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Endothelins in inflammatory neurological diseases☆

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ABSTRACT

Endothelins were discovered more than thirty years ago as potent vasoactive compounds. Beyond their well-documented cardiovascular properties, however, the contributions of the endothelin pathway have been demonstrated in several neuroinflammatory processes and the peptides have been reported as clinically relevant biomarkers in neurodegenerative diseases. Several studies report that endothelin-1 significantly contributes to the progression of neuroinflammatory processes, particularly during infections in the central nervous system (CNS), and is associated with a loss of endothelial integrity at the blood brain barrier level. Because of the paucity of clinical trials with endothelin-1 antagonists in several infectious and non-infectious neuroinflammatory diseases, it remains an open question whether the 21 amino acid peptide is a mediator/modulator rather than a biomarker of the progression of neurodegeneration. This review focuses on the potential roles of endothelins in the pathology of neuroinflammatory processes, including infectious diseases of viral, bacterial or parasitic origin in which the synthesis of endothelins or its pharmacology have been investigated from the cell to the bedside in several cases, as well as in non-infectious inflammatory processes such as neurodegenerative disorders like Alzheimers Disease or central nervous system vasculitis.

Contents

1. Introduction

In the central nervous system (CNS), the response to adverse events such as infection and the development disorders is accompanied by an upregulation of the inflammatory response and alterations in the vasculature. In this regard, the endothelins have been demonstrated to mediate these responses (Fig. 1). The endothelin (ET) family is comprised of three isoforms of 21-

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Abbreviations: AD, Alzheimer's Disease; APP, Amyloid precursor protein; Aβ, Beta-amyloid protein; BBB, Blood-brain barrier; CNS, Central nervous system; CBF, Cerebral blood flow; CM, Cerebral malaria; CXCL, Chemokine (C-X-C motif) ligand; CCL, Chemokine (C-C motif) ligand; CNSV, CNS vasculitis; CMV, Cytomegalovirus; DENV, Dengue virus; ET, Endothelin; ET-1, Endothelin-1; ECE, Endothelin converting enzyme; ET_B, Endothelin subtype B; ET_A, Endothelin subtype A; EAE, Experimental Autoimmune Encephalomyelitis; GCA, Giant cells arteritis; HSV-1, Herpes simplex virus 1; HSV-2, Herpes simplex virus 2; HHV, Human herpesvirus; HIV, Human immunodeficiency virus; HAND, HIV-associated neurocognitive disorders; ICAM-1, Intercellular cell adhesion molecule 1; KS, Kaposi's sarcoma; KSHV, Kaposi's sarcoma-associated herpesvirus; MS, Multiple Sclerosis; NEP, Neutral Endopeptidase; NO, Nitric oxide; SLE, Systemic lupus erythematosus; VCAM-1, Vascular cell adhesion protein 1; VSMC, Vascular smooth muscle cell.

☆ This review is dedicated to the memory of Dr. Herbert B. Tanowitz, MD (September 6, 1941 - July 17, 2018), Professor of Pathology and Medicine at the Albert Einstein College of Medicine. Dr. Tanowitz was an esteemed colleague, a friend and mentor who pioneered the studies of endothelin in parasitic diseases.

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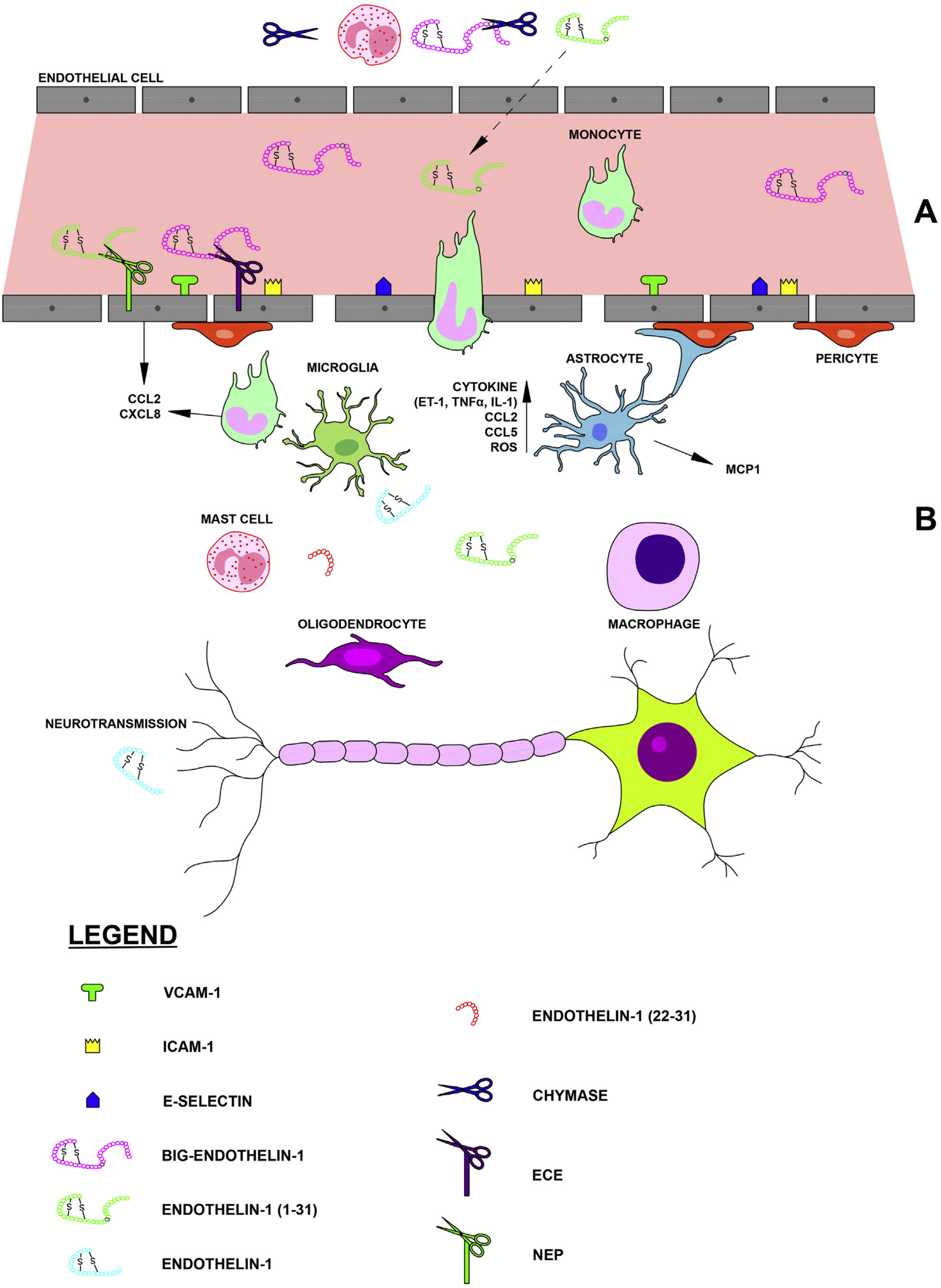
amino acid cyclic vasoactive peptides (ET-1, ET-2 and ET-3). A fourth isoform (ET-4) has been reported in the rat and mouse as the analogue to human ET-2 (Cunningham, Huribal, Bala, & McMillen, 1997; Khimji & Rockey, 2010; Motte, McEntee, & Naeije, 2006; Yanagisawa et al., 1988).

ETs are synthesized from inactive precursor pro-polypeptides. The first product of the ET-1 gene is Pre-proendothelin, a peptide constituted of 212 amino acids. This peptide is processed by a carboxypeptidase to form proendothelin. Furin, an enzyme of the subtilisin family cleaves



the proendothelin further to generate Big ET-1 (Blais et al., 2002; D'Orleans-Juste, Plante, Honore, Carrier, & Labonte, 2003). The endothelin converting enzyme (ECE) then cleaves the bond between Trp ^{21} and Val ^{22} of Big ET-1 to generate ET-1 [Fig. 1; (D'Orleans-Juste et al., 2003; McMahon, Palomo, Moore, McDonald, & Stern, 1991)]. ECE is a zinc-dependent metalloendopeptidase localized in several cell types such as endothelial cells, smooth muscle cells, cardiomyocytes and macrophages (Barnes & Turner, 1997, 1999; Hioki, Okada, Ito, Matsuyama, & Yano, 1991; Hisaki et al., 1993; Korth, Bohle, Corvol, & Pinet, 1999; Takahashi et al., 1995).

The membrane bound-ECE family is comprised of the ECE-1, ECE-2 and ECE-3 isoforms with the former two moieties subdivided in functional sub-isoforms (Emoto & Yanagisawa, 1995; Hasegawa et al., 1998; Shimada, Takahashi, & Tanzawa, 1994; Xu et al., 1994). These sub-isoforms possess different N-terminal endings, are differently localized within the cell and preferably hydrolyze the ET-1 precursor Big ET-1 (D'Orleans-Juste et al., 2003).

The ECE-dependent pathway is not the sole pathway leading to the formation of ET-1. In embryos of mice whose ECE-1 and ECE-2 genes were knocked out, the production of ET-1 is only decreased by 33% (Yanagisawa et al., 2000). This suggests that other pathways involved in the production of ET-1 exist, independently of the canonical endothelin converting enzymes. One of those alternate pathways involves the contribution of mast cell-derived chymase. This serine protease matures Big ET-1 to ET-1. Chymase cleaves the 38-amino acid precursor Big ET-1 at the Tyr ^{31}-Gly ^{32} bond leading to the formation of an intermediate 31-amino acid peptide, ET-1 (1−31). ET-1 (1-31) is further processed by the Neutral Endopeptidase, which hydrolyzes the Trp ^{21}- Val ^{22} bond to form ET-1 *in vitro* (Hanson, Andersson, Gyllstedt, Hogestatt, & Lindberg, 1997; Nakano et al., 1997) and *in vivo* (Fecteau et al., 2005) (Fig. 1).

The three human ET isoforms bind to two seven transmembrane G-protein-coupled cell surface receptors commonly known as ET receptor subtype A (ET_A) and subtype B (ET_B) (Arai, Hori, Aramori, Ohkubo, & Nakanishi, 1990). ET-1 binds to ET_A with the highest affinity compared to ET-2 and ET-3. On the other hand, all of the ET isoforms show equal binding affinity for ET_B (Masaki, 2004; Rubanyi & Polokoff, 1994; Sakurai et al., 1990). ET-1 is by far the most abundant and best described isoform (Struck, Morgenthaler, & Bergmann, 2005).

Some of the important functions of ET-1 include eliciting vasoconstriction and vasodilatation via release of nitric oxide (NO), ET clearance, salt balance and water homeostasis, inflammation, cell proliferation and extracellular matrix production (Bouallegue, Daou, & Srivastava, 2007; Khimji & Rockey, 2010; Kohan, Rossi, Inscho, & Pollock, 2011; Speciale, Roda, Saresella, Taramelli, & Ferrante, 1998; Wallace, Cirino, De Nucci, McKnight, & MacNaughton, 1989). ET-1 is synthesized by a variety of cells, including endothelial cells, macrophages, cardiomyocytes, astrocytes, microglia and neuronal cells (D'Haeseleer et al., 2013; Ehrenreich et al., 1992; Kedzierski & Yanagisawa, 2001; Kuwaki et al., 1999; Miller, Monsul, Vender, & Lehmann, 1996; Naidoo, Naidoo, Mahabeer, & Raidoo, 2004; Naidoo, Naidoo, & Raidoo, 2004; Yanagisawa et al., 1988). The plasma concentration of ET is usually low, approximately 0.2–5 pg/mL, with a short blood circulating half-life of 4–7 min (Kedzierski & Yanagisawa, 2001).

1.1. ET-1: the vascular tone regulator

Although big ET-1, which has some vasoconstrictive properties, is found in the peripheral circulation, ET-1 has a 140-times higher vasoconstrictive potency (Rubanyi & Polokoff, 1994). ET-1 activation of ET_A receptors mediates vasoconstriction through activation of phospholipase C, leading to the formation of inositol triphosphate (IP3), inducing the release of Ca^{2+} from the endoplasmic reticulum stores. Increased cytosolic Ca^{2+} concentrations result in contraction of the vascular smooth muscle cells (Bouallegue et al., 2007; Khimji & Rockey, 2010; Wagner et al., 1992). Conversely, the binding of ET-1 to endothelium-localized-ET_B receptors mostly mediates vasodilation through activation of the PI3/Akt pathway, with ensuing activation of endothelial NO synthase, generating NO to cause relaxation of the vascular smooth muscle cells. Activation of ET_B receptors present on vascular smooth muscle cells elicits vessel contraction (Khimji & Rockey, 2010; Tsukahara, Ende, Magazine, Bahou, & Goligorsky, 1994). Therefore, ET-1 acts as a local modulator of vascular tone. As such, ET-1 plays significant roles in controlling vascular tone by acting directly or indirectly on vascular smooth muscle cells under normal homeostatic (non-disease) state. However, there are some suggestions that enhanced ET-1 secretion might be involved in the pathophysiology of many vascular diseases (Feldstein & Romero, 2007; Iglarz & Clozel, 2007; Marasciulo, Montagnani, & Potenza, 2006).

1.2. ET-1: the inflammatory mediator

Initially regarded solely as a spasmogen, ET-1 is also recognized as a pro-inflammatory cytokine (Sessa, Kaw, Hecker, & Vane, 1991; Teder & Noble, 2000). Production and secretion of ET-1 in endothelial cells are significantly higher during stress to the endothelium, and after exposure to inflammatory cytokines and reactive oxygen species (Kedzierski & Yanagisawa, 2001). ET-1 is also abundant in macrophages, leukocytes and fibroblasts (Gu et al., 1991; Sessa et al., 1991), indicating that ET-1 is closely associated with the inflammatory process. In this regard, several investigators have reported that ET-1 stimulates production of the chemokine (C-X-C motif) ligand 8 (CXCL-8) and (C-C motif) ligand 2 (CCL2) in monocytes and mesangial cells, which are known chemoattractants for neutrophils and monocytes (Helset, Sildnes, & Konopski, 1994; Ishizawa et al., 2004), suggesting that ET-1 contributes to leukocyte activation and trafficking. Moreover, ET-1 also acts as a mast cell activator, inducing degranulation and release of inflammatory cytokines from mast cells (Matsushima, Yamada, Matsue, & Shimada, 2004). Interestingly, investigators have shown that ET-1 is also important in inducing traversal of inflammatory cells through endothelial cells into different tissues. shRNA knockdown of ET-1, the ET_B receptor, and ECE-1 demonstrate that these components are independently involved in monocyte diapedesis (Reijerkerk et al., 2012). In addition, ET-1 induces the upregulation of cellular adhesion molecules, such as Intercellular cell adhesion molecule 1 (ICAM-1), Vascular cell adhesion protein 1 (VCAM-1), and e-selectin in human brain microvascular endothelial cells, facilitating margination, adherence, and infiltration of leukocytes across these cells into injured tissue (McCarron, Wang, Stanimirovic, & Spatz, 1993). Furthermore, ET-1 causes platelet aggregation, and plays a role in the increased expression of leukocyte adhesion molecules and their synthesis of inflammatory

Fig. 1. ET-1 and cell-cell interactions in Central Nervous System diseases. (A) In the sub-endothelial matrix (top of the figure), the biologically inactive precursor Big ET-1 (1-38) is cleaved by mast cell derived chymase, yielding ET-1 (1-31) which is subsequently released into the circulation where it is enzymatically-activated to ET-1 via the membrane bound neutral endopeptidase (NEP). As the major circulatory enzyme involved in the generation of ET-1, the endothelin converting enzyme (ECE) directly converts the 38-amino acid precursor to ET-1. Within the vessel lumen, the later peptide signals via two distinct G protein coupled receptors, namely ET_A and/or ET_B (not shown). In response to insults to the endothelium, ET-1 can induce remodeling of endothelial cells, with an increase in adhesion molecule production, and loss of BBB integrity. (B) After endothelial insults, ET-1 also increases the expression of chemokines such as CCL2 from endothelial cells and triggers the release of monocyte-derived CXCL8, resulting in margination of inflammatory cells and diapedesis across the BBB. Macrophages are well known to convert big-ET-1 to ET-1 and can secrete several cytokines such as interleukin-1 and TNFα, chemokines, including CCL2 and CCL5, reactive oxygen species, and ET-1 once differentiated within the CNS. ET-1 can also prompt astrocyte activation and proliferation and subsequent activation of microglial cells, resulting in reactive microgliosis. In neurons, ET-1 via its two receptors may act as a modulator of neuronal conductivity and/or neurotransmission.

mediators, thus contributing to vascular dysfunction (Matsuo, Mihara, Ninomiya, & Fujimoto, 2001; Teder & Noble, 2000).

ET-1 is produced at significantly higher rates during a variety of infections (Dai et al., 2012; Dietmann et al., 2008; Koedel, Gorriz, Lorenzl, & Pfister, 1997; Machado et al., 2006; Martins et al., 2016; Petkova et al., 2000; Petkova et al., 2001; Wanecek, Weitzberg, Rudehill, & Oldner, 2000). In fact, ET-1 has been shown to contribute to the pathogenesis and severity of bacterial, viral and parasitic disease processes including sepsis, meningitis, pneumonia, rickettsial infections, Chagas disease and cerebral malaria (Dai et al., 2012; Davi et al., 1995; Freeman et al., 2016; Goto et al., 2012; Koedel et al., 1997; Martins et al., 2016; Petkova et al., 2000; Petkova et al., 2001; Samransamruajkit et al., 2002; Schuetz et al., 2008; Tschaikowsky, Sagner, Lehnert, Kaul, & Ritter, 2000; Wanecek et al., 2000; Wenisch et al., 1996).

1.3. ET-1 in the brain

In the brain, ET-1 is synthesized by vascular endothelial cells as well as by a variety of other cells including neurons and astrocytes (Kedzierski & Yanagisawa, 2001; Schinelli, 2002). The components of this pathway are found throughout the brain suggesting a variety of potential functions. The receptors (ET_A, ET_B) as well as ET-1 and ET-3 are expressed by vascular, neuronal, and glial cells. ET immunoreactivity is present in neurons of the cerebral cortex, striatum, amygdala, hippocampus, paraventricular and supraoptic nuclei of the hypothalamus, subfornical organ, median eminence, raphe nuclei, and pituitary gland (Giaid et al., 1991; Lee, de la Monte, Ng, Bloch, & Quertermous, 1990; Takahashi et al., 1991).

ET-1 is the predominant neural ET, but ET-3 predominates in the pituitary gland (Matsumoto, Suzuki, Onda, & Fujino, 1989; Yoshizawa et al., 1990). The ET_A receptor is found on various neurons (Yamada & Kurokawa, 1998). ET_B is localized to the neurons of the diagonal band of Broca, the fibers of the organum vasculosum of the lamina terminalis, the fibers of the median eminence, and the thick fibers of hypothalamic neurons (Yamamoto & Uemura, 1998), which are also luteinizing hormone-releasing hormone-rich. ECE-1 and ECE-2 are also found in the brain. Observations from several studies suggest that the ET receptors mediate signal transduction in the brain. In this regard, intraventricular injection of ET-1 in rats results in behavioral changes, including barrel rolling, body tilting, nystagmus, clonus, and tail extension; effects which occur at doses that do not cause any changes in cerebral blood flow (CBF) (Chew, Weaver, & Gross, 1995). Moreover, injection of ET-1 into the periaqueductal gray matter reduces pain responses in mice subjected to the hot plate paradigm in a dose-dependent manner (D'Amico et al., 1996). These data indicate that ET-1 has a role in neurotransmission that is important for an animal's proprioception. Of note, ET-1 also exacerbates apoptosis and neuronal cell death in ischemic models (Giuliani et al., 2007; Leung, Ho, Lo, Chung, & Chung, 2004). In addition, endothelin both enhances glutamate-induced neuronal toxicity and reduces clearance of glutamate by inducing a down regulation of glutamate transporters in astrocytes thereby, intensifying ischemic brain damage (Kobayashi et al., 2005; Matsuura, Ikegaya, Yamada, Nishiyama, & Matsuki, 2002).

ET-1 secreted under normal physiological conditions is beneficial in promoting cell proliferation. However, pathologically increased secretion of ET-1 from reactive astrocytes, microglia and neuronal cells in response to endothelial stress, triggered by irritants from drugs, cytokines, chemokines, reactive oxygen species and infections, may be harmful and potentially detrimental to hosts (Kedzierski & Yanagisawa, 2001). It has been demonstrated in both animal models and human patients that elevated levels of ET-1 in blood or tissue subserve pathological roles of ET-1 (Dietmann et al., 2008; McCarron et al., 1993; Rolinski et al., 1999). Furthermore, ET-1 exerts numerous effects on the immune system leading to neuroinflammation. For example, increased ET-1 production has been observed in various autoimmune diseases such as rheumatoid arthritis, giant cell arteritis, and Kawasaki disease (Miyasaka et al., 1992). Interestingly, plasma levels of ET-1 are increased in Multiple Sclerosis (D'Haeseleer et al., 2013; Haufschild, Shaw, Kesselring, & Flammer, 2001); HIV (Chauhan et al., 2007; Ehrenreich et al., 1993; Hebert, Crenshaw, Romanoff, Ekshyyan, & Dugas, 2004); Herpesvirus (Bagnato et al., 2001; Rosano et al., 2003) and other diseases which affect the brain. We will herein attempt to summarize the contributions of ET-1 and components of the ET system in the pathogenesis of diseases of the central nervous system.

2. Role of ET-1 in CNS infections

Bacterial toxins act on macrophages to synthesize pro-inflammatory cytokines. These cytokines mediate the production of ET-1 from various sources, including brain microvascular endothelial cells (Figueras-Aloy et al., 2003; Figueras-Aloy et al., 2004; McCarron et al., 1993; Piechota et al., 2007; Tschaikowsky et al., 2000; Weitzberg, Lundberg, & Rudehill, 1991). For instance, during bacterial meningitis, organisms cross the blood-brain barrier (BBB) into the brain parenchyma by a number of mechanisms (Kim, 2010). Once in the brain, bacteria and bacterial factors activate glia which increase their production and secretion of inflammatory cytokines, prompting activation of endothelial cells, an upregulation in cellular adhesion molecules and the margination of immune cells in the brain microvasculature (Saez-Llorens & McCracken, 2003). Infiltrating leukocytes secrete a variety of proteolytic products and toxins which damage the integrity of the endothelium. During these pathological processes, upregulated ET-1 causes further loss of endothelial integrity and increased BBB permeability, activates astrocytes, induces abnormal expression and production of cellular adhesion molecules including ICAM-1, VCAM-1, and e-selectin, enhanced production of chemoattractants by endothelial cells, besides acting as a neurotransmitter (Ehrenreich et al., 1990; Hofman et al., 1998; Koyama et al., 2013; Koyama, Baba, & Matsuda, 2007; McCarron et al., 1993; Miller et al., 1996; Narushima et al., 2003; Schwarting et al., 1996; Wang, Hong, Wu, & Li, 2013; Zidovetzki, Chen, Chen, & Hofman, 1999). Adhesion molecules are then able to continue the cycle, inducing margination and binding of leukocytes to areas of injury.

2.1. Bacterial infections

2.1.1. Bacterial meningitis

Despite appropriate antimicrobial strategies, adjunctive corticosteroids and supportive therapy, bacterial meningitis continues to be associated with high mortality and persistent residual neurological deficits, including stroke and paralysis (Grimwood et al., 1995; Grimwood, Anderson, Anderson, Tan, & Nolan, 2000; Kim, 2010; Merkelbach, Sittinger, Schweizer, & Muller, 2000; Sellner, Tauber, & Leib, 2010). Meningitis is characterized by inflammation of meninges, usually by hematogenous spread following bloodstream infection or by direct extension of infectious organisms from contiguous foci (Chavez-Bueno & McCracken, 2005; Saez-Llorens & McCracken, 2003). An important role for ET-1 in the pathogenesis of bacterial meningitides has been described using animal models of *Streptococcus pneumoniae* infection (Koedel, Lorenzl, Gorriz, Arendt, & Pfister, 1998). Koedel and colleagues have demonstrated that after infection with *S. pneumoniae*, Wistar rats develop cerebrospinal fluid pleocytosis as well as an increase in intracranial pressure, brain water content and CBF (Koedel et al., 1998). Pre-treatment of the animals with a selective ET_B receptor antagonist, BQ-788, abrogated these abnormalities (Koedel et al., 1998), suggesting that ET-1 is important in the pathological presentation of bacterial meningitis. Leib et al. demonstrated that infant rats with *S. pneumoniae* meningitis exhibited extensive damage in the cortex and dentate gyrus (Leib, Kim, Chow, Sheldon, & Tauber, 1996), likely induced by ET-1. When infected rats were treated with the non-selective (or dual) ET_A/ET_B receptor antagonist, bosentan, the cortical brain injury was mitigated and CBF was restored to levels comparable to that of uninfected controls (Pfister et al., 2000).

Several groups have examined possible cellular mechanisms for the etiologic role of ET-1 in the pathogenesis of bacterial meningitis and the induction of host responses during the disease. ET-1 levels in the cerebrospinal fluid are increased in both patients with bacterial meningitis and in experimental models of the disease as a result of increased production in several cell types that make up the neurovascular unit (Koedel et al., 1997; Koedel et al., 1998). Astrocytes have been suggested as a possible source of this increase in ET-1 secretion. Using an *in vitro* model of rat astrocytes infected with *S. pneumoniae*, investigators showed significant increases in astrocytic production of ET-1 (Koedel et al., 1997). Treatment of cells with the ECE/NEP inhibitor phosphoramidon prevented the increase in ET-1 (Koedel et al., 1997). Brain microvascular endothelial cells also contribute to the increase in ET-1 during bacterial meningitis, as *S. pneumoniae* infected brain endothelial cells exhibited an increase in both NO and ET-1 upon activation of ET_B receptors (Koedel et al., 1998). ET-1 is also likely to be critical in the trafficking of immune cells into the brain during bacterial meningitis. ET-1 and its components have been shown to induce monocyte diapedesis across the BBB (Reijerkerk et al., 2012). In this regard, ET-1 has been shown to induce the production of potent chemoattractants by endothelial cells, such as CCL2 and CXCL-8, which are significantly elevated in bacterial meningitis (Chen et al., 2001; Hofman et al., 1998; Koyama et al., 2007; Koyama et al., 2013; Sprenger et al., 1996; Zidovetzki et al., 1999).

ET-1 plays a critical role in generating the host response during bacterial meningitis, causing cerebral vascular and CNS injuries. These abnormalities are likely mediated, in part, by increased ET-1 production in endothelial cells (Koedel et al., 1997; Koedel et al., 1998). There are still several gaps in our understanding of the precise processes involved in inducing leukocyte infiltration to the CNS, and these areas would benefit from further investigations.

2.2. Parasitic infections

2.2.1. ET-1 and malaria

Malaria is a potentially life-threatening disease which affects approximately 216 million individuals and results in >400,000 deaths yearly (World Health Organization, 2017). Cerebral malaria (CM) is the most severe and potentially fatal neurological complication with *Plasmodium* infection (Hunt & Grau, 2003; Newton & Krishna, 1998), and children younger than 5 years-old are the most susceptible, accounting for >70% of the malaria-related deaths (Birbeck et al., 2010; Carter et al., 2006; Idro, Marsh, John, & Newton, 2010; World Health Organization, 2014). Despite significant advances in the reduction of global transmission of malaria since 2000 (World Health Organization, 2017), CM continues to have a mortality rate of 20%, and, >25% of the survivors develop long-term neurological deficits (Birbeck et al., 2010; Carter et al., 2006; Idro et al., 2010; World Health Organization, 2014), creating enormous social and economic burdens in malaria-endemic regions (Onwujekwe, Chima, & Okonkwo, 2000; World Health Organization, 2014).

Characterized by adherence of parasitized red blood cells to the brain microvasculature, vasospasms, and changes in levels of vasoregulatory molecules, hypoperfusion and ischemia, inflammation and impairment of the BBB (Adams, Brown, & Turner, 2002; Cabrales, Zanini, Meays, Frangos, & Carvalho, 2010; Dai et al., 2010; Desruisseaux et al., 2008; Dorovini-Zis et al., 2011; Grab, Chakravorty, van der Heyde, & Stins, 2011; Kennan et al., 2005; Potchen et al., 2010; Renia et al., 2012), one could certainly deduce that ET-1 contributes to the pathogenesis of CM. Investigators have long demonstrated that plasma levels of ET-1 and Big ET-1 are elevated in patients with *P. falciparum* infection in association with damage to the cerebral endothelium (Dietmann et al., 2008; Wenisch et al., 1996). The elevated levels of ET-1 and of components of the ET system, i.e. ECE, ET_A and ET_B have been tied to glial activation, a reduction in CBF and in damage to neuronal axons in animal models of experimental CM (Kennan et al., 2005; Machado et al., 2006).

Recent studies from the Desruisseaux laboratory, employing experimental models of CM demonstrate that ET-1 is critical in inducing the pathological sequelae of the disease (Dai et al., 2012; Freeman et al., 2016; Martins et al., 2016). In mice infected with a non-neurotropic strain of *Plasmodium berghei*, which causes malaria in rodents, Martins et al. demonstrated that daily injections of ET-1 induced a CM-like phenotype in the mice, with decreased CBF, increased infiltration of inflammatory cells to cerebral vessels, leakage of the BBB, behavioral changes, and accelerated mortality (Martins et al., 2016). Other investigators from our group have demonstrated that treatment of mice infected with a neurotropic strain of *P. berghei*, with a selective ET_A receptor antagonist decreased the incidence of brain hemorrhages, improved survival, and prevented malaria-associated cognitive decline, with or without concomitant use of an anti-malarial artemisinin derivative (Dai et al., 2012; Freeman et al., 2016). The protective effects of the ET_A receptor blocker were shown to result from mitigation of CM-associated cerebral vasculopathy. ET_A antagonism prevented vasospasms, led to a decrease in leukocyte infiltration of the cerebral vasculature, likely as a result of decreased production of chemokines and cellular adhesion molecules, and resulted in decreased secretion of circulating inflammatory cytokines (Freeman et al., 2016)

As with humans, experimental models of CM demonstrate persistent cognitive deficits and impairment of motor coordination, even after antimalarial treatment (Dai et al., 2010; Desruisseaux et al., 2008; Lackner et al., 2006). Treatment with an ET_A receptor antagonist prevented the long-term neurological sequelae in mice with experimental CM (Freeman et al., 2016). Treatment also improved the survival of affected mice (Dai et al., 2012; Freeman et al., 2016).

Although the present data indicate that ET-1 is involved in the pathogenesis of cerebral malaria, studies to determine the precise cells responsible for the increased levels of ET-1 and targets of ET-1 actions during CM are needed.

2.2.2. ET-1 and Chagas disease

Chagas disease is a neglected tropical disease caused by the protozoan parasite, *Trypanosoma cruzi,* and is a major cause of morbidity and mortality in endemic areas of Latin America and among immigrants to non-endemic areas (Bern & Montgomery, 2009; Roca et al., 2011; Salvador et al., 2013; Tanowitz, Weiss, & Montgomery, 2011). The most important manifestations of Chagas disease are cardiomyopathy and the megasyndromes involving the gastrointestinal tract (Tanowitz et al., 1992). Infection with *T. cruzi* results in an upregulation of pro-inflammatory cytokines, chemokines, Toll-like receptors, components of the mitogen-activated protein kinase pathway, ET-1 and thromboxane A_2 (Ashton et al., 2007; Petkova et al., 2001; Tanowitz et al., 1990). Using selective deletion of the ET-1 gene in endothelial cells and in cardiomyocytes, Tanowitz et al. have shown that ET-1 is pivotal to the development of fibrosis and remodeling of the cardiomyocytes during infection (Tanowitz et al., 2005).

CNS involvement in Chagas disease, however, while recognized since the discovery of *T. cruzi* more than a century ago (Carod-Artal, 2013; Carod-Artal & Gascon, 2010; Chagas, 1911, 1913; Pittella, 2009; Vianna, 1911), has been greatly understudied (Masocha & Kristensson, 2012); as the majority of research has been focused on the cardiomyopathic aspects. Nevertheless, Chagas disease is clearly associated with significant CNS disease. Intracellular *T. cruzi* in the amastigote stage have been reported in brain tissue in autopsy specimens; within CNS monocytic cells and glial cells (Chagas, 1911, 1913; De Queiroz, 1973; Mortara et al., 1999; Pittella, 2009; Torres & Villaça, 1919; Vianna, 1911) as well as free organisms within inflammatory foci (De Queiroz, 1973). Intracellular replicating parasites within glial cells have been observed in animal models during acute disease, and parasites have also been observed within neurons (Ben Younes-Chennoufi et al., 1988; Buckner, Wilson, & Van Voorhis, 1999; Caradonna & Pereiraperrin, 2009).

In 1913, Carlos Chagas described an encephalopathy dubbed "forma nervosa" in over 200 individuals with Chagas disease (Chagas, 1913; Koberle, 1968). Since then, investigations increasingly point toward cerebral microvascular and CNS-derived etiologies in the pathogenesis of neuro-Chagas disease (Mangone et al., 1994; Nisimura et al., 2014; Pentreath, 1995). It has been reported that CNS microvasculature is disrupted in Chagas disease (Carod-Artal, Vargas, & Falcao, 2011; Nisimura et al., 2014; Prado et al., 2011; Tanowitz et al., 1996); *T. cruzi* infection in mice results in a vasculitis associated with increased cerebral oxidative stress and an increase in leukocyte rolling/adhesion and arteriolar endothelial dysfunction (Nisimura et al., 2014). The presence of small vessel disease, in several vascular beds in the CNS, is often an underlying etiology of stroke syndromes in Chagasic patients, suggesting an association with microcirculatory alterations (Carod-Artal, et al.; Prado et al., 2011; Tanowitz et al., 1996). Both acute and chronic CNS infection with *T. cruzi* are marked by lymphocyte infiltration (Britto-Costa, 1971; Pentreath, 1995; Silva et al., 1999). Additionally, population studies and experimental models demonstrate brain atrophy and loss of neurons in several regions of the CNS during Chagas disease, including cortex, cerebellum and hypothalamus (Alencar, 1964; Brandao & Zulian, 1966; Britto-Costa, 1971; Chuenkova & Pereiraperrin, 2011; Oliveira-Filho et al., 2009). These pathological changes result in diverse manifestations of acute Chagasic CNS disease which include meningoencephalitis, which can be fatal if left untreated, (Alencar & Elejalde, 1960; Bern, Martin, & Gilman, 2011; Diazgranados et al., 2009; Pittella, 2009; Py, 2011; Rassi, Rassi, & Marcondes de Rezende, 2012; Silva et al., 1999), and microcephaly and subependymal hemorrhage similar to TORCH syndromes (Bittencourt, 1976; Flores-Chavez et al., 2008; Mendoza Ticona et al., 2005).

ET-1 has been shown to contribute to the development of Chagasic cardiomyopathy (Tanowitz et al., 2005). However, the modulations of ET-1 and its downstream effectors on virulence of the parasite with regard to entry into the CNS, inflammation, and glial and neuronal dysfunction have yet to be explored in CNS Chagas disease.

2.3. Viral infections

Past and recent studies in virus-mediated infections, have demonstrated that viral-induced inflammatory reactions of the CNS, triggers activation of neurons, astrocytes and microglia cells in the brain, resulting in the pathogenesis and processes of neurodegenerative diseases (Karim et al., 2014; Zhou, Miranda-Saksena, & Saksena, 2013). A wide range of viruses have been shown to be associated with different types of neurodegenerative diseases by inducing widespread neuronal dysfunctions and degenerations with devastating effects (Hou, Baker, Zhou, & Klein, 2016; Koyuncu, Hogue, & Enquist, 2013; McGavern & Kang, 2011). Once in the host, viral infection of the CNS can induce activation of both innate and adaptive immune response (Rivest, 2009). Activated microglial, monocytic, neuronal and astrocytic cells release proinflammatory cytokines (endothelins, TNF-alpha, IL-1), chemokines (CCL2 and CCL5) and reactive oxygen species, which mediate the neuroinflammation-induced neurodegenerative diseases (Das Sarma, 2014; Perry & Teeling, 2013; Ransohoff & Brown, 2012; Ransohoff & Perry, 2009; Varvel et al., 2016). Activation of microglia and neuroinflammation may also result in the break-down of the BBB and corresponding leakage of complement into the CNS, chronic neuroinflammation and neurodegenerative disease (Orsini, De Blasio, Zangari, Zanier, & De Simoni, 2014; Strazza, Pirrone, Wigdahl, & Nonnemacher, 2011; Xanthos & Sandkuhler, 2014).

2.3.1. HIV and HIV-associated neurocognitive disorders (HAND)

It has been demonstrated that the human immunodeficiency virus (HIV) causes neurodegeneration by disrupting the BBB, infiltrating the brain, infecting circulatory peripheral blood monocytic cells which then also migrate into the CNS (Miner & Diamond, 2016), resulting in a chronic neuroinflammatory disease and HIV-associated neurocognitive disorder (HAND) (Malik & Eugenin, 2016; Zayyad & Spudich, 2015). HIV-1 and HAND continue to be a major concern in the infected population, despite the use of anti-retrovirals (Carroll & Brew, 2017; Heaton, et al., 2011; Tan & McArthur, 2012).

Abnormally elevated release of the vasoactive mediator ET-1 from activated monocytes, which persists despite anti-retroviral therapy, has been linked to HIV progression, mortality, and HIV-associated cardiovascular and neurocognitive disorders (Didier, Banks, Creminon, Dereuddre-Bosquet, & Mabondzo, 2002; Ehrenreich et al., 1993). Enhanced ET-1 secretion due to HIV infection induces endothelial damage and dysfunction and has been associated with cardiovascular and other HIV-associated comorbidities (Fitzpatrick et al., 2016), including HAND (Didier et al., 2002; Ehrenreich et al., 1993). HAND is characterized by cognitive, motor, and behavioral abnormalities (Ances & Ellis, 2007; Antinori et al., 2007; Antinori, Trotta, et al., 2007; Gonzalez-Perez et al., 2017; Kaul, Zheng, Okamoto, Gendelman, & Lipton, 2005; Letendre, 2011; McArthur, 2004; Sacktor, 2002; Sacktor et al., 2001). Despite recent advances in antiretroviral therapy and in understanding of the pathogenesis of HIV, and its associated neuronal effects, the mechanisms by which HIV infection causes endothelial dysfunction and subsequent development of HAND remains poorly defined (Ances & Ellis, 2007). Early work by Lane and colleagues and by Fauci demonstrated that the HIV virus transmigrates into the CNS through infected monocytes which infiltrate the BBB (Fauci, 1996; Lane et al., 1996). It has been demonstrated that once these HIV-infected monocytes/macrophages from the bloodstream have crossed the BBB into the CNS, the virus can then further infect microglia and brain monocytic/macrophagic cells (Boven et al., 2000; Dallasta et al., 1999; Trillo-Pazos et al., 2003). The activated HIV-infected glial cells, including astrocytes, microglia and monocytes/macrophages secrete high levels of ET-1, and other neurotoxic inflammatory mediators, including cytokines (TNF-alpha, IL-1, IL-6), platelet activating factor, and nitric oxide, all of which can cause neuronal injury (Chauhan et al., 2007; Didier et al., 2002; Didier et al., 2003; Ehrenreich et al., 1993; Kaul, Garden, & Lipton, 2001; Swindells, Zheng, & Gendelman, 1999). In addition, viral products, especially the HIV proteins gp120, Tat, Nef, and Rev. have been shown to be both neurotoxic and cytotoxic to endothelial cells (Bennett, Rusyniak, & Hollingsworth, 1995; Dreyer, Kaiser, Offermann, & Lipton, 1990; Huang, Hunter, & Bond, 1999; Kanmogne, Kennedy, & Grammas, 2001; Kaul et al., 2001; Lannuzel, Lledo, Lamghitnia, Vincent, & Tardieu, 1995; Magnuson, Knudsen, Geiger, Brownstone, & Nath, 1995; Patel, Mukhtar, & Pomerantz, 2000; Scutari, Alteri, Perno, Svicher, & Aquaro, 2017), and contribute to key processes in HAND through increased vasoconstriction, ET-1 secretion and neuroinflammation (Ramesh, MacLean, & Philipp, 2013; Rolinski et al., 1999). The HIV envelope glycoprotein gp120 stimulates macrophages and pulmonary arterial endothelial cells to secrete ET-1 (Didier et al., 2002; Ehrenreich et al., 1993; Kanmogne, Primeaux, & Grammas, 2005), which is critical in monocyte diapedesis across the BBB (Hong & Banks, 2015; Scutari et al., 2017). Cerebral macrophages in patients with HIV encephalopathy strongly express ET-1 (Avalos et al., 2017; Cotter et al., 2002; Ehrenreich et al., 1993). Elevated ET-1 secretion has been linked to neuroinflammation and neuronal damage during HIV (Chauhan et al., 2007; Rolinski et al., 1999), but there has been no assessment of the role of ET-1 in the development of HAND.

Increased levels of ET-1 in the cerebrospinal fluid of patients with HIV encephalopathy has been observed in association with neuronal injury, neuroinflammation, increased BBB leakage and edema, and neurological deficits (Rolinski et al., 1999; Scutari et al., 2017; Zhang, Yeung, McAlonan, Chung, & Chung, 2013). In addition, in vitro studies demonstrate that ET-1 is secreted in a human BBB model of astrocytes and brain microvascular endothelial cells exposed to HIV (Didier et al., 2002). Furthermore, ET-1 has been shown to act as a chemoattractant for monocytes in the brain via associated increases in the secretion of MCP-1 and IL-8 (Helset et al., 1994; Ishizawa et al., 2004), properties which suggest a potential role for ET-1 in the development of HAND. In this regard, ET-1 likely contributes to the increased activation of macrophages and microglia in the CNS which have been shown to play a role in the development of HAND (Chauhan et al., 2007; Ishikawa et al., 1997; Lake et al., 2017; Ma, Nie, Hoog, Olsson, & Zhang, 1994; Perry & Teeling, 2013; Werner & Engelhard, 2007).

2.3.2. Herpes viruses

Herpes viruses are neurotropic pathogens that infect mostly humans (Deigendesch & Stenzel, 2017; Munawwar & Singh, 2016; Swanson 2nd & McGavern, 2015). Currently, there are nine (9) herpesvirus types known to infect humans: herpes simplex viruses 1 and 2 (HSV-1 and HSV-2), varicella-zoster virus, Epstein–Barr virus, cytomegalovirus (CMV), human herpesvirus (HHV) 6A and 6B (HHV-6A and HHV-6B), HHV-7, and Kaposi's sarcoma-associated herpesvirus (KSHV) or HHV-8 (Alba et al., 2011; Cunningham et al., 2010; Davison, 2010; Meyding-Lamade & Strank, 2012; Norberg, 2010), all of which can migrate the immune system and induce the activation of innate and adaptive immune responses by triggering higher secretion and expression of pro-inflammatory cytokines (Scheglovitova, Romanov, Maksianina, Svintsitskaya, & Pronin, 2002).

KSHV, or HHV-8, is the causative agent of Kaposi's sarcoma (KS), a tumor of lymphatic endothelial origin characterized by proliferating spindle cells containing elements of endothelial and inflammatory cells (Curtiss, Strazzulla, & Friedman-Kien, 2016; Gramolelli & Ojala, 2017; Kahn, Bailey, & Marks, 2002; Naldi, Venturuzzo, & Invernizzi, 2018; Weninger et al., 1999).

Although rare, particularly after the advent of highly active antiretroviral therapy, KS can disseminate to the CNS in immunosuppressed patients (Bahat et al., 2002; Gorin, Bale, Halks-Miller, & Schwartz, 1985; Jellinger et al., 2000; Levy, Pons, & Rosenblum, 1984; Mossakowski & Zelman, 1997; Myers et al., 1974; Pantanowitz & Dezube, 2008; Post et al., 1986). CNS lesions, when present, typically occur in individuals with concurrent visceral involvement (Gorin et al., 1985). Lesions are highly vascularized, often display central necrosis, and can be associated with contemporaneous infection with other opportunistic organisms (Bahat et al., 2002; Barton, Safai, Nielsen, & Posner, 1983; Myers et al., 1974; Rwomushana, Bailey, & Kyalwazi, 1975; Vilaseca et al., 1982; Welch et al., 1984). KS-associated tumors can involve the cerebrum, cerebellum and dura matter (Ariza & Kim, 1988; Barton et al., 1983; Buttner, Marquart, Mehraein, & Weis, 1997; Myers et al., 1974; Rwomushana et al., 1975; Vilaseca et al., 1982; Welch et al., 1984), resulting in subdural hematoma, paresis, tonic clonic seizures, among neurological deficits (Ariza & Kim, 1988; Bahat et al., 2002; Gorin et al., 1985).

KSHV has long been shown to increase the secretion of angiogenic factors and inflammatory factors and to induce the activation of the PI3K/Akt signaling pathway (Dimaio & Lagunoff, 2012; Kang, Ye, Gao, & Wang, 2008; Purushothaman, Uppal, Sarkar, & Verma, 2016). However, the role of ET-1 in the pathogenesis of KSHV infection is still unclear. While some investigators demonstrate no increase in ET-1 during KS (Cacoub et al., 1995), others have reported an increase in Big ET-1, the ET-1 precursor, during infection with KSHV (Speciale et al., 2006). Bagnato and colleagues have demonstrated that ET-1 and its receptors are critical to angiogenesis and proliferation of KS tumors (Bagnato et al., 2001; Bagnato, Loizidou, Pflug, Curwen, & Growcott, 2011; Rosano et al., 2003), with dual ET_A/ET_B receptor blockage abrogating ET-1-induced KS cell invasion and tumor growth and migration both in vitro and in an in vivo model of local cutaneous invasion (Bagnato et al., 2001; Rosano et al., 2003). While these data suggest that ET-1 is involved in the virulence and dissemination of KSHV-induced tumors, the effects of ET-1 on distant disease, including CNS disease, remains to be investigated.

Studies on the involvement of ET-1 in the pathogenesis of other herpes viruses are limited. There is evidence that CMV infection causes an increase in ET_B receptor expression (Yaiw et al., 2015), suggesting a potential role for ET-1 and its receptors in the pathogenesis of the virus. Scheglovitova and colleagues demonstrated that the effects of HSV-1 on endothelial production of ET-1 is pleiotropic and is dependent on the baseline spontaneous production of ET-1 from those cells and on interferon activation (Scheglovitova, Skliankina, Boldyreva, Babayants, & Frolova, 2013). However, although herpesviruses are associated with CNS pathology, including increased secretion of pro-inflammatory mediators from circulatory immune cells which can traverse the BBB (Conrady, Drevets, & Carr, 2010; DeBiasi, Kleinschmidt-DeMasters, Richardson-Burns, & Tyler, 2002; Deigendesch & Stenzel, 2017; Harris & Harris, 2015; Koyuncu et al., 2013; Marques, Hu, Sheng, & Lokensgard, 2006; Martino et al., 2000), there is a paucity of investigations on a role for ET-1 in this process.

2.3.3. Flaviviruses

The *Flaviviridae* family consists of positive, single-stranded enveloped RNA viruses which can occasionally cause severe disease and mortality in humans and animals (Fernandez-Garcia, Mazzon, Jacobs, & Amara, 2009; Kimura, Sasaki, Okumura, Kim, & Sawa, 2010). These vector-transmitted viruses include - Yellow Fever, Dengue virus (DENV), Japanese encephalitis virus, Chikungunya virus, West Nile virus and Zika virus (Brehin et al., 2008; Chen & Wilson, 2016; Das et al., 2010; Fernandez-Garcia et al., 2009; Huang, Higgs, Horne, & Vanlandingham, 2014; Jhan et al., 2017; Kimura et al., 2010; Lannes, Summerfield, & Filgueira, 2017; Lindenbach & Rice, 2003; Lum et al., 2017). Disease from flaviviruses can range from asymptomatic to symptomatic manifestations, with high fever, chills, headache, back and muscle aches, dizziness, anorexia, nausea, and vomiting (Gould & Solomon, 2008; Murphy & Whitehead, 2011), and can sometimes result in fatal illness, such as encephalitis and hemorrhagic fever (Basu et al., 2016; Imaizumi et al., 2005). In addition, flavivirus infections can cause inflammation of the CNS (Furr & Marriott, 2012; Roach & Alcendor, 2017; Tsai et al., 2016).

DENV infection results in important clinical symptoms which include fever, headache and rash (Guabiraba & Ryffel, 2014; Singhi, Kissoon, & Bansal, 2007; Thomas, John, & Kanish, 2010). However, acute infection may result in severe disease such as in dengue hemorrhagic fever and dengue shock syndrome (Guabiraba & Ryffel, 2014; Halstead, 2002). DENV has been shown to affect several vital organs, including the liver, heart, kidneys, and the brain (Basu & Chaturvedi, 2008). DENV invades the CNS by migrating through CNS through BBB disruption, inducing encephalitis (Li et al., 2017; Li, Ning, Liu, & Li, 2017; Verma, Sahu, & Holla, 2014). These syndromes prominently feature vascular leakage (Tsai et al., 2016; van de Weg et al., 2014). Interestingly, van de Weg and colleagues recently demonstrated that endothelial damage in patients infected with DENV was associated with significantly increased plasma levels of ET-1 (van de Weg et al., 2014). Plasma leakage during DENV infection can lead to hypovolemic shock, coagulopathy, bleeding, organ impairment and death (Simmons, Farrar, Nguyen v, & Wills, 2012). Furthermore, DENV infection of endothelial cells may induce injury to the brain microvasculature, resulting in increased secretion of pro-inflammatory cytokines and chemokines in the cerebral microvascular milieu (Basu & Chaturvedi, 2008; Cardier et al., 2006; Hendarto & Hadinegoro, 1992; Solomon et al., 2000; van de Weg et al., 2014).

While it is well established that flaviviruses enter into the CNS, to infect glial cells, and elicit a robust immune response, a relationship between such events and ET-1 has not been established.

Several viral infections of the CNS are associated with an increase in the secretion of ET-1 by activated endothelial cells, inflammatory cells, and glial cells, particularly astrocytes and microglia (Chauhan et al., 2007; Didier et al., 2002; Didier et al., 2003; Ehrenreich et al., 1993; Ma et al., 1994; Zhang et al., 1994). As of the time of this review, causative relationships between the pathological increase in ET-1 secretion and vascular dysfunction with resultant loss of BBB integrity or the robust immune response that occur during infection remains to be assessed. However, previous studies of parasitic diseases of the brain suggest that ET-1 likely plays an integral role in the pathogenesis of these infections in the CNS (Dai et al., 2012; Freeman et al., 2016; Freeman, Machado, Tanowitz, & Desruisseaux, 2014; Martins et al., 2016). Thus, further investigations are warranted to determine the role of ET-1 in the pathogenesis of neurological dysfunction during viral illnesses.

3. Endothelin-1 and central nervous system vasculitis

3.1. Potential roles of the endothelin-1 pathway in central nervous system vasculitis

ET-1 secreted predominantly by the endothelial cells (Yanagisawa et al., 1988) is found in high intramural concentrations in several inflammatory diseases of the vascular wall (Battistini, D'Orleans-Juste, & Sirois, 1993). Of relevance to the present section, systemic lupus erythematosus (SLE) has been associated with high levels of plasma levels of ET-1 in patients (Dhaun et al., 2009; Julkunen, Saijonmaa, Gronhagen-Riska, Teppo, & Fyhrquist, 1991). Furthermore, cultured endothelial cells exhibited increased secretion of ET-1 after exposure to sera from patients with SLE (Yoshio et al., 1995). Nakamura and colleagues previously demonstrated that selective ET_A antagonism prevented the progression of lupus nephritis in a murine model (Nakamura, Ebihara, Tomino, & Koide, 1995), and more recently, Li Guo and colleagues showed that SLE patients with autoantibodies to ET_A were more likely to develop pulmonary hypertension (Guo et al., 2015). Although there has not been any clear associations between ET-1 and neuropsychiatric SLE, high concentrations of vascular ET-1 have been observed in vasculitis-prone MRL/lpr mice (Sugimoto et al., 2017), an established model of SLE (Perry, Sang, Yin, Zheng, & Morel, 2011), which has been well characterized as a model of spontaneous neuropsychiatric lupus (Gao et al., 2009; Gulinello & Putterman, 2011; Gulinello, Wen, & Putterman, 2012; Stock et al., 2015; Wen et al., 2013), with clear leukocyte infiltration to the choroid plexuses and breach of the blood-brain barrier (Mike et al., 2018).

In Experimental Autoimmune Encephalomyelitis (EAE), a murine model of multiple sclerosis (MS), mice overexpressing endothelial and astrocytic ET-1 present more severe inflammation and demyelination (Guo et al., 2014). These outcomes are possibly the result of ET-1- induced alteration of the integrity of myelin sheets in the spinal cord via a Notch-1-dependent mechanism as well as suppression of oligodendrocyte progenitor cell-dependent repair of demyelinated neurons by the peptide (Hammond et al., 2015). Correspondingly, investigators have demonstrated that repression of one of the mouse chymases, mouse Mast Cell Protease 4 (mMCP-4), mitigates disease-related increases in brain ET-1 levels during EAE (Desbiens et al., 2016).

Thus, repressing the brain production of ET-1 with a chymase inhibitor may facilitate myelin repair in neurogenerative diseases such as MS. Interestingly, >30 years ago, inflammatory vasculitis had been reported especially in lesioned sections of the spinal cord of MS patients >30 years ago (Adams, Poston, Buk, Sidhu, & Vipond, 1985). The role of chymase-dependent production of ET-1 in the development of vasculitis in MS patients, however, remains poorly understood. Nonetheless, in light of the importance of mast cell-derived chymase in ET-1 generation (see Introduction), we suggest that targeting chymase rather than the ECE to treat CSNV may be preferable. Indeed, homozygous repression of mMCP-4 does not prompt the impairment of embryonic development in genetically engineered mice (Tchougounova, Pejler, & Abrink, 2003). Furthermore, pharmacological interference with an ECE inhibitor enhances amyloid plaque formation (Eckman, Reed, & Eckman, 2001; Pacheco-Quinto, Herdt, Eckman, & Eckman, 2013; Wang et al., 2010).

3.2. ET-1 and ET receptors in giant cell arteritis

Tissular levels of ET-1 and of its ET_B receptors are significantly increased in arteries derived from inflammation prone-patients with giant cells arteritis (GCA). In a recent study, Regent et al. (2017) reported that the dual ET_A/ET_B antagonist macitentan combined with glucocorticoids, reduced vascular smooth muscle cell (VSMC) proliferation in vessels of patients with GCA (Regent et al., 2017). Planas-Rigol and colleagues demonstrated that ET-1 immunoreactivity was predominant in leucocytes infiltrating the medial-intima interphases of vessels derived from GCA patients and that both ET_A and ET_B receptors in VSMC proliferation in such vessels through activation of Focal Adhesion Kinase (Planas-Rigol et al., 2017).

3.3. Mast cells and central nervous system vasculitis

The role of mast cells in the etiology of CNS vasculitis (CNSV) remains controversial. While some groups have suggested protective roles of those cells in large vessel vasculitis via histamine-dependent repression of pro-inflammatory IL-6 (Springer, Raveendran, Gierer, Maz, & Dileepan, 2017), others have suggested that hyperactivated mastocytes contribute to inflammatory-dependent deterioration of blood vessels (Kiely, Pecht, & Oliveira, 1997; Lipitsa, Naukkarinen, & Harvima, 2015). Kiely and colleagues reported a role for mast cells in the genesis of mercuric chloride-induced vasculitis in Brown Norway rats (Kiely et al., 1997). Furthermore, Lipïtsa et al. demonstrated that mastocyte-derived chymase is directly involved in intramural deposition of immunoreactants in the vascular wall (Lipitsa et al., 2015). Pro-inflammatory mast cells are predominantly located on the abluminal side of blood vessels and can readily cross the BBB to gain direct contact with astrocytes, glial cells and other cellular moieties involved in the maintenance of the brain integrity, especially in diseases states (Silverman, Sutherland, Wilhelm, & Silver, 2000).

Furthermore, cross-talk between mast-cells and Kallikrein-Kinin has been implicated in inflammatory propagation and enhanced cardiac parasitism and fibrosis in *T. cruzi*-infected mice (Nascimento et al., 2017) yet it remains to be investigated if a similar cross talk comes into play within the BBB in CNSV.

The current state of knowledge on potential roles of ET-1 in inflammation-prone vasculitis of the CNS has been summarized. The mechanistic basis of this type of vascular dysfunction remains to be investigated, although its occurrence increases in several bacterial and viral-induced infections of the CNS. Targeting chymase rather than the overall mastocytic activity might represent a more effective approach to treating CNSV due to the neuroprotective roles mast cells reported in large vessel vasculitis.

4. Role of ET-1 in Alzheimer's disease

Alzheimer's Disease (AD) is one of the most common and devastating neurodegenerative diseases (Xie, Gao, Xu, & Meng, 2014), and is characterized by a substantial loss of neurons in the brain, which may lead to progressive memory decline and a deficits in cognitive functions (Ubhi & Masliah, 2013). These neuronal degenerative alterations in AD are induced by a number of factors which include beta-amyloid deposition, microtubule destabilization, deficiencies in neuronal communication and secretion of pro-inflammatory cytokines and chemokines (Wang, Dayton, Zweig, & Klein, 2010). The development of neurodegenerative pathologies, such as Alzheimer's disease, may be linked to environmental and genetic factors (Barber, 2012; El Gaamouch, Jing, Xia, & Cai, 2016; Grant, Campbell, Itzhaki, & Savory, 2002; Tanzi & Bertram, 2001; Tol, Roks, Slooter, & van Duijn, 1999).

While the etiology of neurodegenerative diseases such as AD is multifactorial, the primary factors that initiate AD pathogenesis are soluble and aggregated neurotoxic beta-amyloid protein (Aβ) and hyperphosphorylated tau which induce inflammatory activation of glial cells (Guerriero et al., 2016; Schwartz & Deczkowska, 2016). Amyloid plaques, consisting of extracellular Aβ deposits from amyloid precursor protein (APP), and neurofibrillary tangles, composed of aggregates of misfolded and tau proteins, within neurons are typical characteristics of AD pathology (Lacosta, Insua, Badi, Pesini, & Sarasa, 2017; Murphy & LeVine 3rd., 2010). Levels of Aβ in the brain are regulated by the relative rates of Aβ production and clearance over time (Jeong, 2017; Sun, Chen, & Wang, 2015), which under normal homeostatic conditions, are both rapid (Bateman et al., 2006; Mawuenyega et al., 2010). There are two Aβ peptides that result from the amyloidogenic processing of APP, namely the soluble $A\beta_{1-40}$ and the less soluble and more toxic $A\beta_{1-42}$ (Kirkitadze & Kowalska, 2005; Serrano-Pozo, Frosch, Masliah, & Hyman, 2011). Excessive increase in $A\beta_{1-42}$ or an increase in the $A\beta_{1-42}$: $A\beta_{1-40}$ ratio are thought to be pivotal to the etiology of the pathological cascade in AD patients (Palmer & Love, 2011).

Vascular dysfunction also plays an important role in the development of AD (Dickstein et al., 2010). Recent data from brain imaging studies in humans and in experimental AD animal models suggest that cerebrovascular dysfunction may precede cognitive decline and onset of neurodegenerative changes in AD (Klohs, Rudin, Shimshek, & Beckmann, 2014; Montagne, Zhao, & Zlokovic, 2017). ET-1 has been studied extensively as a mediator of vasomodulation, and the dysregulation of the endothelin system is instrumental to the progression of AD (Palmer, Tayler, & Love, 2013). Many studies have demonstrated that the concentration of ET-1 is increased in both the cerebral cortex (Minami, Kimura, Iwamoto, & Arai, 1995; Palmer, Barker, Kehoe, & Love, 2012) and in cerebral blood vessels in AD (Luo & Grammas, 2010; Palmer et al., 2013). This is in association with significant increases in Aβ which indirectly stimulates production of ET-1 (Pacheco-Quinto et al., 2013; Pacheco-Quinto & Eckman, 2013; Palmer et al., 2013). The exposure of human neuroblastoma cells and brain microvascular endothelial cells to Aβ induced increases in the expression of ECE-2 and ECE-1, resulting in increased production and secretion of ET-1 (Palmer et al., 2012; Palmer et al., 2013; Palmer, Baig, Kehoe, & Love, 2009). In addition, ET-1 production is increased in the cerebral vasculature of mice infused with Aβ (Paris et al., 2003). ET-1 expression is also modulated by astrocytes in AD and a number of other brain pathologies (D'Haeseleer et al., 2013; Hammond et al., 2014; Palmer et al., 2012; Petrov, Steiner, Braun, & Rafols, 2002; Schinelli, 2006; Stiles et al., 1997). Both astrocyte and glial cells can contribute to the development of secondary brain damage by activating ET receptors in both an autocrine and paracrine manner (Barker et al., 2014; Esiri, 2007; Hostenbach, D'Haeseleer, Kooijman, & De Keyser, 2016).

Most individuals with AD exhibit cognitive impairment and a reduction in CBF before the onset of dementia. (Palmer et al., 2013). The correlation between cerebral vasoconstriction and microvascular endothelial cell dysfunction further leads to further ET-1 secretion and the release of free radicals which are toxic to neurons (Stankowska, Krishnamoorthy, Ellis, & Krishnamoorthy, 2017). Hypoxia itself can upregulate components of the endothelin system (Ao, Hao, Xiong, & Wang, 2002; Kang, Kleinhenz, Murphy, & Hart, 2011; Li et al., 1994; Yamashita, Discher, Hu, Bishopric, & Webster, 2001). In AD, chronic cerebral hypoperfusion and glucose hypometabolism can result in cognitive decline with time (Daulatzai, 2017). Brain hypoperfusion is assessed by documenting a reduced ratio of myelin-associated glycoprotein compared to proteolipid protein-1 (Barker et al., 2014; Barker, Wellington, Esiri, & Love, 2013; Thomas, Miners, & Love, 2015) and the decrease in this ratio strongly correlates with the increased expression in ET-1 during AD (Barker et al., 2014; Love & Miners, 2016; Thomas et al., 2015). Significant reduction in CBF has been associated with the presence of white matter lesions in AD resulting in more rapid progression to cognitive impairment compared to AD patients without white matter lesions (Hanaoka et al., 2016; Kimura, Nakama, Nakamura, Aso, & Kumamoto, 2012).

While there is a clear vascular component to the development of AD, it should be noted that neurological and neurodegenerative diseases may be influenced by other factors such as aging, infection (bacteria, virus, parasite) and inflammatory activation (Amor, Puentes, Baker, & van der Valk, 2010; De Chiara et al., 2012). In fact, there are several reports of chronic neuroinflammation due to injury or infection in association with the onset and progression of AD and other neurodegenerative diseases including Parkinson's disease and Multiple Sclerosis (Chen, Zhang, & Huang, 2016), manifested by activation of microglia, astrocytes, mast cells, T-cells, and inflammatory mediators released from these cells (Shabab, Khanabdali, Moghadamtousi, Kadir, & Mohan, 2017). AD is characterized by glial cell activation, transmigration of macrophages into the brain parenchyma, and accumulation of several essential proteins (Sokolova et al., 2009; Walter et al., 2007). It is widely thought that the accumulation of the Aβ is central in the pathogenesis of the disease, as it causes dysfunction and loss of synapses that lead to cognitive deficits (Murphy & LeVine 3rd., 2010; Sadigh-Eteghad et al., 2015). Interestingly, ET-1 has been shown to contribute to the inflammatory process induced by Aβ. In a study by Bryial and colleagues, animals were treated with amyloid beta, resulting in increased the expression of the components of ET signaling, oxidative stress, and in cognitive impairment. Treatment with a selective ET_A receptor antagonist mitigated these changes (Briyal, Philip, & Gulati, 2011).

In summary, recent evidence suggests that ET-1 likely contributes to loss of endothelial functional integrity and cerebrovascular inflammation, by both direct and indirect actions on the cerebral vasculature, leading to neurodegeneration. This provides a potential role for ET-1 in the pathogenesis of AD and a target of therapy.

5. Conclusion

The mechanisms associated with the roles of the endothelin pathways in neuroinflammatory diseases are highly complex. A common pattern nonetheless is recognizable as in all the above described diseases, pathogen-triggered inflammatory response plays a pivotal role in the increase of tissue and/or blood levels of ET-1. This important cross-talk occurs within and outside of the CNS and involves the activation of either or both ET_A and ET_B receptors whose expression, in some of the diseases discussed above, can be independently or conjointly modulated. In most parasitic diseases described, ET-1 appears to be closely associated with a loss of endothelial integrity as well as changes in BBB permeability. Although interfering with the ET-1 pathway has been successful in reducing morbidity in experimental models of neuro-inflammatory infections, it remains to be validated whether the potent vasoactive peptide is a marker or a mediator in most neurological diseases studied in patients.

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Conflict of interest statement

The authors declare that there are no conflicts of interest.

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