Box 16.1 The blood-brain barrier in vertebrates

More than 100 years ago Paul Ehrlich, a German bacteriologist, discovered that injection of a water-soluble blue dye into the blood of different vertebrates stained all tissues blue except for the brain and the spinal cord. Conversely, injection of the dye into the **cerebrospinal fluid** - the extracellular fluid surrounding the neurons in the brain and the spinal cord- by one of Ehrlich's students, stained the brain and the spinal cord, but not the peripheral tissues. The term 'blood-brain barrier' was coined by another German scientist, Max Lewandowsky, to highlight the fact that some type of barrier must exist between the blood and the cerebrospinal fluid to explain this compartmentalisation of staining.

Reliable signalling in the central nervous system (CNS) of vertebrates requires a very stable and accurately regulated extracellular environment, which differs in its composition from the blood plasma (and the interstitial fluid) as we discuss in Section 16.1.2. In this context, the blood-brain barrier (or BBB) is meant to represent the specific physical barriers that maintain the composition of the cerebrospinal fluid within narrow limits, working in concert with various cellular transporting systems.

Two main physical barriers between blood and CNS exist at the level of CNS capillaries. One barrier, called the **endothelial barrier**, occurs at the level of endothelium, which forms the lining of the CNS blood capillaries. As shown in Figure A(i), each endothelial cell forms a ring around the entire circumference of the capillary, with tight junctions where its edges meet and at the interface with other endothelial cells along the capillary. This arrangement can form an efficient physical barrier, which prevents diffusion across the capillary wall of all plasma molecules that cannot pass through the cellular membranes of the endothelial cells.

The second barrier that potentially can prevent plasma molecules from entering the cerebrospinal fluid is the **perivascular glial cell barrier**. This barrier is made of the feet-like processes of astrocytes[1] covering the outer surface of CNS capillaries, as illustrated in Figures A(i) and 16.3.

The effectiveness of the endothelial barrier is determined by the activity of **pericytes**, a type of (smooth muscle[2]) contractile cell in contact with endothelial cells with which they share a common basement membrane[3] as shown in Figure A(i). Pericytes regulate blood flow and passage of particles of a certain size through the capillary. They also regulate the expression of proteins that control the efficiency of the tight junctions between endothelial cells and, therefore, the overall effectiveness of the endothelial barrier.

Interestingly, there is evidence that the BBB in the ancestral vertebrates was a glial cell barrier, which is still present in elasmobranchs (sharks, rays and skates) and lungfish. However, most vertebrates (teleosts fish, amphibians, reptiles, birds and mammals) have an endothelial-type BBB.

Both types of BBBs are made out of cells that restrict the diffusion of large and hydrophilic molecules into the cerebrospinal fluid, while allowing the diffusion of small hydrophobic molecules such as oxygen, carbon dioxide and alcohol[4]. The presence of specific carrier-based transporting systems in the cellular membranes of the BBBs ensures that compounds that are important for brain function—such as glucose, amino acids, monocarboxylic acids, metallic ions, etc.—cross the barrier in a regulated fashion. The BBB is a dynamic system in which its permeability and transport properties can be modulated to ensure a very stable composition of the cerebrospinal fluid. The BBB also protects the brain from common bacterial infections and toxins, which enter the vertebrate's body but which cannot cross the BBB.

In contrast to the CNS capillaries, the blood capillaries in other parts of the vertebrate's body are leaky. This leakiness is the con-

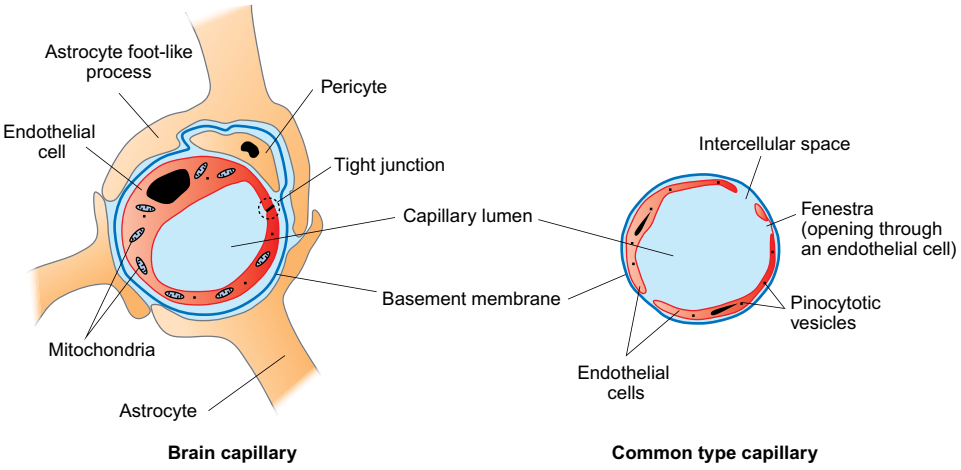

Figure A Schematic cross-sectional representation of a brain capillary (i) and a common type capillary found in other parts of the vertebrate's body (ii)

The lumen of the brain capillary is surrounded along its entire circumference by one endothelial cell, which can form tight junctions where its edges meet. Endothelial cells in brain capillaries are rich in mitochondria and communicate with a different type of cells, known as pericytes, located on their outer surface. Both cell types are surrounded by the basement membrane. The brain capillary is surrounded over most of its area by astrocyte foot-like processes as shown in Figure 16.3. In contrast, the lumen of the common type capillary is surrounded by two or more endothelial cells enclosed within the basement membrane. In the common capillaries, water and small molecules can pass through the intercellular gaps between endothelial cells and the openings through individual endothelial cells, called fenestrae (singular fenestra).

sequence of the space between endothelial cells forming the wall of the capillary, and the window-like openings (called fenestrae) within the endothelial cells, as shown in Figure A(ii). At the level of these capillaries a process of ultrafiltration[5] takes place, where water, small molecules and ions dissolved in plasma, but not plasma proteins, can readily pass through the gaps between endothelial cells and the fenestrae.

The BBB is also leaky in certain regions of the brain where, for example, neurosecretory products enter the blood circulation like in the posterior pituitary gland[6]. However, these leaky areas are separated from the rest of the brain by specialised structures to ensure that the overall integrity of the BBB is not compromised.

Find out more:

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[1] Astrocytes are the most abundant glial cells in the CNS of vertebrates as we discuss in Section 16.1.

[2] We discuss smooth muscle in Section 18.4

[3] The basement membrane is made of a thin layer of fibrous proteins, which is not an effective barrier for the diffusion of molecules dissolved in the plasma, but provides mechanical support to the endothelial cells forming the capillary wall.

[4] The rapid diffusion of alcohol across the BBB explains why ingestion of alcohol has a relatively fast effect on brain function.

[5] We discuss ultrafiltration in Section 4.2.

[6] We discuss neurosecretion in Chapters 3.3.3 and 19.1.1.