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# Endothelial calcium dynamics, connexin channels and blood–brain barrier function

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ABSTRACT

Situated between the circulation and the brain, the blood–brain barrier (BBB) protects the brain from circulating toxins while securing a specialized environment for neuro-glial signaling. BBB capillary endothelial cells exhibit low transcytotic activity and a tight, junctional network that, aided by the cytoskeleton, restricts paracellular permeability. The latter is subject of extensive research as it relates to neuropathology, edema and inflammation. A key determinant in regulating paracellular permeability is the endothelial cytoplasmic $Ca^{2+}$ concentration ($[Ca^{2+}]_i$) that affects junctional and cytoskeletal proteins. $Ca^{2+}$ signals are not one-time events restricted to a single cell but often appear as oscillatory $[Ca^{2+}]_i$ changes that may propagate between cells as intercellular $Ca^{2+}$ waves. The effect of $Ca^{2+}$ oscillations/waves on BBB function is largely unknown and we here review current evidence on how $[Ca^{2+}]_i$ dynamics influence BBB permeability.

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## Contents



*Abbreviations:* ARC, arachidonate-regulated $Ca^{2+}$ entry channels; BBB, blood–brain barrier; BCEC, bovine brain capillary endothelial cells; BK, bradykinin; CaM, calmodulin; CaMKII, $Ca^{2+}$/calmodulin-dependent kinase II; cGMP, cyclic guanosine monophosphate; CRAC, $Ca^{2+}$ release-activated channels; Cx, connexin; ER, endoplasmic reticulum; GPCR, G-protein coupled receptor; ICAM1, intercellular adhesion molecule 1; $InsP_3$, inositol 1,4,5-trisphosphate; $InsP_3R$, inositol 1,4,5-trisphosphate receptor; MAPK, mitogen-activated protein kinase; MDCK, Madine–Darby canine kidney cells; MLC, myosin light chain; MLCK, myosin light chain kinase; MMP, matrix-metalloproteinase; NADPH oxidase, nicotinamide adenine dinucleotide phosphate oxidase; NFκB, nuclear factor κB; NMDA-R, N-methyl-D-aspartate-sensitive receptor; NOS, nitric oxide synthase; PAR, protease-activated receptor; p/sGC, particulate/soluble guanylyl cyclase; PKC, protein kinase C; PLA2, phospholipase A2; PLC, phospholipase C; ROS, reactive oxygen species; STIM, stromal interaction molecule; TRP, transient receptor potential; VASP, vasodilator-stimulated phosphoprotein; VEGF, vascular endothelial growth factor; ZO, zonula occludens.

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## 1. Introduction

Reliable electrical signaling in the brain requires a strict composition of the extracellular milieu around synapses and axons which is maintained by the blood–brain barrier (BBB). The BBB is a highly selective, lipophilic barrier situated between the systemic blood circulation and the cerebral tissue that plays an essential role in maintaining brain homeostasis: it determines the ionic interstitial microenvironment, it prevents exo- and endogenous toxins from entering the brain and it separates peripheral from central neurotransmitter pools. The BBB is therefore crucial for normal neuronal and glial activity (Abbott et al., 2010; Bradbury, 1993). The first indications of the presence of a BBB were, in sequential order, provided by Ehrlich, Lewandowski and Goldman who reported that aniline dyes are only able to stain the brain tissue when administered *via* the intracerebroventricular route but not when injected into the blood stream, and that ferrocyanide is lethal at low doses when injected in the brain but requires doses a 100 times higher when injected in the blood stream [see (Bechmann et al., 2006) for original citations]. Reese and Karnovsky finally indicated that the anatomical basis of the vertebrate BBB is the structurally and functionally unique endothelium that lines the brain capillary lumens. The BBB endothelial cells are interconnected by a sophisticated inter-endothelial junctional complex which consists of adherens junctions and tight junctions that limit paracellular diffusion of solutes from blood to brain (and *vice versa*) (Abbott et al., 2006; Bechmann et al., 2006; Ge et al., 2005; Wolburg and Lippoldt, 2002). This restricted paracellular movement of (charged) solutes is reflected in a relatively high transendothelial electrical resistance. The absence of pinocytotic activity and the presence of a strictly regulated set of transport proteins and enzymes add up to the specific features of BBB endothelial cells (Abbott et al., 2010), altogether rendering these vessels far less permeable to endogenous molecules (and tracer compounds) than their peripheral counterparts. However, many, if not all, central nervous system disorders including stroke, inflammation, Alzheimer's disease, Parkinson's disease, epilepsy and multiple sclerosis are associated with an increased permeability of the BBB, either as a cause or consequence, further aggravating the course of the disease (Hawkins and Davis, 2005; Stanimirovic and Friedman, 2012; Zlokovic, 2008). Most of the current knowledge focuses on the harmful effects of a BBB permeability increase; it is however worth to note here that BBB permeability changes are not always deleterious, but may, for example, lead to attenuation of brain edema (Campbell et al., 2012).

It is long known that $Ca^{2+}$ ions play an important role in the control of BBB permeability. Normal BBB function is indeed disturbed when the extracellular $Ca^{2+}$ concentration [normally ~1.5 mM at the blood side and ~1 mM at the brain interstitial side (Somjen, 2004)] is decreased and/or the *intra*cellular free $Ca^{2+}$ concentration [$[Ca^{2+}]_i$, normally 50–100 nM (Hess et al., 1989; Koenig et al., 1989)] is increased. Decreased extracellular $Ca^{2+}$ levels result in a disruption of cell–cell and cell–matrix adhesive interactions (Wilhelm et al., 2007), but also give rise to dynamic changes in $[Ca^{2+}]_i$ (De Bock et al., 2012a). With regard to $[Ca^{2+}]_i$-dependent BBB alterations, most of the current knowledge is derived from work in ischemic conditions or work with vasoactive, inflammatory substances. Many of these share the ability to trigger a substantial increase in endothelial $[Ca^{2+}]_i$ thereby activating $Ca^{2+}$-sensitive signaling pathways. Preventing the $[Ca^{2+}]_i$ increase protects against BBB malfunctioning in many different experimental scenarios; hence, $[Ca^{2+}]_i$ was identified as a major regulator of BBB function (Abbott, 1991, 1998, 2000; Brown and O'Neil, 2009). In the $Ca^{2+}$ field it is largely acknowledged that $Ca^{2+}$ signals do not only appear as simple one-time events restricted in time and space (as for instance observed in neurotransmitter release), but often occur as repetitive, oscillatory $[Ca^{2+}]_i$ changes or spatially spreading $[Ca^{2+}]_i$ elevations that traverse the cell boundaries and propagate as an intercellular $Ca^{2+}$ wave. In the BBB field, the effect of $Ca^{2+}$ oscillations and intercellular $Ca^{2+}$ waves on barrier function has hardly been studied and we here explore how such $[Ca^{2+}]_i$ dynamics can influence the BBB. Modulation of barrier function can occur at different levels including alterations in (*i*) paracellular permeability, (*ii*) pinocytotic activity and, (*iii*) transporter and enzyme activity. Since little is known on $Ca^{2+}$-regulation of pinocytosis, enzymes or transporters in BBB endothelial cells, we will focus in this review on the $Ca^{2+}$-mediated increase in paracellular permeability. The original observations outlined in this overview are all derived from work with primary or immortalized brain 'microvascular' endothelial cells unless stated otherwise. It is however not always clear whether these microvascular cells have a capillary origin and it is sparsely documented to what extent BBB characteristics are maintained in arteriolar and venular endothelial cells. Notably, in pre- and post-capillary segments where endothelial BBB characteristics are less pronounced, the barrier function is aided by phagocytic scavenging in the vessel wall and perivascular spaces, a process that is not available in brain capillaries (Abbott et al., 2006; Bechmann et al., 2006; Ge et al., 2005).

### 1.1. $Ca^{2+}$ as a major determinant of BBB function

About three decades ago, research on the participation of $Ca^{2+}$ in the regulation of BBB function was initiated by Søren-Peter Olesen who published a series of reports highlighting the role of an endothelial $[Ca^{2+}]_i$ increase as an important determinant of BBB permeability. Comparing a variety of vasoactive agents from different chemical classes, Olesen concluded that substances stimulating changes in permeability shared the common characteristic of increasing $[Ca^{2+}]_i$ in endothelial cells from pial microvessels (Olesen, 1985, 1989). Evaluating different second messenger systems, Olesen further concluded that only a rise in $[Ca^{2+}]_i$ but not in the other major second messenger, cyclic adenosine monophosphate (cAMP), decreased resistance in these microvessels (Olesen, 1987). In the years that followed, the role of $Ca^{2+}$ as an important second messenger involved in the regulation of barrier function was further emphasized for different $Ca^{2+}$-mobilizing, vasoactive and inflammatory agents as well as in ischemic conditions. The study of pathogen and leukocyte passage over the BBB has additionally brought up interesting insights on endothelial $[Ca^{2+}]_i$ changes and their relation to BBB functioning.

Free cytoplasmic $Ca^{2+}$ represents only a small part of the total cellular $Ca^{2+}$ reserve as most of the intracellular $Ca^{2+}$ is sequestered into intracellular stores in order to prevent a potential deleterious action of $Ca^{2+}$ ions in the cytoplasm, mitochondria and nucleus where it can lead to the aggregation of proteins and nucleic acids, to the precipitation of phosphates and to disruption of lipid membranes (Case et al., 2007). The endoplasmic reticulum (ER) is considered the predominant $Ca^{2+}$ store as it contains approximately

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