Supplementary Online TABLE 1: Modulators that affect the permeability of the blood-brain barrier					
Pathogenic Event	**Mediator**	**Mechanism**	**Examples**	**Effect on BBB**	**Diseases Implicated**
Bacterial or viral infection	LPS	EC activation P-glycoprotein regulation Systemic cytokine secretion		↓	Bacterial meningitis[73]
	Viral proteins	Tight junction dysfunction by HIV-infected monocytes; activations of perivascular macrophages and sentinel microglia	HIV	↓	HIV encephalitis[74]
Systemic inflammation	Cytokines	EC activation Tight junction dysfunction	TNFα	↓ ↑	Parkinson's disease[27, 75,76]
			IL1β	↓	Multiple sclerosis[28] Meningitis[28]
			IL6	↓	Bacterial meningitis[29] Meningococcal septic shock
			IFNα/β [35]	↑	
	Circulating antibodies[77,78]	EC activation? Receptor mediated endocytosis?	Anti-FHA antibodies	↓	*Bordetella Pertussis* infections ?
			Anti-AQ4 antibodies	↓	Devic's disease (neuromyelitis optica)[78]
Stress, trauma, ischemia	Epinephrine[30,33]	Increased blood flow due to transient hypertension?	Epinephrine	↓	Hypertension
	Glutamate[79,80]	Vasodilatation? EC activation?	Glutamate MSG in food	↓	Ischemic stroke Neurodegenerative diseases
	Vasoactive substances[81,82]	Activation of arachidonic acid cascade[81]	Bradykinin	↓	Ischemic stroke
		H2R-dependent activation of adenylate cyclase[82]	Histamine	↓	Ischemic stroke
Hormonal alterations	Estrogen[37,38]	Inhibition of MMP2 and MMP9	17β estradiol	↑	Alzheimer's disease Ischemia
	Glucocorticoids[36]	Regulation of angiopoietin and VEGF	Dexamethasone	↑	Rheumatoid Arthritis SLE
Addictive substances	Ethanol[83,84]	Choroid plexus dysfunction	Ethanol	↓	Wernicke's encephalopathy
	Narcotics[31]	Tight junction dysfunction. Increased leukocite migration Vasculitis	Cocaine	↓	HIV encephalitis
	Nicotine[32]	Tight junction modulation over nicotinic acetycholine receptors	Nicotine	↓	
	Caffeine[85,86]	Blockade of alterations on junctional proteins (induced by neurotoxins and other agents)	Caffeine	↑	Alzheimer's disease Parkinson's disease

Abbreviations: AQ4, aquaporin 4; EC, endothelial cell; Anti-FHA; Anti-filamentous hemagglutinin; H2R, histamine 2 receptor; HIV, human immuno-deficiency virus; LPS, lipopolysaccharide; MMP2, matrix metallo-protein 2; MMP9, matrix metallo-protein 9; SLE, systemic lupus erythematosus; VEGF, vascular endothelial growth factor.