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Review

Targeting transporters: Promoting blood–brain barrier repair in response to oxidative stress injury

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ABSTRACT

The blood–brain barrier (BBB) is a physical and biochemical barrier that precisely regulates the ability of endogenous and exogenous substances to accumulate within brain tissue. It possesses structural and biochemical features (i.e., tight junction and adherens junction protein complexes, influx and efflux transporters) that work in concert to control solute permeation. Oxidative stress, a critical component of several diseases including cerebral hypoxia/ischemia and peripheral inflammatory pain, can cause considerable injury to the BBB and lead to significant CNS pathology. This suggests a critical need for novel therapeutic approaches that can protect the BBB in diseases with an oxidative stress component. Recent studies have identified molecular targets (i.e., putative membrane transporters, intracellular signaling systems) that can be exploited for optimization of endothelial drug delivery or for control of transport of endogenous substrates such as the antioxidant glutathione (GSH). In particular, targeting transporters offers a unique approach to protect BBB integrity by promoting repair of cell–cell interactions at the level of the brain microvascular endothelium. This review summarizes current knowledge in this area and emphasizes those targets that present considerable opportunity for providing BBB protection and/or promoting BBB repair in the setting of oxidative stress.

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Contents

Abbreviations: ABC, ATP Binding Cassette; ALK, activin receptor-like kinase; BBB, blood–brain barrier; BCRP, Breast Cancer Resistance Protein; CNS, central nervous system; GSH, glutathione; GSSG, glutathione disulfide; JAM, junctional adhesion molecule; MAGUK, membrane-associated guanylate kinase-like; MCAO, middle cerebral artery occlusion; MDR, multidrug resistance; MRP, Multidrug Resistance Protein; Nrf2, nuclear factor E2-related factor-2; OATP, organic anion transporting polypeptide; P-gp, P-glycoprotein; SLC, solute carrier; SOD, superoxide dismutase; TEMPOL, 4-hydroxy-2,2,6,6-tetramethylpiperidine-N-oxyl; TGF, transforming growth factor; ZO, zonula occluden

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1. Introduction

The blood–brain barrier (BBB) is an essential physical and biochemical barrier that separates the central nervous system (CNS) from the peripheral circulation. This barrier is primarily formed by cerebral endothelial cells that interact with each other to maintain CNS homeostasis and reduce the probability of cerebral toxicity due to xenobiotic accumulation. Pathologies with an oxidative stress component (i.e., cerebral hypoxia/ischemia, peripheral inflammatory pain) are known to disrupt BBB inter-endothelial cell interactions, which can cause profound pharmacotherapeutic challenges. Therefore, there is a essential need for novel therapeutic strategies that can protect the BBB from pathological damage and, by extension, ensure more effective drug delivery across the endothelial cell plasma membrane. One approach is to target endogenous transporters localized to BBB endothelial cells. Here, we review BBB molecular characteristics (i.e., tight junction and adherens junction protein complexes, influx and efflux drug transporters) and those mechanisms associated with oxidative stress that can cause BBB injury. Additionally, we provide insights on endothelial transporter targets that have great potential to be exploited for promoting BBB repair in the setting of oxidative stress.

2. The Blood–brain barrier

The CNS is the most critical and sensitive organ system in the body. Proper function requires precise control of the brain extracellular milieu. Additionally, metabolic demands of brain tissue are considerable with the CNS accounting for approximately 20% of human oxygen consumption (Rolfe and Brown, 1997). Therefore, the interface between CNS and systemic circulation must possess highly effective mechanisms that can facilitate transport of specific nutrients, exactly regulate ion balance, and limit blood-to-brain uptake of toxic substances. The absolute necessity for a tissue that is both a physical and biochemical barrier is emphasized by the sensitivity of brain parenchyma cellular compartments to xenobiotics. That is, brain entry of specific substances must be permitted while flux of other molecules into brain parenchyma must be excluded. This function of the cerebral microvasculature primarily occurs at the level of the endothelial cell. It is essential to note that brain microvessel endothelial cells are not intrinsically capable of forming a fully functional BBB. In fact, formation and maintenance of the BBB phenotype requires interactions with adjacent glial cells as well as neurons, pericytes, and extracellular matrix (Ronaldson and Davis, 2012; Ronaldson and Davis, 2013). This intricate relationship implies existence of a neurovascular unit, a concept that emphasizes the requirement for coordinated cell–cell interactions and signaling that precisely regulates BBB homeostasis.

Anatomically, BBB endothelial cells are characterized by a lack of fenestrations, limited pinocytotic activity, and presence of tight junction protein complexes between apposing endothelial cells (Abbott et al., 2010). Additionally, the cerebral microvascular endothelium is identified by increased mitochondrial content as compared to endothelial cells from other tissues (Oldendorf et al., 1977). This increased content of mitochondria is required for both protection against deleterious effects of oxidative stress and maintenance of brain Ca^{2+} homeostasis (Sochocka et al., 2013). Additionally, several receptors, ion channels, uptake transporters, and efflux transporters are prominently expressed in brain microvascular endothelial cells. Functionally, these transport systems are similar to well-characterized systems in other tissues (i.e., D-glucose transporter, L-amino acid carrier systems, Na^+/K^+ ATPase), although transport kinetics can vary. Transporters involved in transendothelial flux of drugs have also been identified and characterized at the BBB and include ATP-dependent efflux transporters such as P-glycoprotein (P-gp) (Roberts et al., 2008; Yousif et al., 2008; McCaffrey et al., 2012; Ohtsuki et al., 2013), Multidrug Resistance Proteins 1-6 (MRP1-6 in humans; Mrp1-6 in rodents) (Dallas et al., 2006; Bauer et al., 2008; Roberts et al., 2008; Cartwright et al., 2013), and Breast Cancer Resistance Protein (BCRP in humans; Bcrp in rodents) (Yousif et al., 2012; Ohtsuki et al., 2013). Transporters that facilitate BBB drug permeation include organic anion transporting polypeptides (OATPs in humans; Oatps in rodents) (Ose et al., 2010; Ronaldson et al., 2011; Thompson et al., 2014), organic anion transporters (Hawkins et al., 2007; Ose et al., 2009; Miyajima et al., 2011), monocarboxylate transporters (Vijay and Morris, 2014), nucleoside transporters (Lepist et al., 2013), and peptide transporters (Dogrukol-Ak et al., 2009).

2.1. *Molecular characteristics of the BBB*

2.1.1. *Tight junction protein complexes*

BBB endothelial cells are interconnected by tight junctions (Fig. 1), which are large multi-protein complexes maintained by astrocytic trophic factors. Evidence for this role of astrocytes comes from in vivo experiments in which male Fisher F344 rats were injected with 3-chloropropanediol, an astrocyte-selective toxin (Willis et al., 2004a, 2004b). Focal astrocyte loss induced by treatment with 3-chloropropanediol led to disassembly of tight junction protein complexes and increased paracellular dextran leak (Willis et al., 2004a, 2004b), suggesting a central role for