Increased Activity</td>
<td>Hepatic encephalopathy</td>
<td>Confirmed</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Undernutrition</td>
<td>Confirmed</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chronic hypertension</td>
<td>Unconfirmed</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Thiamine deficiency</td>
<td>Unconfirmed</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Insulin</td>
<td>Conflicting reports</td>
</tr>
<tr>
<td></td>
<td>Decreased Activity</td>
<td>Hypothyroidism</td>
<td>Unconfirmed</td>
</tr>
<tr>
<td>Monocarboxylic Acid</td>
<td>Increased Activity</td>
<td>Ketosis (Neonatal, fasting, fatty diet)</td>
<td>Confirmed</td>
</tr>
<tr>
<td></td>
<td>Decreased Activity</td>
<td>Hepatic Encephalopathy</td>
<td>Confirmed</td>
</tr>
</tbody>
</table>

Table 2

In addition to these subtle perturbations of the barrier, more dramatic BBB perturbations have been recognized.

A. Tumors have long been known to alter barrier status. Typically, brain tumors elicit the formation of a fenestrated vasculature, which appears similar to that vasculature seen in non-neural tissues. Such fenestrations allow for the penetration of numerous substances, normally restricted from entering the brain parenchyma.

B. Insults, such as head injury or acute hypertension, can also alter BBB status. Through overt endothelial damage or increased transendothelial vesicular activity the BBB is opened to many substances, normally excluded. Overt disruption of the BBB, with the passage of water and serum proteins into the brain parenchyma results in edema.
V. The Blood-Cerebrospinal Fluid Barrier

Similar to the BBB, the blood-cerebrospinal fluid barrier (blood-CSF barrier) restricts the passage of various substances into the CSF, wherein they ultimately could influence the brain parenchyma. (Remember that neither the ventricular ependymal lining nor the superficial glia limitans restricts the passage of CSF born constituents into the brain.) The blood-CSF barrier resides in the choroid plexuses. As previously noted, the vasculature of the choroid plexuses lacks barrier properties. However, the choroidal plexus epithelial cells are joined by tight junctions and display barrier properties similar to those of the cerebral endothelium. Thus, they like the endothelial cells regulate what ultimately reaches the ventricular/brain front.

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