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Invited Review

The blood-brain barrier in systemic inflammation

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ABSTRACT

The blood-brain barrier (BBB) plays a key role in maintaining the specialized microenvironment of the central nervous system (CNS), and enabling communication with the systemic compartment. BBB changes occur in several CNS pathologies. Here, we review disruptive and non-disruptive BBB changes in systemic infections and other forms of systemic inflammation, and how these changes may affect CNS function in health and disease. We first describe the structure and function of the BBB, and outline the techniques used to study the BBB *in vitro*, and in animal and human settings. We then summarise the evidence from a range of models linking BBB changes with systemic inflammation, and the underlying mechanisms. The clinical relevance of these BBB changes during systemic inflammation are discussed in the context of clinically-apparent syndromes such as sickness behaviour, delirium, and septic encephalopathy, as well as neurological conditions such as Alzheimer's disease and multiple sclerosis. We review emerging evidence for two novel concepts: (1) a heightened sensitivity of the diseased, versus healthy, BBB to systemic inflammation, and (2) the contribution of BBB changes induced by systemic inflammation to progression of the primary disease process.

Contents

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1. Introduction

The effects of systemic inflammation on central nervous system (CNS) function may be adaptive, as an appropriate response to systemic upset (Hart, 1988), but deleterious effects are commonly seen in clinical practice. Acute syndromes of CNS dysfunction are frequently seen to accompany non-neurotropic systemic infections such as pneumonia or urinary tract infections. In chronic conditions such as multiple sclerosis or Alzheimer's disease, systemic inflammation can be associated with a transient or permanent deterioration (Buljevac et al., 2002; Holmes et al., 2009).

In this review, we focus on the effects of systemic inflammation on the blood-brain barrier (BBB), which may be desirable or deleterious. The foremost role of the BBB is to maintain homeostasis for optimal brain function. BBB changes may be disruptive or non-disruptive. Disruptive BBB changes are likely to be deleterious. Non-disruptive changes may also be deleterious but could provide a mechanism for communication across a morphologically intact BBB, and without unselected compromise of the barrier functions essential to CNS homeostasis.

2. Anatomy and function of the BBB

The anatomy of the BBB is best described at histological and molecular levels; its function is carried out by structures at these two levels. Histologically the BBB is a specialized multi-layered unit composed of a thick continuous glycocalyx, non-fenestrated endothelial cells with reduced vesicular activity and linked by tight junctions, two basement membranes (vascular basement membrane and glia limitans), and astrocytic end-feet. All elements of this 'neurovascular unit' contribute to the functional BBB. At the molecular level, there are ectoenzymes, receptors and transporters in several of these layers which regulate or reverse traffic across the BBB. Together, these components enable a stable CNS environment that is unique in the following ways: (1) different ionic composition, needed for neuronal function (2) specialized neurotransmitter pool (3) low protein concentration, to minimize cell proliferation (4) low exposure to systemic toxins, to minimize neuronal damage (5) reduced traffic of inflammatory cells and molecules, to minimize local inflammation.

3. Assessing BBB function

3.1. In vitro

A number of methods may be used to study BBB functions (He et al., 2014). Histological techniques such as freeze-fracture and electron microscopy permit snapshot visualisation of changes in tight junctions and vesicles, from which changes in function can be inferred.

Endothelial monolayers allow quantitative assessment of barrier function and are a relatively simple model in which experimental conditions can be easily modified (Helms et al., 2016). Primary or immortalized human or animal brain microvascular endothelial cells (BMECs or BMVECs) are cultured into a confluent monolayer on permeable cell culture plate inserts (e.g. Transwell). The solutes or cells of interest are added to the top compartment, and the fraction that migrates through the endothelial layer into the bottom compartment is measured. This technique allows study of the polarity of the BBB. Measurement may employ radiolabelled compounds or fluorescent dyes, or techniques such as enzyme-linked immunosorbent assay (ELISA) or liquid chromatography-mass spectrometry (LC-MS). Transendothelial electrical resistance (TEER) across the monolayer can be measured, and reflects paracellular ion flux; reduced resistance suggests opening of tight junctions. The significant limitation of such models is that cells cultured in an artificial environment will not differentiate or function appropriately, and may lack features relevant to the BBB functions under investigation. Co-culture with other relevant components such as abluminal astrocytes may improve the fidelity of the model. Simulation of flow may also influence differentiation of endothelial barrier characteristics (Tarbell, 2010). Endothelial cells may be seeded onto porous hollow fibres (Stanness et al., 1997) or microfluidic devices (Booth and Kim, 2012), to create a three-dimensional tissue culture through which flow can be re-created.

Isolated cerebral microvessels can be prepared from brain tissue and provide a more functional model than endothelial monolayers, with preservation of differentiated BBB characteristics. Importantly, transport, receptor, and metabolic systems are preserved, allowing detailed study of these processes (Choi and Pardridge, 1986), as well as patch-clamp studies of membrane ionic channels (Hoyer et al., 1991). Alternatively endothelial plasma membrane vesicles can be isolated from microvessels, providing a useful method to compare differences between luminal and abluminal surfaces which contribute to the polarity of the BBB (Sánchez del Pino et al., 1992).

3.2. In vivo

In vitro BBB models can never fully recapitulate the natural microenvironment, and therefore *in vivo* methods are more realistic. In humans, a number of techniques can be used, as summarised

Table 1
Concepts in methodology for *in vivo* study of BBB disruption in humans.

Concept	Method	Example
CNS concentration of a plasma protein not usually synthesized within the CNS correlates with BBB permeability	Post-mortem study of brain tissue can detect ante-mortem BBB leakage of plasma protein	Immunohistochemistry for albumin on brain tissue (van Vliet et al., 2007)
	Paired cerebrospinal fluid (CSF) and serum analysis to estimate the ratio of CSF to serum concentration of plasma protein	CSF/serum albumin quotient, Q_{alb} (Akaishi et al., 2015)
Serum concentration of a CNS protein not usually synthesized outside the CNS correlates with BBB permeability	Serum analysis of the CNS protein	Serum S100β (Kapural et al., 2002)
Intravital injection of tracers	Injection of low molecular weight paramagnetic substances before magnetic resonance brain imaging	Dynamic contrast-enhanced magnetic resonance imaging (Cramer et al., 2014)
	Injection of radiolabelled substances before nuclear medicine brain imaging	Gallium injection positron emission tomography (Iannotti et al., 1987)
	Injection of radiolabelled test and BBB-impermeable reference substances into carotid artery, or antecubital vein, and detection in internal jugular vein	Double-indicator diffusion technique (Knudsen, 1994)

in Table 1. Animal studies afford a higher degree of experimental manipulation and observation. Experiments may employ one or several of a wider array of tracers, injection sites, compartments assayed, time points, detection techniques and analytical approaches; this is illustrated in Fig. 1, grouped by steps in experimental design. The combinatorial possibilities are many. For instance, in one experiment, a radiolabelled exogenous substance (sucrose) was delivered systemically with a single injection into the femoral vein while arterial blood was sampled over 60 min to follow its circulating concentration (Bickel et al., 1998), while in another experiment the brain was perfused *in situ* for 30 min with a solution of radiolabeled endogenous peptide (Nonaka et al., 2005). At the point of sacrifice brain tissue was collected in both experiments (i.e. the CNS compartment was assayed at one time point) and a scintillation counter was used to quantitate amounts of each substance. Different experimental designs call for different analytical methods. Hence, in the first experiment using intravenous injection, pharmacokinetic modelling was employed to track a changing circulating concentration while in the second experiment, the concentration of the perfusate was known and fixed, so pharmacokinetic modelling was not required. In experiments where the CNS compartment is assayed several times, multiple time-point regression analysis is used (Patlak et al., 1983; Kastin et al., 2001). The choice of analytical method determines the index used to quantify BBB permeability, of which there are several (Panel 6 in Fig. 1).

It is important to note that measurements of 'permeability' may be inaccurate if the substance is actively transported, metabolised, or secreted by the BBB. In addition, the experimental situation may cause increased systemic production, or may trigger CNS production, of an endogenous substance being used to study BBB function, or may result in reduced systemic clearance with potential confounding effects.

4. Disruptive and non-disruptive BBB change

Although there is a tendency to refer to the effect of systemic inflammation on 'BBB permeability', this terminology can be confusing, since permeability usually reflects diffusibility of substances across the BBB and traffic across the BBB is not governed by diffusion alone. The concept of BBB permeability arose from early studies which used solutes to measure BBB function. We now know that BBB function is highly regulated and, while diffusion is an important process, both molecules and cellular traffic are subject to specific or regulated processes distinct from diffusion. Hence we propose the terminology 'BBB change' which indicates BBB responsiveness. BBB change can be disruptive or non-disruptive, reflecting the presence or absence of physical disruption of the BBB. Disruptive BBB change is accompanied by changes at the histological level, such as endothelial cell damage or tight junction changes, while non-disruptive change occurs at the molecular level. Studying the BBB using inert substances will detect disruptive BBB change but is unlikely to detect non-disruptive BBB change. Table 2 summarises the fundamental differences between disruptive and non-disruptive BBB change, and Fig. 2 illustrates their anatomical context and possible mechanisms. Both disruptive and non-disruptive BBB changes may occur in systemic inflammation, and both have important consequences.

5. Disruptive BBB change in systemic inflammation

5.1. LPS models

Systemic challenge with lipopolysaccharide (LPS), an immunogenic component of Gram-negative bacteria, is widely used to model systemic inflammation. A number of *in vitro* BMEC studies have shown that LPS challenge results in disruptive BBB change to ions (by TEER) (de Vries et al., 1996a) as well as solutes such as albumin (Tunkel et al., 1991).

When administered *in vivo*, the effect of LPS on BBB function is variable. In a systematic review, we analysed studies examining disruptive BBB change after LPS challenge *in vivo*. Papers were identified by searching MEDLINE and Web of Science in February 2016, as well as by collecting references from relevant articles. Various search terms were used in full and abbreviated form including 'lipopolysaccharide', 'endotoxin', 'blood-brain barrier', and 'systemic inflammation'. We looked for animal studies in which a systemically-delivered solute was assayed in the CNS after systemic challenge with LPS or control. We did not include studies examining non-disruptive BBB change involving cellular traffic. We excluded studies if the solute could be subject to BBB transport mechanisms, if the experiment for a particular solute was not replicated elsewhere, if the relevant lethal dose could not be ascertained for the animal model, or if the study examined solute efflux rather than influx. In total, 22 studies were excluded, of which 68% showed increased solute traffic after LPS challenge.

47 papers including 74 studies were eligible for analysis. Experimental characteristics and results were extracted from these studies, and are available from the University of Southampton repository at http://dx.doi.org/10.5258/SOTON/387995. 60% of studies reported disruptive BBB change after LPS; this figure may be subject to publication bias since papers reporting disruptive

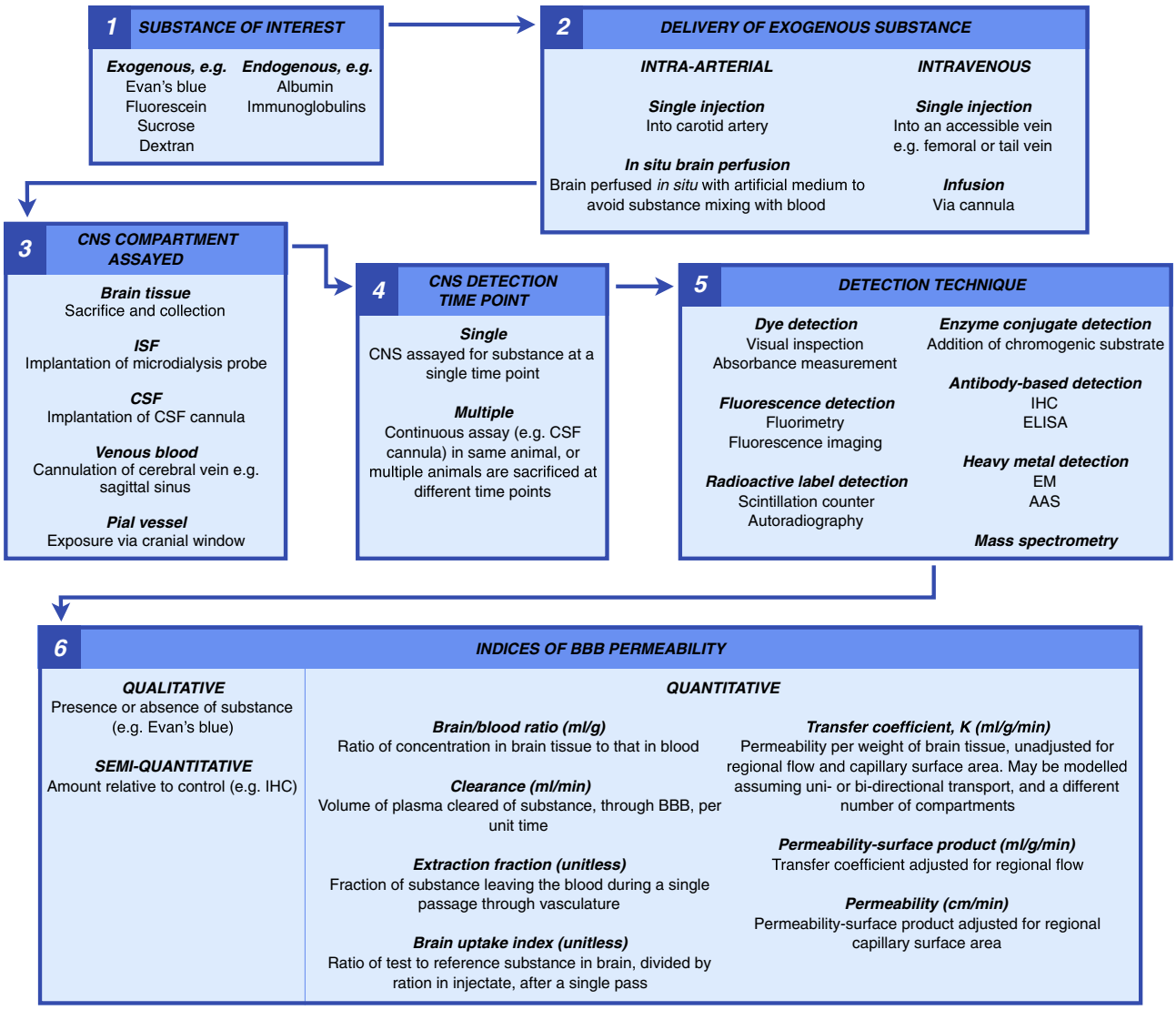

Fig. 1. Concepts in experimental design for *in vivo* study of BBB disruption in animals. A number of methods can be used, creating potential variability between studies. AAS, atomic absorption spectroscopy; CSF, cerebrospinal fluid; ELISA, enzyme-linked immunosorbent assay; EM, electron microscopy; IHC, immunohistochemistry; ISF, interstitial fluid.

Table 2
Distinction between disruptive and non-disruptive BBB changes.

Disruptive BBB change	Non-disruptive BBB change
Usually occurs at a histological level	Usually occurs at a molecular level
Visible change in histological architecture	No visible change in histological architecture
Change in anatomy	Change in function
Detected using inert tracers	Not detected using inert tracers
Generally not substance-specific	Substance-specific
Not a prerequisite for cellular traffic; may occur if cellular traffic is intense	Main mechanism underlying change in cellular traffic
Nature of possible changes: tight junction changes, denudation of glycocalyx, endothelial cell damage, increased vesicular traffic, re-induction of fenestrae, breakdown of glia limitans, astrocytopathy in combination with endothelial changes	Nature of possible changes: cytokine production by endothelial cells, upregulation of endothelial cell receptors and transporters, modulation of astrocyte function, enhanced pathogen neuroinvasion

BBB change may have been more likely to be published. Hence it is clear that the effects of LPS on the BBB are not universal. Since some of the variability could be attributable to differences in experimental technique, a multivariate logistic regression was performed, with disruptive BBB change as the binary dependent variable, and a number of predictor variables capturing differences in experimental techniques:

- LPS dose, expressed as an absolute value or as a percentage of species-specific lethal dose to correct for inter-species variation (taken to be 2000 μg/kg in rodents (Dinges and Schlievert, 2001), 500 μg/kg in rabbits (Lee et al., 1991), and 1 μg/kg in foetal sheep (Yan et al., 2004)). Since absolute LPS dose and % lethal dose were correlated, the regression was performed twice with either one or the other.
- Dosing protocol, classified as single or multiple, since the total LPS dose was calculated cumulatively for multiple challenges.
- Species of experimental animal.
- Solute, classified as either an 'indicator' (unaltered solute) or a 'tracer' (solute altered for detection).

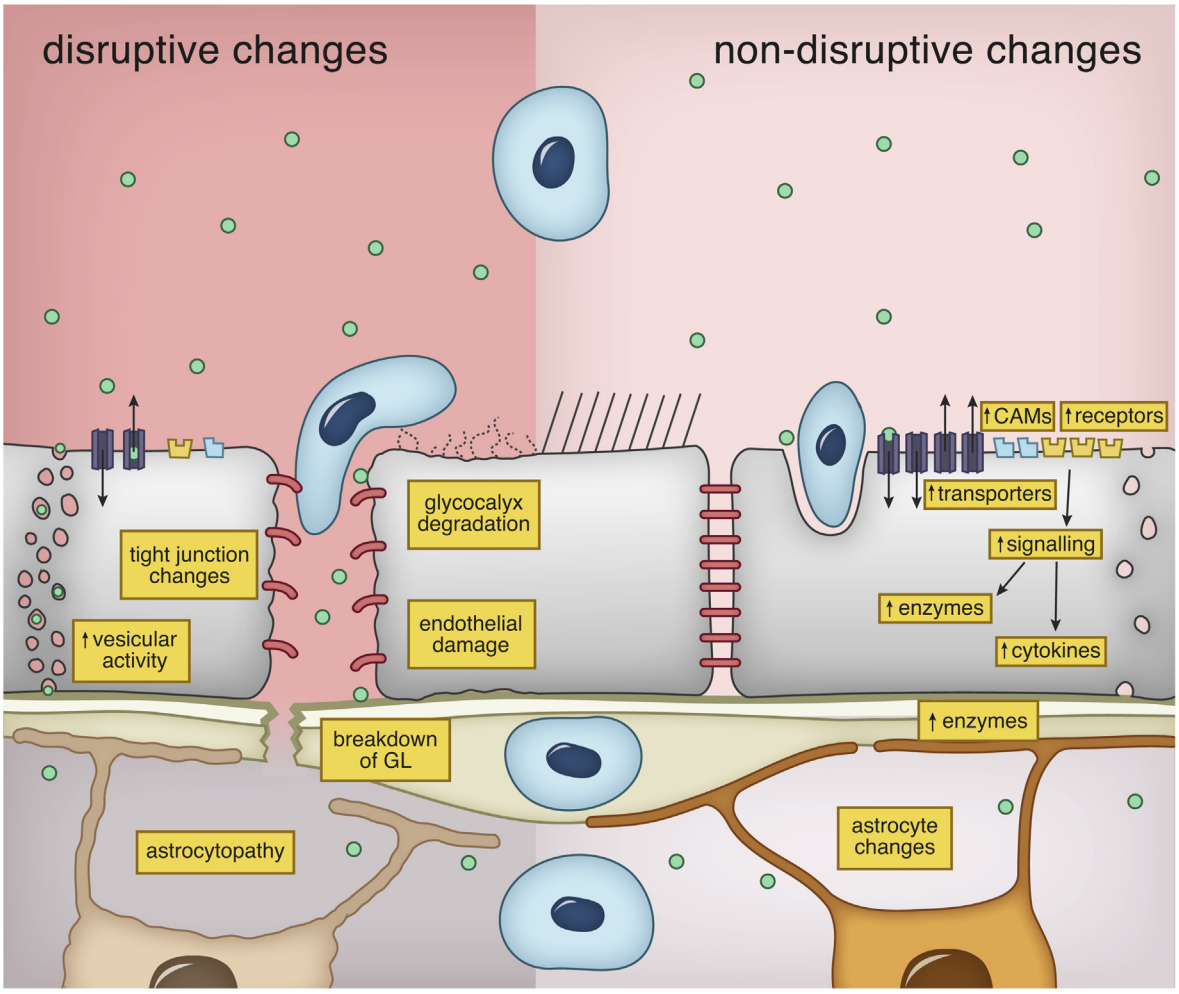

Fig. 2. Schematic illustration of disruptive and non-disruptive BBB changes during systemic inflammation. Relative proportions are not intended to be realistic. CAMs, cellular adhesion molecules; GL, glia limitans.

- Solute, classified as 'synthesised' if it could be produced by the animal, potentially confounding estimates of permeability. The remaining solutes were classified as 'non-synthesised'. By these criteria, immunoglobulin was classified as 'synthesized', labelled albumin as 'non-synthesised', and in studies detecting the animal's own unaltered albumin, we classified albumin as 'synthesised', as there is evidence that albumin may be produced with the brain and this process is enhanced by LPS exposure (Ahn et al., 2008).
- Age of experimental animal, as either adult or infant (the latter including all cases described as infant, neonatal, or foetal). An age-related effect has been demonstrated (Stolp et al., 2005).
- Health of experimental animal, as either healthy or diseased. An effect has been demonstrated in a number of disease models compared to healthy controls, for example Alzheimer's disease (Takeda et al., 2013).
- Time course of permeability estimation, as either single (solute assayed at single time point) or multiple (solute assayed at multiple time points). A time-dependent effect has been demonstrated (Banks et al., 2015).
- Gender of experimental animal, as either male or female. An effect of gender has been demonstrated (Maggioli et al., 2016). 17% of studies were missing data for this variable, leading to its exclusion from the final analysis.

Species was the only significant predictor explaining 16% of the variance ($p = 0.023$) and correctly classifying 69% of cases. BBB change was 4.1 times more likely in mice versus rats ($p = 0.008$). LPS dose was not a significant predictor (absolute dose or percentage of lethal dose). However, a dose-dependent effect of LPS on the BBB was observed when considering single studies using several LPS doses (Allen, 1965; Banks et al., 2015; Jaeger et al., 2009; Oshima et al., 2009). This indicates the confounding potential of technical differences between studies, which when minimized allow the detection of a dose-dependent effect of LPS dose on BBB change. Finally, it is important to bear in mind that most studies used septic doses of LPS, which limits the generalizability of findings to more common less severe infections in human patients.

5.2. Mechanisms of disruptive BBB change in LPS models

A number of mechanisms have been described to account for the BBB disruptive effects of LPS. Central to these mechanisms are prostanoids and nitric oxide (NO) (Banks et al., 2015; Iwase et al., 2000), both of which are synthesized by the LPS-stimulated cerebrovascular endothelium and surrounding cells (Cao et al., 1995; Minami et al., 1998).

5.2.1. Modification of tight junctions

Evidence using TEER as a reflection of tight junction integrity suggests that tight junction modification may be secondary to prostanoids (de Vries et al., 1996a) and NO (Wong et al., 2004). Other diffusible mediators include matrix metalloproteinases (MMPs) (Qin et al., 2015) and reactive oxygen species (Yu et al., 2015). Intracellular pathways include mitogen-activated protein (MAP) kinase signalling (Qin et al., 2015), myosin light chain phosphorylation and F-actin rearrangement (He et al., 2011), and mitochondrial dysfunction (Doll et al., 2015). At protein translational level, miR-155 contributes to changes in gene expression (Lopez-Ramirez et al., 2014), which include decreased expression of occludin and claudin-5 (Zhou et al., 2014). NFκB plays a role at gene transcription level (Han et al., 2016).

5.2.2. Endothelial damage

Endothelial damage during systemic inflammation may contribute to barrier dysfunction. Features include endothelial apoptosis, membrane abnormalities, and mitochondrial damage (Cardoso et al., 2012). The induction of apoptosis may be mediated by MAP kinase signalling (Karahashi et al., 2009).

5.2.3. Degradation of glycocalyx

Of emerging importance is the glycocalyx, a complex structure of proteoglycans and sialoproteins lining the apical endothelium. Although poorly studied in the CNS, accumulating evidence suggests that a continuous glycocalyx is an important contributor to barrier function, and that dysfunction leads to increased paracellular permeability (Woodcock and Woodcock, 2012). LPS models of systemic inflammation demonstrate glycocalyx degradation (Wiesinger et al., 2013). Degradation can be mediated by components of the systemic inflammatory response, including tumour necrosis factor-α (TNF-α) (Wiesinger et al., 2013), heparanase (Chappell et al., 2008), ROS (Moseley et al., 1997), MMPs (Lipowsky, 2012), and thrombin (Wiesinger et al., 2013).

5.2.4. Breakdown of glia limitans

The glia limitans is the innermost layer of the BBB. MMPs may contribute to degradation of extracellular matrix components and breakdown of the glia limitans (Cardoso et al., 2010).

5.2.5. Astrocyte changes

Astrocytes induce and maintain the BBB, and in particular form the glia limitans (Sofroniew, 2015). Indeed, astrocyte destruction is associated with BBB disruption (Asgari et al., 2015). Systemic LPS may induce a number of structural and functional changes in astrocytes which could be relevant to disruptive BBB change. Some *in vivo* studies show astrocyte proliferation and activation, followed by astrocyte loss (Biesmans et al., 2013; Cardoso et al., 2015), and another study demonstrates structural changes in astrocytic end-feet (Fan et al., 2014), which could lead to disruptive change. However, another study showed no morphological change (Jeong et al., 2010). Systemic LPS also induces broad changes in astrocyte gene transcription, including pro-inflammatory and cytotoxic pathways (Zamanian et al., 2012), and astrocytes are capable of producing a range of substances associated with disruptive BBB change, including interleukin-1β (IL-1β), interleukin-6 (IL-6), TNF-α, and prostaglandins (Sofroniew, 2015). *In vitro* results are mixed; LPS-induced disruptive BBB change was indifferent to the presence of astrocytes in one study (Banks et al., 2015), but not another (Gaillard et al., 2003).

5.3. Disruptive BBB change in other models of systemic inflammation

Other models of systemic inflammation have been used to study their effects on BBB function, including polyinosinic:polycytidylic acid (poly I:C, a mimic of viral double-stranded RNA), live non-neurotropic pathogens, sterile inflammatory stimuli, and inflammatory mediators and cytokines. Table 3 summarises this information, showing further evidence for BBB disruption during systemic inflammation, and recapitulating mechanisms from LPS models.

6. Non-disruptive BBB change in systemic inflammation

If disruptive BBB change is absent during systemic inflammation, this does not mean that the BBB is unaltered, since non-disruptive changes may occur. Morphological studies demonstrate that tight junctions may remain intact during systemic inflammation (Papadopoulos et al., 1999), and changes in function may arise through other routes, as described below. Importantly, the CNS effects of systemic inflammation are not predicated on disruptive BBB change (Banks et al., 2015).

6.1. Transporters

Models demonstrate a number of BBB transport pathways which can be modified by systemic inflammation, including down-regulation of the multi-functional efflux transporter P-glycoprotein (Hartz et al., 2006), located on astrocytic foot processes (Pardridge et al., 1997). Other transporters down-regulated by systemic inflammation include those for organic anions (Wittmann et al., 2015a), monocarboxylates (Wittmann et al., 2015a), amino acids (Wittmann et al., 2015b), β-amyloid (Jaeger et al., 2009), leptin (Nonaka et al., 2004), and prostaglandin E_2 (Akanuma et al., 2011). There is also evidence for inflammation-induced up-regulation of influx carriers responsible for TNF-α (Osburg et al., 2002), insulin (Xaio et al., 2001), monoamines (Wu et al., 2015), lysosomal enzymes (Urayama et al., 2015), β-amyloid (Jaeger et al., 2009), leukemia inhibitory factor (Pan et al., 2008), and the viral protein gp120 (Banks et al., 1999).

6.2. Cytokines

Cytokines directly mediate some non-disruptive BBB changes. Receptors for IL-1β, IL-6, and TNF-α are expressed on cerebral endothelium (Ericsson et al., 1995; Vallières and Rivest, 1997; Nadeau and Rivest, 1999), and systemic IL-1β and TNF-α cause cerebral endothelial activation (Skelly et al., 2013). IL-1β causes activation of endothelium preceding that of neighbouring brain areas (Herkenham et al., 1998), suggesting that BBB activation is an intermediate step. This is in keeping with LPS models mapping expression of the nuclear transcription factor IκBα (Quan et al., 2003). Interestingly, interferon-β (IFN-β) reduces transmigration of Th1 lymphocytes, without any effect on diffusibility of albumin (Prat et al., 2005), suggesting that the effect is not due to a change in tight junctions but instead due to cytokine-induced non-disruptive changes that discourage neuroinflammation.

6.3. Prostaglandins

LPS, TNF-α, and IL-1β promote cyclo-oxygenase (COX) expression in cerebral endothelium (Cao et al., 1995; Skelly et al., 2013). The transcriptional profile of cerebral endothelial cells is altered by systemic inflammation, to favour the production of prostaglandin E_2 (PGE_2) (Vasilache et al., 2015). The response is polarised, and PGE_2 secretion is four times higher from the basal compared to the luminal side (Moore et al., 1988). This provides a mechanistic role for non-disruptive BBB changes in communicating inflammatory signals across the intact BBB, particularly in the generation of fever. Systemic LPS also acts on BBB transport

Table 3
Disruptive BBB change in models of systemic inflammation, other than LPS.

Model	Evidence for BBB disruption	Evidence for possible mechanisms
Viral RNA	Effect demonstrated with poly I:C (Daniels et al., 2014; Wang et al., 2004).	• Dependent on TLR3 (Wang et al., 2004) • Dependent on TNFR (Wang et al., 2004); likely involves systemic production of TNF-α • Local production of ROS and endothelial apoptosis shown in systemic endothelium (Zimmer et al., 2011) • Reduction in ZO-1 and claudin-5 co-localisation may impair tight junctions (Daniels et al., 2014) • Activation of calcium signalling and release of TNF-α and IL-6 from brain tissue (Ott et al., 2012)
Systemic infection	Effect demonstrated with: • *Staphylococcus aureus* (Gregorius et al., 1976) • *Clostridium perfringens* (Gregorius et al., 1976) • *Escherichia coli* (du Moulin et al., 1985; Tsao et al., 2001) • *Streptococcus pneumoniae* (Tsao et al., 2001) • Caecal ligation and puncture (polymicrobial infection) (Hofer et al., 2008; Yang et al., 2015)	• Dependent on TNF-α (Tsao et al., 2001)
Non-infective systemic inflammation	Effect demonstrated with: • Colitis (Natah et al., 2005; Hathaway et al., 1999) • Pancreatitis (Farkas et al., 1998) • Peripheral inflammatory pain induced by irritant injection into paw (Huber et al., 2002)	• Reduced expression of endothelial barrier antigen (a key BBB marker in rats) during colitis (Natah et al., 2005) • Raised levels of TNF-α and IL-6 during pancreatitis (Hathaway et al., 1999) • Altered tight junction expression during peripheral inflammatory pain (Huber et al., 2002)
Inflammatory mediators	Effect demonstrated with (reviewed in Abbott, 2000): • Bradykinin • Serotonin • Histamine • Arachidonic acid • Nitric oxide	
Cytokines	Effect demonstrated with: • TNF-α (Tsao et al., 2001) • IL-1β (de Vries et al., 1996b) • IL-6 (de Vries et al., 1996b) • IFN-γ (Daniels et al., 2014)	• TNF-α: some evidence for reduced tight junction expression (Förster et al., 2008; Daniels et al., 2014) • IL-1β: effect dependent on COX (de Vries et al., 1996b) • IFN-γ: down-regulation of tight junction proteins (Minagar et al., 2003)

pathways to reduce the efflux of PGE_2, again contributing to increased brain concentrations (Akanuma et al., 2011). Conversely, changes in prostaglandin levels may also modify transport functions, for example insulin influx (Xaio et al., 2001).

6.4. Cellular transmigration

Passage of cells across the BBB occurs primarily at the post-capillary venules (Bechmann et al., 2007) and may occur through a paracellular or transcellular route. Micrographs clearly demonstrate the encapsulation of a small amount of plasma that accompanies the cell through its course across the endothelium (Wolburg et al., 2005), and earlier descriptions of transendothelial channels observed in various CNS pathologies (Lossinsky and Shivers, 2004) may be the aftermath of diapedesis. Hence although cellular influx into the CNS is physiologically non-disruptive, it may result in disruptive BBB change if pronounced.

Leucocyte recruitment across the BBB in response to systemic inflammation can be demonstrated for lymphocytes (Banks et al., 2012), neutrophils (Bohatschek et al., 2001) and monocytes (Wang et al., 2008). Mechanistically, systemic inflammation can promote leukocyte transmigration at various points during the two-step passage through (1) endothelium and (2) glia limitans.

6.4.1. Passage through endothelium

(a) *Rolling* is mediated mainly by endothelial P- and E-selectins binding to leukocyte P-selectin glycoprotein 1 (PSGL1). BBB endothelial cells do not constitutively express P-selectin, which may play a role in immune privilege, but P-selectin expression can be induced by exposure to TNF-α or IL-1β *in vitro* (Barkalow et al., 1996). *In vivo* systemic TNF-α promotes expression of brain microvessel P- and E-selectin, which are both required for cellular recruitment (Carvalho-Tavares et al., 2000). Systemic LPS has a similar effect on P-selectin (Zhou et al., 2009). Degradation of the glycocalyx in systemic inflammation enhances and may be required for leukocyte interactions, possibly due to exposure of endothelial markers which are normally obscured (Lipowsky, 2012).

(b) *Activation* of the leucocyte for subsequent arrest is induced by chemokines, which lead to conformational changes in leukocyte integrins such as LFA-1 (lymphocyte function-associated antigen 1) and VLA-4 (very late antigen-4) which enhance their binding to endothelial ligands. BBB endothelial production of CCL2 (CC-motif ligand 2) is stimulated by pro-inflammatory cytokines or LPS (Chui and Dorovini-Zis, 2010). The predominant source of CXCL2 (CXC-motif ligand 2) appears to be microglia (Zhou et al., 2009), which are also stimulated by LPS via TLR4 (Zhou et al., 2006). Activated astrocytes may also be a source of chemokines (Sofroniew, 2015), although some evidence suggests that reactive astrocytes may suppress cellular infiltration (Bush et al., 1999).

(c) *Arrest* of the leucocyte occurs when endothelial cell adhesion molecules (CAMs) bind to leucocyte integrins, and is followed by diapedesis. The expression of CAMs such as ICAM-1 (intercellular adhesion molecule 1) on the BBB is usually low, but is promoted by inflammation (Bohatschek et al., 2001). The effect of systemic inflammation on neutrophil recruitment across the BBB is dependent on ICAM-1 (Bohatschek et al., 2001). Cytokine mixtures from the serum of septic patients cause leucocyte adhesion to BMECs *in vitro*, which is dependent on integrins and ICAM-1 (Blom et al., 2015).

6.4.2. Passage through glia limitans

After transendothelial passage, leukocytes enter the perivascular space. The second step of neuroinflammation requires passage across the glia limitans to enter the brain parenchyma proper (Bechmann et al., 2007), and is dependent on degradation of basement membrane components by MMP-2 and MMP-9 (Agrawal et al., 2006). LPS up-regulates endothelial MMP-2 expression (Qin et al., 2015). Macrophages also play a crucial role in the second step (Tran et al., 1998), and perivascular macrophages are activated by systemic LPS (Mato et al., 1998). Pericytes, located in the perivascular space, are also stimulated by LPS and are able to attract neutrophils and produce MMPs (Pieper et al., 2013).

6.5. Pathogen neuroinvasion

A wide variety of mechanisms underlie invasion of the CNS with pathogens. It has been shown that LPS may enhance entry of virus (Lustig et al., 1992) or virus-infected cells (Wang et al., 2008) into the CNS, associated with disruptive change. However, non-disruptive BBB changes during systemic inflammation may also promote neuroinvasion of pathogens. For example, systemic LPS enhances the transcellular transport of the human immunodeficiency virus (HIV), independent of changes in TEER, via a mechanism involving luminal stimulation by IL-6 and granulocyte-macrophage colony-stimulating factor (GM-CSF) (Dohgu et al., 2011), and intracellular MAP kinase signalling (Dohgu and Banks, 2008). This effect of LPS also involves pericytes, in response to polarised secretion from endothelial cells (Dohgu and Banks, 2013).

7. Clinical relevance

7.1. BBB is altered in CNS pathology

Alzheimer's disease (AD), multiple sclerosis (MS), and CNS dysfunction in systemic infection are examples of conditions which are primarily neurodegenerative, neuroinflammatory, or systemic. In many cases it is not clear whether BBB changes are the cause or effect of neuropathology, and it is possible that BBB changes and neuropathology drive each other in a self-perpetuating manner, contributing to disease progression.

7.1.1. Alzheimer's disease

As reviewed in detail elsewhere (Erickson and Banks, 2013), BBB changes in AD may be an early and important step in pathogenesis. Accumulation of β-amyloid may damage the neurovascular unit and lead to disruption. Other changes result in the decreased clearance of β-amyloid, via changes in transport proteins such as P-glycoprotein, LRP-1 (low-density lipoprotein receptor-related protein 1), and RAGE (receptor for advanced glycation end products).

7.1.2. Multiple sclerosis

A key step in the pathogenesis of MS is thought to be the infiltration of auto-reactive CD4+ T-lymphocytes into the CNS, after activation in the periphery. BBB disruption has been demonstrated in experimental autoimmune encephalomyelitis (EAE), and the clinical severity can be linked to the degree of BBB disruption (Fabis et al., 2007). EAE involves loss of tight junction proteins (Wolburg et al., 2003). Up-regulation of miR-155 in active MS lesions (Junker et al., 2009), with corresponding down-regulation of BBB tight junction components (Lopez-Ramirez et al., 2014), may be involved. Imaging studies show BBB disruption in normal-appearing white matter in MS (Cramer et al., 2014), and BBB breakdown precedes the development of new lesions (Alvarez et al., 2015). Non-disruptive BBB changes which favour neuro-inflammation are also an important feature of MS, and include increased expression of adhesion markers such as P-selectin (Kerfoot and Kubes, 2002) and ICAM-1 (Bö et al., 1996) as well as chemokines such as CXCL12 (CXC-motif ligand 12) (Krumbholz et al., 2006).

7.1.3. CNS dysfunction during systemic infection

CNS dysfunction associated with systemic infection is common, and syndromes include sickness behaviour and delirium. In the context of sepsis this syndrome is known as septic encephalopathy. A key step in pathogenesis is the systemic production of pro-inflammatory cytokines such as TNF-α and IL-1β, which then act on the brain. BBB cytokine transport systems are likely to play a role in permitting the passage of these signals (Banks, 2005).

The degree of systemic inflammation may be relevant. During mild systemic infections, non-disruptive BBB changes are likely to be more relevant while both non-disruptive and disruptive changes may occur during sepsis. As discussed above, the BBB acts as a signalling intermediate, secreting prostaglandins such as PGE_2 into the brain, in response to systemic stimuli, leading to fever, anorexia, and malaise. Blood-to-brain transport of TNF-α is increased during systemic inflammation, by up-regulation of receptor-mediated transcytosis (Osburg et al., 2002). Brain uptake of insulin is also increased (Xaio et al., 2001), where it could promote anorexia and weight loss. During sepsis, there is some evidence for disruptive BBB change, based on increased CSF protein (Young et al., 1992) and MRI changes (Sharshar et al., 2007).

7.2. Neuropathology sensitises the BBB to systemic inflammation

The BBB in pathology may not have the same response to systemic inflammation as the healthy brain. Subtle BBB changes in the initial stages of disease could make the BBB more vulnerable to systemic inflammation than is normal, and in particular may predispose to disruption.

7.2.1. Alzheimer's disease

For example, BBB disruption during systemic inflammation is greater in AD mice than in wild-type controls (Takeda et al., 2013). This correlates with the magnified brain inflammatory responses seen in AD models in response to systemic inflammation, despite normal systemic inflammatory responses (Takeda et al., 2013). Microglial priming could sensitise the BBB to disruptive change and cellular infiltration during systemic inflammation, as demonstrated in a mouse model of ageing (Raj et al., 2015).

7.2.2. Multiple sclerosis

BBB changes in MS models include increased pinocytotic activity across the BBB (Claudio et al., 1989), and increased activity of the TNF-α transporter system (Pan et al., 1996); both of which would potentiate the central effects of circulating cytokines during systemic inflammation. Astrocytopathy in conditions such as MS and neuromyelitis optica could also contribute to BBB sensitization since lack of astrocytes sensitises the BBB to disruptive changes induced by systemic inflammation (Asgari et al., 2015; Gaillard et al., 2003). Microglia are the major source of CXCL2 (Zhou et al., 2009), and endothelial-bound chemokines at the BBB could alter the conformation of LFA-1 on leucocytes to induce their arrest and subsequent transmigration.

7.2.3. Stroke

The BBB is disrupted in ischaemic stroke (Sandoval and Witt, 2008), and is sensitised to further disruptive changes by systemic inflammation (Denes et al., 2011). Correspondingly, brain damage and mortality is exacerbated by systemic inflammation in experi-

mental models (Denes et al., 2011), and is borne out by clinical outcomes (Palasik et al., 2005).

7.3. BBB changes induced by systemic inflammation may contribute to disease progression

Systemic inflammation, typically in the form of urinary or chest infection, is a common cause for deteriorating symptoms in neurological diseases like AD and MS. An established mechanism is the increased sensitivity to systemic inflammation of primed CNS-resident immune cells in these conditions (Perry and Holmes, 2014); this is facilitated by the BBB changes discussed in this review. In addition, there is some evidence that BBB changes during systemic inflammation may contribute to disease progression by affecting the primary pathological process, separate from the increased sensitivity of the ongoing CNS inflammatory process to systemic inflammation.

7.3.1. Alzheimer's disease

Both acute and chronic systemic inflammation accelerate the progression of AD (Holmes et al., 2009). Systemic inflammation in AD is associated with several non-disruptive BBB changes which further favour β-amyloid partitioning into the brain, by increasing influx and decreasing efflux (Jaeger et al., 2009). Correspondingly, systemic inflammation accelerates hippocampal amyloid deposition (Weintraub et al., 2014). Reduced expression and abnormal localisation of LRP-1, which exports β-amyloid has been reported *in vitro* (Erickson et al., 2012). Systemic inflammation also results in reduced bulk flow of CSF/ISF across the BBB, which could further impair β-amyloid clearance (Erickson et al., 2012). In summary, BBB alterations induced by systemic inflammation in AD may increase amyloid deposition and contribute to disease progression.

7.3.2. Multiple sclerosis

Systemic inflammation exacerbates CNS disease in relapsing-remitting MS (RRMS), and these exacerbations have been shown to occur in the absence or presence of disruptive BBB changes in both EAE (Moreno et al., 2011; Serres et al., 2009) and MS (Buljevac et al., 2002; Correale et al., 2006). In EAE, lesional heterogeneity in the occurrence of disruptive BBB change during systemic inflammation has been demonstrated (Serres et al., 2009). Disruptive BBB change in other pathologies has been found to be associated with increased serum levels of myelin basic protein (Hill et al., 2000), a major immunological target in MS. Thus BBB changes induced by systemic inflammation have potential to alter MS disease.

8. Conclusion

In this article we have reviewed the current evidence on the effects of systemic inflammation on BBB function in animals and humans, in the healthy and diseased brain. Unanswered biological questions remain regarding the nature and mechanisms of BBB changes in systemic inflammation in humans, including:

- How do BBB responses to systemic inflammation differ between health and disease in the human brain?
- How significant is the role of the BBB in mediating the effects of systemic inflammation on neurological disease progression?
- What is the regional variability of BBB changes in systemic inflammation, and how does this correlate with clinical features of inflammation-associated CNS dysfunction?
- What role does the glycocalyx play in mediating BBB changes?
- What therapeutic strategies can be safely used to mitigate the undesirable effects of systemic inflammation on the BBB in humans?

The development of techniques to quantify disruptive BBB changes will aid human study, including advanced imaging protocols such as dynamic contrast-enhanced MRI, as well as serum biomarkers. The exploration of brain-specific glycocalyx markers would be invaluable. Additional techniques are also required to investigate non-disruptive BBB changes *in vivo*, for example PET imaging of transport proteins and cellular adhesion markers. Such techniques will help determine to what degree BBB changes contribute to disease expression. Finally, the clinical implications of these findings raise the possibility of designing treatments to modify neurological disease by targeting systemic inflammation and the BBB.

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