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Review

Looking at the blood–brain barrier: Molecular anatomy and possible investigation approaches

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ABSTRACT

The blood–brain barrier (BBB) is a dynamic and complex interface between blood and the central nervous system that strictly controls the exchanges between the blood and brain compartments, therefore playing a key role in brain homeostasis and providing protection against many toxic compounds and pathogens. In this review, the unique properties of brain microvascular endothelial cells and intercellular junctions are examined. The specific interactions between endothelial cells and basement membrane as well as neighboring perivascular pericytes, glial cells and neurons, which altogether constitute the neurovascular unit and play an essential role in both health and function of the central nervous system, are also explored. Some relevant pathways across the endothelium, as well as mechanisms involved in the regulation of BBB permeability, and the emerging role of the BBB as a signaling interface are addressed as well. Furthermore, we summarize some of the experimental approaches that can be used to monitor BBB properties and function in a variety of conditions and have allowed recent advances in BBB knowledge. Elucidation of the molecular anatomy and dynamics of the BBB is an essential step for the development of new strategies directed to maintain or restore BBB integrity and barrier function and ultimately preserve the delicate interstitial brain environment.

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Abbreviations: ABC, ATP-binding cassette transporter; AIDS, acquired immune deficiency syndrome; AJ, adherens junction; BBB, blood–brain barrier; BMVEC, brain microvascular endothelial cell; CAM, cell adhesion molecules; cAMP, cyclic AMP; cGMP, cyclic GMP; CNS, central nervous system; EC, endothelial cell; eNOS, endothelial nitric oxide synthase; ERK 1/2, extracellular signal-related kinases; GLUT-1, glucose transporter-1; HBMVEC, human brain microvascular endothelial cell; HIV, human immunodeficiency virus; ICAM, intercellular adhesion molecule; IL, interleukin; JAM, junctional adhesion molecule; JNK, c-Jun N-terminal kinase; LPS, lipopolysaccharide; MAGUK, membrane-associated guanlylate kinase; MAPK, mitogen-activated protein kinase; MLC, myosin light-chain; MLCK, myosin light-chain kinase; MMP, matrix metalloproteinase; NO, nitric oxide; NVU, neurovascular unit; PI3K, phosphatidylinositol-3 kinase; P-gp, P-glycoprotein; PKA, protein kinase A; PKB, protein kinase B; PKC, protein kinase C; PKG, protein kinase G; PTK, protein tyrosine kinase; ROCK, Rho kinase; ROS, reactive oxygen species; SEM, scanning electron microscopy; SFK, Src family of kinases; TEER, transendothelial electrical resistance; TEM, transmission electron microscopy; TJ, tight junction; TNF-α, tumor necrosis factor-alpha; VCAM, vascular CAM; VE, vascular endothelial; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor; ZO, zonula occludens

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1. Introduction

In 1885, Paul Ehrlich experimentally demonstrated that vital dyes injected into the circulatory system stain all organs of the mammalian body except the brain and spinal cord and attributed this observation to a low affinity of nervous tissue to the dye (Ehrlich, 1885, 1906). About 30 years later, an Ehrlich's student, Edwin Goldmann, noticed the opposite phenomenon by injecting trypan blue directly into the cerebro-spinal fluid, which stained all central nervous system (CNS) and none of the peripheral organs (Goldmann, 1913), suggesting the presence of a barrier between the CNS and the circulation. The term *bluthirnschranke*, blood–brain barrier (BBB), was first used by Lewandowsky (1900) while studying the limited permeation of potassium ferrocyanate into the brain. Further studies showed that endothelial tight junctional complexes physically limit solute exchanges between the blood and the brain. This was achieved by injecting horseradish peroxidase intravascularly, showing diffusion between endothelial cells (EC) lining skeletal and cardiac vessels, thought it did not pass between EC in cerebral microvasculature (Reese and Karnovsky, 1967) (Fig. 1). Major BBB functions include: (1) maintenance of CNS homeostasis, (2) protection of brain from extracellular environment, (3) constant supply of nutrients by specific transport systems and (4) direct inflammatory cells to act in response to changes in local environment (Petty and Lo, 2002; Lee et al., 2006; Persidsky et al., 2006a). Maintenance of homeostasis is achieved through the regulation of ion balance (Wolburg and Lippoldt, 2002; Hawkins and Davis, 2005; Persidsky et al., 2006a) and of compounds influx/efflux (Chaudhuri, 2000; Khan, 2005). This is essential in protection against harmful substances, variations in blood composition and breakdown of concentration gradients (Kniesel and Wolburg, 2000; Petty and Lo, 2002; Wolburg and Lippoldt, 2002).