ELSEVIER

Archives of Medical Research 45 (2014) 610–638

Archives of Medical Research

REVIEW ARTICLE

Role of the Blood–Brain Barrier in the Nutrition of the Central Nervous System

Patricia Campos-Bedolla,[a] Fruzsina R. Walter,[b] Szilvia Veszelka,[b] and Mária A. Deli[b]

[a]*Unidad de Investigación Médica en Enfermedades Neurológicas, Hospital de Especialidades, Centro Médico Nacional Siglo XXI, Instituto Mexicano del Seguro Social, México, D.F., México*

[b]*Institute of Biophysics, Biological Research Centre of the Hungarian Academy of Sciences, Temesvári körút, Szeged, Hungary*

Received for publication November 19, 2014; accepted November 24, 2014 (ARCMED-D-14-00683).

The blood–brain barrier (BBB) is a dynamic and complex interface between the blood and the central nervous system regulating brain homeostasis. Major functions of the BBB include the transport of nutrients and protection of the brain from toxic compounds. This review summarizes the most important transport pathways contributing to the nutrition of the brain. Carrier-mediated transport selectively delivers small molecules like sugars, amino acids, vitamins, and trace elements. Large biomolecules, lipoproteins, peptide and protein hormones cross the BBB by receptor-mediated transport. Active efflux transporters participate in the brain efflux of endogenous metabolites as well as toxins, xenobiotics and drugs. Dysfunction in the transport of nutrients at the BBB is described in several neurological disorders and diseases. The BBB penetration of neuroprotective nutrients, especially plant polyphenols and alkaloids, their potential protective effect on brain endothelium and the interaction of nutraceuticals with active efflux transporters at the BBB are discussed. *In vitro* BBB models to examine nutrient transport are also presented. © 2014 IMSS. Published by Elsevier Inc.

Key Words: Blood–brain barrier, Solute carriers, ABC transporters, Nutrition, Nutraceuticals.

Introduction

The blood–brain barrier (BBB) is a dynamic and complex interface between the blood and the central nervous system (CNS). The primary role of the BBB is to regulate the brain microenvironment for neuronal functions (1). The BBB also provides nutrients for the brain, protects the CNS from toxic compounds and pathogens, and serves as an interface for communication between the periphery and the brain (2). The BBB is composed of brain microvascular endothelial cells surrounded by pericytes, astrocytic endfeet, microglia and neurons. The interactions of these cells constitute a functional unit, the neurovascular unit (NVU) (3) (Figure 1). Intercellular tight junctions (TJ), lack of fenestrations, low pinocytotic activity and efflux pumps in cerebral endothelium block the free entry of cells and molecules between the blood and the brain. Interendothelial TJs not only restrict paracellular permeability but also maintain the polarized distribution of brain endothelial membrane proteins, among them nutrient transporters. In addition to TJs, influx and efflux transporter proteins, intracellular metabolic and enzymatic processes play a part in the functions of the BBB (4). Table 1 summarizes the major mechanisms at the level of BBB that restrict nutrient transport to the CNS.

The flux of nutrients and metabolites from blood to CNS is well regulated by the BBB, which controls their availability by transport systems (1). Transport across the BBB occurs via six major pathways: lipid-mediated diffusion, paracellular diffusion, carrier-mediated transport, receptor-mediated transcytosis, absorptive-mediated transcytosis and active efflux transport (Figure 2) (5). The major routes of nutrient delivery to the CNS across the BBB are passive diffusion of lipid soluble compounds, solute carriers (SLCs) and receptor-mediated transcytosis (Table 2). Small lipophilic molecules can easily diffuse through cell

Address reprint requests to: Patricia Campos-Bedolla, PhD, Unidad de Investigación Médica en Enfermedades Neurológicas, Centro Médico Nacional Siglo XXI. México, IMSS, Av. Cuauhtémoc 330, Col. Doctores, D.F., México; Phone and Fax: (+52) (55) 5578-0240; E-mail: camposbedollap@hotmail.com

0188-4409/$ - see front matter.
http://dx.doi.org/10.1016/j.arcmed.2014.11.018

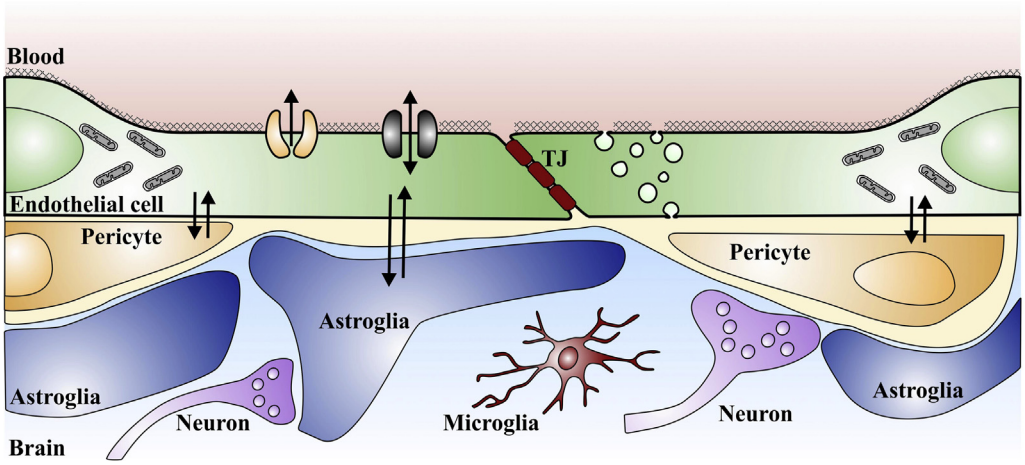

Figure 1. Cerebral capillary endothelial cells, astroglia, pericytes, microglia and neurons form the neurovascular unit. The schematic drawing describes the close spatial relationship and the complex interactions between these cells. Pericytes share a common basal membrane with the endothelial cells. Astroglia foot processes surround the capillaries. Tight junctions (TJ) form a barrier at the paracellular pathway for small, aqueous molecule diffusion. Neurons modulate blood–brain barrier functions via neurotransmitters affecting cerebral blood flow. Microglia are the resident immunocompetent cells of the brain. Based on Abbott et al. (1,5).

membranes of capillary endothelial cells. The brain is supplied with small hydrophilic nutrients by SLC transporters, and with peptides, proteins and lipoproteins by receptor-mediated transcytosis. The rate of adsorptive-mediated transcytosis is very low at the BBB effectively blocking the penetration of serum proteins to the brain in physiological conditions (2,5). Active efflux transporters pump harmful metabolites from the brain to the blood and prevent xenobiotics and drugs to enter the CNS. This complex network of transport systems is expressed in a polarized way on the luminal (blood) and abluminal (brain) membranes of cerebral endothelial cells (6).

The present review focuses on the role of the BBB; however, the blood-cerebrospinal fluid barrier located anatomically at the epithelial cells of the choroid plexus also participates in the maintenance of the CNS homeostasis and the transport of nutrients. The choroid plexus transports amino acids, small peptides, vitamins, inorganic ions, and hormones to cerebrospinal fluid (CSF) through active and selective mechanisms (7). Because the surface area of the BBB is 5000 times larger than that of the blood-CSF barrier, it has a dominant role in providing nutrients for the brain.

In this review we discuss the transport systems participating in nutrient delivery to CNS and how these processes change in aging and diseases. The interaction of nutrients and nutraceuticals with active efflux transporters at the BBB and the protection of brain endothelial cells and BBB functions by nutraceuticals are also described.

Table 1. Major mechanisms at the level of the blood–brain barrier that restrict nutrient transport

BBB feature	Limited pathway	Restricted transport of molecules
Tight junctions	Paracellular diffusion	Hydrophilic compounds
Low non-specific vesicular transport	Transcellular diffusion	Serum proteins, lipoproteins, large biomolecules
Efflux transporters	Lipid-mediated diffusion	Lipophilic compounds
Enzymes	Transendothelial transport	Peptides, neurotransmitters

Nutrient Transport Systems at the BBB

Carrier-Mediated Transport

Carrier-mediated transport is the most important at the BBB from the point of view of nutrient delivery to the CNS. SLCs are membrane-fixed transport proteins that transfer relatively small hydrophilic molecules. These carriers are facilitated transporters, ion-coupled transporters or exchangers that do not require ATP for their function. SLCs shuttle metabolic subtrates including hexoses, amino acids, monocarboxylic acids, vitamins, nucleosides, purine and pyrimidine bases, fatty acids, ions, organic anions and organic cations across the plasma membranes of brain endothelium (1,8). From the 400 members of the SLC family (9,10) several groups of carriers were identified at the BBB at gene or protein level in different species including humans (8,11–15) (Table 3).

Glucose transporters. Carbohydrates are the most important components to provide energy in the human diet. D-Glucose is the primary source of energy for brain functions like neurotransmission, biosynthesis and oxidative defense. To get into the CNS glucose crosses brain endothelial