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Review

Metabolite transport across the mammalian and insect brain diffusion barriers

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ABSTRACT

The nervous system in higher vertebrates is separated from the circulation by a layer of specialized endothelial cells. It protects the sensitive neurons from harmful blood-derived substances, high and fluctuating ion concentrations, xenobiotics or even pathogens. To this end, the brain endothelial cells and their interlinking tight junctions build an efficient diffusion barrier. A structurally analogous diffusion barrier exists in insects, where glial cell layers separate the hemolymph from the neural cells. Both types of diffusion barriers, of course, also prevent influx of metabolites from the circulation. Because neuronal function consumes vast amounts of energy and necessitates influx of diverse substrates and metabolites, tightly regulated transport systems must ensure a constant metabolite supply. Here, we review the current knowledge about transport systems that carry key metabolites, amino acids, lipids and carbohydrates into the vertebrate and Drosophila brain and how this transport is regulated. Blood-brain and hemolymph-brain transport functions are conserved and we can thus use a simple, genetically accessible model system to learn more about features and dynamics of metabolite transport into the brain.

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1. Introduction

1.1. Function of the blood-brain barrier

The blood-brain barrier (BBB) is one of the most extreme barriers in the body. It prevents almost all paracellular diffusion and is essential to ensure a constant extracellular milieu in the brain to enable neuronal function. The first to discover that the nervous system is separated from circulation was Paul Ehrlich, who observed that dyes injected into circulation fail to stain the gray matter (Ehrlich, 1885). In 1900, M. Lewandowski noticed that brain capillaries blocked diffusion of certain molecules (Lewandowsky, 1900). Shortly after, Edwin Goldmann showed that trypan blue does not penetrate the cerebrospinal fluid (CSF) when injected into the blood and vice versa (Goldman, 1909; Goldmann, 1913). Decades later, the tightness of the blood-brain and blood-CSF barriers was confirmed using electron microscopy (Brightman and Reese, 1969; Reese and Karnovsky, 1967).

The BBB is a diffusion barrier that is absolutely essential to allow normal nervous system function. It prevents uncontrolled influx of ions, metabolites, xenobiotics, pathogens and other blood-derived harmful substances. Since neuronal function requires a defined and constant extracellular milieu, the nervous system must be uncoupled from the changing solute concentrations in the circulation. Ion, metabolite and protein concentrations in the blood, e.g., are higher than in the nervous system (Table 1, Begley, 2006). To ensure stable solute concentrations in the brain, fluxes over the BBB are tightly regulated. Only lipid soluble molecules smaller than 450 Da with a polar surface area under 90 $Å^2$ and small gases like O_2 and CO_2 can diffuse freely (van de Waterbeemd et al., 1998).

1.2. Structure of the vertebrate neurovascular unit

The BBB of higher vertebrates is built by tight junction (TJ)-forming endothelial cells that are part of the so-called neurovascular unit (NVU). Lower vertebrates such as elasmobranch fish have a glial BBB (not reviewed here, Brightman et al., 1971; Bundgaard and Cserr, 1981). The NVU consists of endothelial cells, pericytes, astrocytes, neurons and the basement membrane (Fig. 1). All these cell types contribute to BBB development and function. Paracrine signaling between endothelial cells, astrocytes and pericytes drives barrier formation and maintenance (reviewed in Abbott et al., 2010; Armulik et al., 2011). During development, blood vessels invade the brain between E11 and E13 in mice and rats (Bauer et al., 1993; Stewart and Hayakawa, 1994). Almost complete electrical resistance is established in rat pial vessels by E21, but the barrier matures further even after birth (Butt et al., 1990; Jones et al., 1992).

The endothelial cells of the brain microvasculature are the central component of the BBB since they prevent paracellular diffusion by building TJs (Fig. 1) (Brightman and Reese, 1969; Reese and Karnovsky, 1967). The endothelial cells are highly polarized cells with luminal and abluminal membranes that differ in their lipid and protein composition and also form adherence junctions that are required for TJ formation (Tietz and Engelhardt, 2015, reviewed in Worzfeld and Schwaninger, 2016). The basement membrane separates endothelial cells from pericytes and pericytes from astrocytic endfeet. It consists primarily of fibronectin, laminin and collagen IV. These components are secreted by endothelial cells, pericytes and astrocytes (reviewed in Obermeier et al., 2013). An intact basement membrane is essential for diffusion barrier maintenance and builds an important scaffold structure for all cell types of the NVU (Yao et al., 2014, reviewed in Baeten and Akassoglou, 2011; Del Zoppo et al., 2006). The pericytes surround capillaries, mediate vessel stability and regulate endothelial cell differentiation (Fig. 1, reviewed in Armulik et al., 2011; Winkler et al., 2011). Pericytes are contractile cells that regulate vascular blood flow via contraction and relaxation like vascular smooth muscle cells on arterioles (Peppiatt et al., 2006, reviewed in Dalkara et al., 2011). They are recruited to the developing central nervous system (CNS) capillaries and are necessary for barrier formation and maintenance (Armulik et al., 2010; Daneman et al., 2010b). Another cell type that is important for BBB formation is astrocytes (Fig. 1) (Janzer and Raff, 1987). They express sonic hedgehog to promote junction formation and thus support barrier development (Alvarez et al., 2011). Astrocytes connect neurons, endothelial cells and pericytes by forming food processes to contact different cell types simultaneously. Hereby, they contribute to neurovascular coupling and e.g. link neuronal metabolism to local cerebral blood flow regulation (Zonta et al., 2003, reviewed in Howarth, 2014). Astrocytes are believed to provide neurons with lactate, a high-energy metabolite, to fuel their citrate cycle and respiratory chain (Hall et al., 2012; Pellerin and Magistretti, 1994, reviewed in Allaman et al., 2011; Pellerin and Magistretti, 2012). The existence of this metabolic support, however, is still under debate (see section "The astrocyte neuron lactate shuttle hypothesis (ANLS) and lactate transport" for details). Furthermore, astrocytes modulate neuronal communication through neurotransmitter recycling and the release of gliotransmitters (reviewed in Abbott et al., 2006; Harada et al., 2015). Importantly, the BBB is not a fix, but a dynamic structure that is permanently influenced by blood- and CNS-derived factors. It acts not just as a barrier, but also as a communication interface between the nervous system and the rest of the body (reviewed in Keaney and Campbell, 2015).

Table 1
Selected ion concentrations in the human blood and cerebrospinal fluid (CSF) (from Begley, 2006). A detailed list of ion, protein and amino acid concentrations can be found in Begley, 2006.

Solute	Blood concentration [mM]	CSF concentration [mM]
Potassium	~4.5	2.5–2.9
Sodium	140	141
Magnesium	1.7	2.4
Calcium	5.0	2.5

1.3. Structure of the invertebrate hemolymph-brain barrier

As in lower vertebrates, invertebrates, like insects, have a glial BBB, which from here on will be termed more accurately hemolymph-brain barrier (HBB), since in invertebrates, the nervous system is not vascularized, but instead is surrounded by the blood-like hemolymph (reviewed in Bundgaard and Abbott, 2008). Here, high potassium concentrations and fluctuating metabolite levels can be found. Thus, free solute exchange between the hemolymph and the nervous system extracellular milieu needs to be prevented. The Drosophila nervous system is small and most cells and neural lineages are known. Furthermore, neuronal communication follows the same basic principles as in mammals and even regulation of complex behaviors seems to be conserved (Anholt and Mackay, 2012; Davis, 2011). The fly HBB shares central properties with the vertebrate BBB. Paracellular diffusion is blocked by junctional complexes and efflux transporters protect the brain from inner and outer toxins (Desalvo et al., 2014; Lane and Treherne, 1972; Mayer et al., 2009; Stork et al., 2008 reviewed in Hindle and Bainton, 2014).