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Review

Glycolysis-mediated control of blood-brain barrier development and function

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ABSTRACT

The blood-brain barrier (BBB) consists of differentiated cells integrating in one ensemble to control transport processes between the central nervous system (CNS) and peripheral blood. Molecular organization of BBB affects the extracellular content and cell metabolism in the CNS. Developmental aspects of BBB attract much attention in recent years, and barriergenesis is currently recognized as a very important and complex mechanism of CNS development and maturation. Metabolic control of angiogenesis/barriergenesis may be provided by glucose utilization within the neurovascular unit (NVU). The role of glycolysis in the brain has been reconsidered recently, and it is recognized now not only as a process active in hypoxic conditions, but also as a mechanism affecting signal transduction, synaptic activity, and brain development. There is growing evidence that glycolysis-derived metabolites, particularly, lactate, affect barriergenesis and functioning of BBB. In the brain, lactate produced in astrocytes or endothelial cells can be transported to the extracellular space via monocarboxylate transporters (MCTs), and may act on the adjoining cells via specific lactate receptors. Astrocytes are one of the major sources of lactate production in the brain and significantly contribute to the regulation of BBB development and functioning. Active glycolysis in astrocytes is required for effective support of neuronal activity and angiogenesis, while endothelial cells regulate bioavailability of lactate for brain cells adjusting its bidirectional transport through the BBB. In this article, we review the current knowledge with regard to energy production in endothelial and astroglial cells within the NVU. In addition, we describe lactate-driven mechanisms and action of alternative products of glucose metabolism affecting BBB structural and functional integrity in developing and mature brain.

Abbreviations: AGEs, advanced glycation end products; ADP, ribose–adenosine diphosphate ribose; ATP, adenosine triphosphate; BBB, blood-brain barrier; BDNF, brain-derived growth factor; CNS, central nervous system; GPR81, (HCAR1)–G-protein coupled receptor 81 (hydroxycarboxylic acid receptor 1); GSK3, glycogen synthase kinase 3; Cx, connexin; HDAC, histone deacetylase; HIF-1, hypoxia-inducible factor 1; IL, interleukin; LDH, lactate dehydrogenase; MCTs, monocarboxylate transporters; MG, methylglyoxal; NAD(P), nicotinamide adenine dinucleotide (phosphate); NAD(P)H, nicotinamide adenine dinucleotide (phosphate) reduced; NGF, nerve growth factor; NFkB, nuclear factor kappa-light-chain-enhancer of activated B cells; NO, nitric oxide; NRF1, nuclear respiratory factor 1; NVU, neurovascular unit; p53, transcription factor p53; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1 α; PDH, pyruvate dehydrogenase; PPARgamma, peroxisome proliferator-activated receptor gamma; RAGE, receptor for advanced glycation end products; SIRT1, NAD+-dependent deacetylase sirtuin-1; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor; TFAM, transcription factor A, mitochondrial; TGF, β–transforming growth factor β; YKL, endothelial glycoprotein named after first three N-terminal amino acids: tyrosine (Y), lysine (K) and leucine (L); Wnt, Wnt-signaling pathway.

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Contents

1. Introduction

The blood-brain barrier (BBB) consists of differentiated cells integrating in one ensemble to control transport processes between the central nervous system (CNS) and peripheral blood. Molecular organization of BBB serves for controlling the extracellular content and cell metabolism in the CNS. Developmental aspects of BBB attract much attention in recent years, and barriergenesis is currently recognized as a very important and complex mechanism of CNS development and maturation. Specific properties of the cells within the neurovascular unit (NVU) – endothelial cells, astrocytes, pericytes, and neurons – allow functioning of the BBB to prevent access for peripheral toxic molecules and to provide trafficking of metabolites from the CNS. All the components of BBB contribute to its structural and functional integrity: (i) endothelial cells regulate bidirectional transport due to expression of transporters, high expression of tight junctions proteins, low levels of fenestration and transcytosis; (ii) pericyte coverage controls vascular permeability; (iii) astrocytes coordinate endothelial cells functioning and metabolism; (iv) synaptic activity of neuronal cells affect BBB properties and local blood flow. It is not surprising that regulation of barriergenesis is also under the control of pericytes, astrocytes, and humoral factors (cytokines, growth factors, neuropeptides, neurotransmitters) secreted by these cells or coming from the periphery (Siegenthaler et al., 2013).

In invertebrates, endothelium of the BBB is incomplete, therefore astroglial cells play much more important role in controlling entry and efflux of molecules in the brain tissue, while endothelial cells appears within the BBB later in the evolution, probably, in order to separate specific functions of endothelial and glial cells (Bundgaard and Abbott 2008; Abbott et al., 2006). Thus, glial blood-brain barrier is replaced with the multicellular complex of the NVU to ensure effective functioning of the barrier in organisms with more complicated neural signaling. Specialization of endothelial and astroglial cells in the BBB might have relation to some other physiological mechanisms important for the adaptation of vertebrates, i.e. living in the conditions of acute or chronic ischemia (Larson et al., 2014). Survival in highly hypoxic conditions requires the existence of adaptive mechanism for rapid shift to anaerobic generation of ATP that is the property of endothelial cells (Fraisl et al., 2009). Active neurogenesis in specialized niches with relatively hypoxic microenvironment requires adequate vascularization, so, endothelial cells are crucial for supporting the neurogenesis in developing and adult brain. Thus, separation of endothelial and glial functions may reflect more complicated regulation of transport and signaling mechanisms in the cells of the NVU.

These evolutionary events are reflected in the individual development of the BBB: endothelial cells populate the brain regions enriched with neuroepithelial cells and radial glia (Lippmann et al., 2012) thus suggesting impact of preexisting glial cells on barriergenesis. Experimental data support such kind of interrelation: radial glia guides vasculogenesis and produces retinoic acid that is one of the most effective regulators of BBB development (Mizee et al., 2013); YKL-immunopositive cells (astroglia precursors and inflammatory cells) locate in embryonic brain in the sites of active angiogenesis and barriergenesis (Bjornbak et al., 2014); specific features of endothelial cells within the BBB could be induced by neuronal progenitors in vitro (Weidenfeller et al., 2007), astrocytes and neuroblasts significantly contribute to BBB development and maturation (Engelhardt and Liebner, 2014; Alvarez et al., 2013; Jian, 2012).

Among all the factors affecting BBB development, vascular endothelial growth factor (VEGF), thrombospondins, transforming growth factor β (TGF-β), nerve growth factor (NGF), brain-derived growth factor (BDNF), and chemokines (Lee et al., 2009; Shibuya, 2009; Errede et al., 2014) which are produced by astroglial cells covering cerebral endothelium, or by neural stem cells in neurogenic niches. Effects of all these soluble and cellular factors may be different in developing and mature brain, and in the brain affected by hypoxia/ischemia (Baburamani et al., 2012). Particularly, angiogenesis is regulated by oxygen-sensing pathways in endothelial cells (Fraisl et al., 2009) being under the control of hypoxia-inducible factor-1 (HIF-1)-mediated molecular mechanisms and metabolic status in endothelial progenitors or mature endothelial cells. In BBB, other cells may also affect angiogenic events, i.e. pericytes and astrocytes which produce wide spectrum of metabolites, growth factors and cytokines with pro- or antiangiogenic activity. As an example, BBB-inductive properties of pericytes are based on their ability to act through Wnt/β-catenin signaling (Cecchelli et al., 2014), while astroglial regulatory activity is mainly dependent on their metabolic coupling with adjacent cells or secretory phenotype. Thus, intercellular communication mediated by metabolic regulators arising from the cells of NVU dynamically shapes structural and functional integrity of the BBB.

2. Characteristics of glycolysis in brain astroglial and endothelial cells

Metabolic control of angiogenesis/barriergenesis may be provided by glycolytic activity of NVU cells (Eichmann and Simons, 2013). It is known from various models of angiogenesis, glycolysis promotes vessel branching (De Bock et al., 2013; Eelen et al., 2013) and cell migration associated with angiogenic events (De Bock et al., 2013), expression of lactate dehydrogenase (LDH) is important for angiogenesis (Parra-Bonilla et al., 2013) while suppression of glycolysis results in angiogenesisi impairment (Schoors et al., 2014a; Goveia et al., 2014). The same effect can be reproduced by anti-VEGF treatment (Schoors et al., 2014b). However, direct effects of glycolysis modulation on BBB development have not been tested yet.

Glycolysis is active in many cells either in hypoxic or normoxic conditions, in latter case it can rapidly increase intracellular adenosine triphosphate (ATP) levels according to current demands of a cell compeled to activation, proliferation, secretion, migration, and apoptosis (Epstein et al., 2014; Chiarugi et al., 2014; Cerella et al., 2014; Cheng et al., 2014a,b). Fast growth of the fetal brain corresponds to higher metabolism of glucose by aerobic glycolysis, while suppression of intensive neurogenesis in postnatal period results in reduction of this metabolic process (Bauernfeind and Babbitt, 2014). Maintenance of neurogenesis within the specialized zones

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