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REVIEW ARTICLE

Blood–Brain Barrier and Bilirubin: Clinical Aspects and Experimental Data

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The blood–brain barrier (BBB) is a complex and dynamic structure that plays a key role in central nervous system (CNS) homeostasis. It strictly regulates the entrance of molecules into the brain parenchyma and prevents the access of neurotoxins and pathogens while promoting the efflux of several molecules. The brain microvascular endothelial cells are the anatomical basis of the BBB, which has unique characteristics such as the elaborate junctional complexes that nearly obliterate the intercellular space as well as the presence of influx and efflux transporters. Endothelial cells establish important interactions with glial cells, neurons, and perivascular pericytes as well as with the acellular components of the basement membrane, which together constitute the neurovascular unit. BBB disruption has been reported in a wide range of CNS pathologies, with an emerging role in the onset and disease progression. Accordingly, recent studies revealed vascular dysfunction in neonatal jaundice, a common pathology in the early neonatal period affecting 1/10 children presenting values of total bilirubin >17 mg/dL (291 μM). Here we summarize the clinical aspects of moderate to severe neonatal jaundice and provide a comprehensive review of the literature regarding bilirubin-induced neurotoxicity from a vascular-centered approach. The collected evidence place endothelial dysfunction and pericyte demise as key players in the disruption of CNS homeostasis, mainly in cases of lasting hyperbilirubinemia, thus pointing to novel targets to prevent neurological dysfunction due to severe neonatal jaundice.

Key Words: Blood–brain barrier, Endothelial cells, Kernicterus, Neonatal jaundice, Neurovascular unit, Pericytes.

Introduction

The central nervous system (CNS) contains cellular barriers that maintain homeostasis by protecting the brain from the effects of internal and external changes, preventing the entrance of plasma molecules and toxins able to induce activation of glial cells and neural tissue damage. Simultaneously, they also assure the uptake of nutrients, together providing a stable environment for neural function. CNS barriers exist at three key sites: the epithelial cells of the choroid plexus, the arachnoid epithelium that lies under the dura mater and completely encases the brain, and the cerebral endothelium that constitutes the barrier between blood and brain (1–3). The latter constitutes the blood–brain barrier (BBB), of which the alterations by neonatal jaundice are the main focus of this review.

BBB Overview

The endothelial cells of brain capillaries are considered the anatomic basis of the BBB. The brain microvascular endothelial cells (BMEC) are characterized by the presence of elaborate junctional complexes that are crucial players in the maintenance of a functional BBB. These structures are formed by tight junctions (TJ) in the luminal area of the cell membrane and by adherens junctions (AJ) located in a basolateral position (4) (Figure 1). The TJ and AJ share common characteristics because they are both formed by transmembrane proteins linked to cytosolic proteins which, in turn, establish the connection with the cytoskeleton. TJ proteins form strains along the intercellular junctions, creating the connection with those of the opposing

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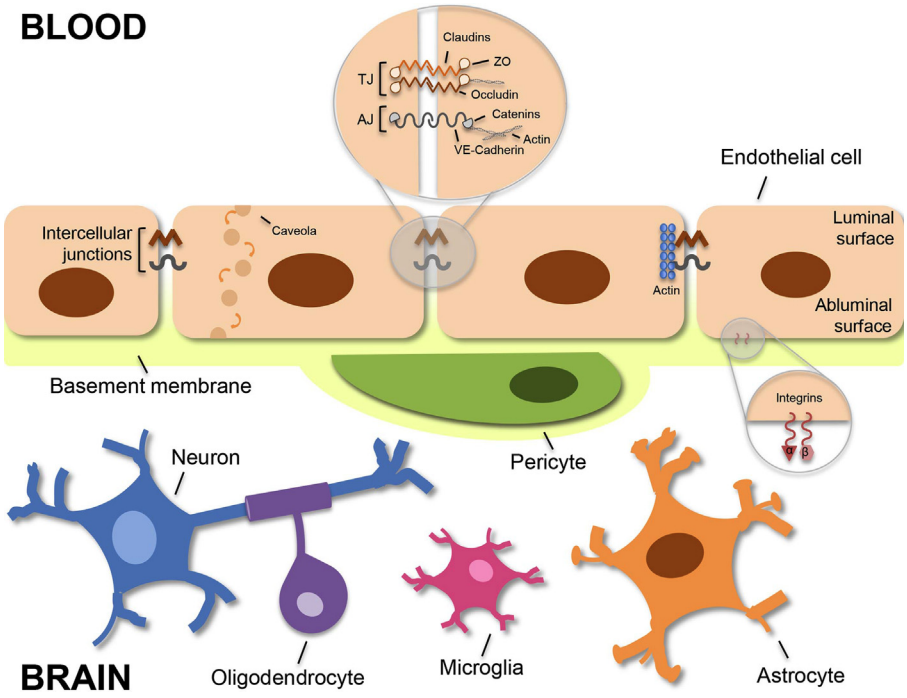

Figure 1. Simplified representation of the blood—brain barrier and of the interplay between the different components of the neurovascular unit. The physical barrier function of brain endothelial cells is achieved by the presence of tight junctions (TJ) and adherens junctions (AJ) that restrict the paracellular permeability. TJ are constituted by transmembrane proteins, such as claudins and occludin, as well as by cytoplasmic accessory proteins including the zonula occludens (ZO) family. The adherens junctions are formed by the transmembrane vascular endothelial cadherin (VE-cadherin) and the cytoplasmic catenins. The cytoplasmic proteins from these two types of junctions establish the connection to the cytoskeleton by interacting with actin filaments. The adhesion of brain endothelial cells to the basement membrane is mediated by integrins in the abluminal surface of endothelial cells. Caveolae are membrane invaginations of endothelial cells responsible for transcytosis. Endothelial cells establish important communication with the basement membrane, pericytes, astrocytes, microglia, neurons and, indirectly, with oligodendrocytes, giving rise to the concept of neurovascular unit.

membrane and obliterating the intercellular space (5), an organization that is more evident in the brain than in other regions of the organism (6). Examples of TJ proteins are the cytosolic zonula occludens-1 (ZO-1) and the transmembrane occludin and claudin-5, as well as the recently discovered tricellulin (5). Among AJ proteins, the most studied are the vascular endothelial-cadherin, an adhesive transmembrane protein, and the cytosolic β-catenin (4,7). Alterations in TJ proteins are directly associated with barrier compromise. However, AJ also play an important role in maintaining barrier function. In fact, they are essential for TJ formation as they directly activate signaling molecules and can regulate gene transcription (8—10). Accordingly, changes in the expression or distribution of AJ proteins should also be considered to be involved in defects of the endothelial barrier (11).

BMEC are additionally characterized by a number of receptors and the presence of influx and efflux transporters that assure the passage of substances into and out of the brain parenchyma. Influx transporters are grouped accordingly with the type of the transported molecule, which includes energy sources, amino acids, organic anions and neurotransmitters, among others (12). One of the most crucial transporters, glucose transporter-1 (GLUT-1), is responsible for the energy supply to the brain (4). BMEC are also equipped with efflux transporters that export unwanted compounds from the brain parenchyma (4). The most studied group of efflux transporters is the ATP-binding cassette (ABC) family that mediates the export of substrates from cells coupled with the hydrolysis of ATP (12,13), among which is the widely studied P-glycoprotein (P-gp) (14—16).

Transport across the endothelium may additionally occur via vesicular mechanisms, also known as transcytosis (17). This type of transport describes the movement of molecules within endocytic vesicles across endothelial cells, from the luminal to the abluminal side. BMEC contain two kinds of vesicles, clathrin-coated vesicles and caveolae, the latter being the principal vesicular structure for transcytosis in these cells (18,19), which are schematically depicted in Figure 1. These vesicles, also involved in various aspects of signal transduction (20), are plasma membrane invaginations rich in caveolins, sphingolipids and cholesterol. Caveolin-1, the major structural protein of caveolae, is expressed in several tissues with the highest levels of expression in endothelial cells, adipocytes, fibroblasts and