Endothelins Role in the Control of the Acute Phase of *Trypanosoma cruzi* Infection

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Abstract: Disturbances of endothelin production or clearance contribute to the pathophysiology of several cardiovascular diseases including Chagas disease cardiomyopathy caused by the protozoan *Trypanosoma cruzi*. In rats, endothelins contribute to control the acute phase, probably by stimulating nitric oxide production. We point out the necessity for new studies to better evaluate high levels of endothelin in the course of other infectious diseases, for which only its detrimental effects have been emphasized.

Keywords: Chagas Disease, cardiomyopathy, cytokines, chemokines, nitric oxide, endothelins, endothelial dysfunction, infectious disease.

INTRODUCTION

Endothelin (ET) family comprises three 21-amino acid-long peptides (ET-1, ET-2 and ET-3). ET-1 was first identified as a powerful vasoconstrictor produced by endothelial cells [1]. It is secreted constitutively, mainly toward the vascular smooth muscle, and has an important physiological role in cardiovascular functions, notably the control of vascular tonus [2]. ET-1 is the predominant form in human plasma and tissues [3], produced by several other cell types, such as cardiomyocytes [4], macrophages [5-7], mast cells [8], cardiac fibroblast [9], some neurons [10, 11], astrocytes [12] and kidney components [13]. ET-2 is a potent constrictor of the intestinal smooth muscle and is mostly expressed by gastrointestinal tract, sex organs and pituitary gland [14, 15]. ET-3 is found mainly in brain neurons [10], astrocytes [16], lung and intestine [17].

Two G-protein-coupled ET receptors, ET_A and ET_B, mediate the endothelin actions in mammals. While ET_A displays ET-1 selective binding with practically no ET-3 binding, ET_B shows similar affinity for all ET isoforms. In the complex regulation of vascular tone, ET-1 vasoconstrictor effect is balanced mainly by endothelial cell-derived nitric oxide (NO), that requests the catalysis by one of the constitutive isoforms of NO synthase (NOS), the endothelial NOS (eNOS or NOS3). In vascular smooth muscle, both ET_A and ET_B receptors mediate vasoconstriction. In the endothelial cells ET_B receptors mediate vasodilatation through NO production. In normal blood vessels, the signaling pathways for the release of NO and ET-1 interact with each other in many ways. Importantly, NO curtails the production of ET-1, and ET-1 stimulates the eNOS [2, 18]. In addition to the systemic action of ET-1 on vascular tonus, renal endothelins play an important role in the blood pressure control acting as natriuretic and diuretic agents, predominantly *via* ET_B receptors [19]. ET_A and ET_B receptors occur throughout the heart, but ET_A predominates in cardiomyocytes and may mediate positive ionotropic effects of endothelins [20] as well as cardiomyocytes hypertrophy [21]. In isolated atrial cardiomyocytes, ET-1 increases the expression and release of atrial natriuretic peptide, probably *via* ET_A receptor [22]. ET_B receptor mediates the endothelin clearance in the lung, liver and kidney [23]. The clearance mechanism involves fast internalization of the ET- ET_B complex that is rapidly targeted to the late endosomes/lysosomes for degradation [24, 25]. ET-1 also promotes growth and proliferation of the vascular smooth muscle cells, probably through ET_A receptors [26]. Disturbances of endothelin production or clearance contribute to the pathophysiology of a variety of cardiovascular system diseases such as essential hypertension, atherosclerosis, pulmonary arterial hypertension and chronic heart failure [2, 18, 27]. The biochemistry, physiology, pharmacology and pathophysiology of endothelins have been object of several reviews [2, 18, 26, 27, 28]. For our present aims, it is important to emphasize that the ET system contributes to several aspects of the inflammatory response, including edema formation, leukocyte infiltration, inflammatory pain and fever [29, 30], mast cell degranulation and mast cell-dependent inflammation [31] and expression of adhesion molecules involved in leukocyte recruitment by endothelial cells [32]. Also, in cultured macrophages or in the anaesthetized rat, ET-1 stimulates the production of tumor necrosis factor-α (TNF-α) *via* activation of ET_A-receptors [33]. In a rat model of lipopolysaccharide (LPS)-induced acute respiratory distress syndrome, the downregulation of ET-1 by angiopoietin-1 correlated with the amelioration of pulmonary inflammation, as indicated by reductions in leukocyte infiltration and intra-alveolar septal thickening [34]. In atherosclerosis, ET-1 may contribute to the pathogenesis because it causes nuclear factor-kappa B (NF-kB) activation in human monocytes, probably *via* ET-A-receptor. Also, ET-1 stimulates expression of the proinflammatory molecule CD40 in a NF-kB-dependent manner [26, 35]. Besides macrophage,

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other inflammatory cells such as neutrophils [36] and eosinophils [37] are influenced by ET-1.

CHAGAS DISEASE

Chagas disease (American trypanosomiasis), a lifelong infection caused by *Trypanosoma cruz*i affects about 17 million people in Latin America [38]. The parasite's biological cycle involves reduviid bugs and mammalian hosts. Natural transmission occurs *via* insect excreta containing the infecting metacyclic trypomastigotes that contaminate skin wounds including the bite site, or mucosal surfaces. In mammals, amastigotes replicate intracellularly by binary divisions and trypomastigotes infect neighboring cells, reach the circulating blood and spread to various tissues [39, 40]. *T. cruzi* exhibits considerable genetic variability compatible with a clonal evolution [41] and distinct populations are distributed in two [42] or three [43, 44] major phylogenetic lineages, *T. cruzi* I, *T. cruzi* II and *T. cruzi* III.

T. cruzi infection has an acute phase characterized by numerous blood-circulating trypomastigotes and amastigote nests (Fig. **1**) in several cell types, mainly muscle cells (cardiac, skeletal and smooth). In the chronic phase, 60 to 70% of the infected people have the latent or indeterminate form that is asymptomatic. About one third of all infected people eventually develop the chronic cardiac form, an inflammatory dilated cardiomyopathy that leads to death by arrhythmia or congestive heart failure. The remainder develops digestive form of the disease characterized by megaeophagus and/or megacolon. The digestive form may occur in patients with the cardiac form [39, 40, 45, 46]. Skeletal muscles are also affected [47, 48]. Herein, the cardiac involvement will be emphasized.

Progressive fibrosing myocarditis, with predominance of mononuclear infiltrating cells, characterizes the chronic chagasic cardiomyopathy, but parasites are seldom found in the heart lesions by histological and immunohistochemical methods. Inflammatory fibrosis is found in other dilated cardiomyopathy, but in Chagasic patients the severity of the inflammatory process is the main hallmark. In contrast, sparse inflammatory foci occur in hearts of patients with the chronic indeterminate form of Chagas disease [45, 46]. This fact taken together with persistence of the parasite, proved by molecular methods, throughout the chronic phase [49, 50] shows that parasites can survive for years in human tissues without inducing the cardiac or digestive chronic forms. The mechanisms involved in the establishment of these symptomatic forms are not completely comprehended [40].

Autoimmunity has been considered important in the pathogenesis of Chagasic cardiomyopathy [39, 46, 51]. Despite this, several studies favor the notion that *T. cruzi* bears primary responsibility for producing the progressive multifocal inflammation and fibrosis [46, 52-54]. Neuronal loss in heart parasympathetic and enteric nervous system ganglia has also been claimed to be important in disease progression, mainly because of the activation of sympathetic activity [47, 55, 56]. Counting neuronal cell bodies may not assess the actual autonomic denervation because neuronal plasticity allows axonal sprouting from preserved neurons. Histochemical techniques for visualization of autonomic nerve fibers show multifocal loss of both sympathetic and parasympathetic nerve terminals, in explanted hearts from patients with Chagasic cardiomyopathy or other dilated cardiomyopathy. In Chagasic patients the denervation is more severe or faster in accordance with the severity of the focal inflammatory process [57]. Conversely, activation of the sympathetic nervous system and the renin-angiotensin system exerts a direct deleterious effect on the heart during heart failure induced by other cardiomyopathies [58]. The focal sympathetic denervation [57] is compatible with the sympathetic activation thought to occur during heart failure. Recently, a modified neurogenic hypothesis was proposed in an attempt to explain the evolution of Chagasic cardiomyopathy by unifying cardiac remodeling and neurohormonal

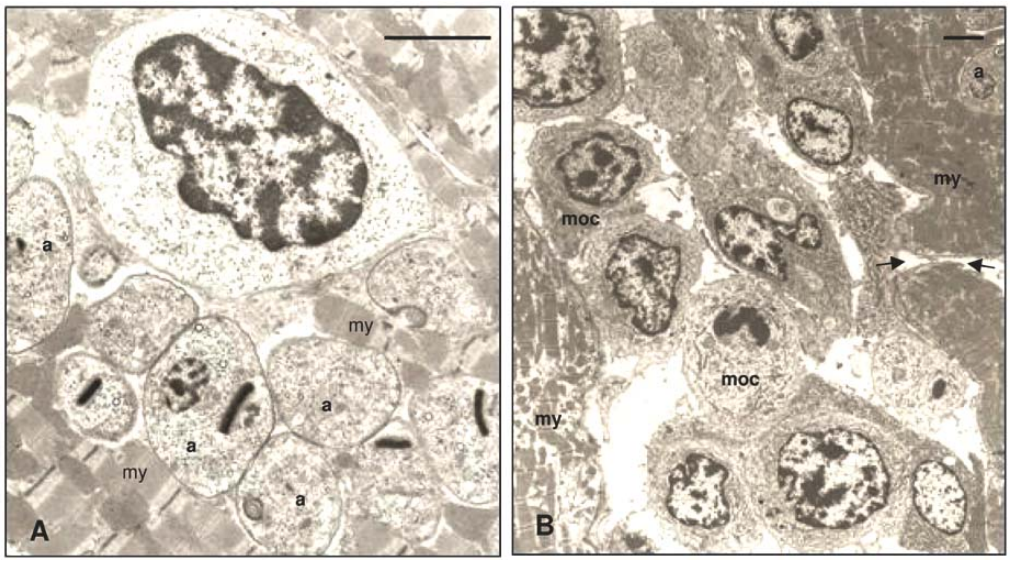

Fig. (1). Electron microscopy of rat myocardium at the the acute phase of experimental *T. cruzi* infection. (A) *T cruzi* amastigotes (a) in the cytoplasm of a cardiomyocyte. (B). Mononuclear cells (moc) in an inflammatory foci next to parasitized cardiomyocytes . Note the disruption of the cardiac muscle fiber (arrows) and myofibril (my) desegregation. Bar = 5μm.

mechanisms [59]. Another factor that is thought to contribute to the pathogenesis of Chagasic cardiomyopathy is related to microvasculature changes [39, 46] as will be discussed in the next section.

Several studies suggest a role for host and parasite genotypes in Chagas disease pathogenesis, as will be exemplified in this section. The ability to invade host cells varies among *T. cruzi* populations. The infectivity tested in mammalian cell lines is associated with differential expression of parasite surface glycoproteins with Ca^{2+} signaling activity [60]. Also, invasion depends on the degree of syalization of host cells [61]. *T. cruzi* trypomastigotes express surface trans-sialidase that enables the parasite to invade and survive in host cells. This enzyme transfers sialyl residues from host glycoconjugates to parasite surface acceptor molecules and is differentially expressed by populations from *T. cruzi* lineages [62]. It is shed in circulating blood and causes damage to the host's immune system [63]. As earlier citations attest [64-66], differential tissue tropism of *T. cruzi* strains has been considered a pathogenic determinant in Chagas disease. This notion was reinforced by using molecular techniques to genetically type the parasite in tissues of BALB-c mice simultaneously infected with an artificial mixture of two monoclonal *T. cruzi* populations [67]. Double infection using the artificial mixture of *T. cruzi* populations but different mouse strains [66] or rats [68] showed the importance of host genetic backgrounds. In the rat, all tested *T. cruzi* populations have higher tropism for striated myocytes, mainly cardiomyocytes, but the severity of the myocarditis and myositis depends on the *T. cruzi* population [69, 70]. The inoculation of an artificial mixture of populations bearing opposite virulence and pathogenicity results in milder infection with low mortality and survival of the less virulent population [68].

The host response to *T. cruzi* infection involves innate and acquired immunity as showed in extensive reviews [40, 71, 72]. In humans, most studies deal with patients with chronic Chagasic cardiomyopathy. One study used cytometric analysis of peripheral mononuclear blood cells to evaluate human immunologic status during early stages of the infection in children. The findings reinforce the hypothesis that *T. cruzi*-derived antigens are able to activate natural killer (NK) cells before the development of T-cell-mediated immunity. Moreover, expansion of conventional B cells occurs in the early acute phase and increased amount of B1 lymphocytes is already present during initial stages of chronic infection [73]. In the heart of patients with chronic Chagasic cardiomyopathy there is predominance of $CD8^+$ lymphocytes, macrophages that express TNF-α, and some $CD4^+$ T cells [74]. There is no data on the frequency of the different mononuclear cell types in tissues of patients during the acute phase. In the rat, the acute infiltrate elicited by amastigote nest rupture shows predominance of macrophages followed by $CD8^+$ T cells and NK cells [70]. C-C chemokines appear to drive the inflammatory response during the experimental *T. cruzi* infection [75, 76].

In vitro and *in vivo* studies indicate that *T. cruzi* infection induces mononuclear cells to produce higher levels of proinflammatory cytokines in patients with chronic Chagas disease [77]. Under stimulation, peripheral mononuclear blood cells (PMBC) from these patients produce higher levels of interferon-gamma (IFN-γ) than those from patients with the indeterminate form. In the latter, the levels are higher than in normal individuals [78]. Exacerbated production of IFN-γ is also reported in patients with Chagasic cardiomyopathy [79] and its expression is higher than in other dilated cardiomyopathy [80]. However, studies during the acute human infection are lacking.

In experimental models of the disease, pro-inflammatory cytokines, mainly interleukin (IL)-12, IFN-γ and TNF-α, as well as NO catalyzed by the inducible NO synthase (iNOS or NOS2), have an essential role in controlling the acute phase either in mouse [81-85] or rat [86-88]. Macrophages are activated by trypomastigotes and amastigotes forms of *T. cruzi* to produce several cytokines and NO. Glycosylphosphatidylinositol (GPI)-anchored glycoconjugates are the parasite activator molecules and the GPI anchor is an essential component for induction of IL-12 and TNF-α synthesis [84]. These two cytokines are able to stimulate or initiate the IFN-γ synthesis by NK and T cells. In turn, IFN- γ stimulates the synthesis of cytokines by macrophages as well as their effector functions [89]. Moreover, *T. cruzi*-derived GPI-mucins in conjunction with IFN-γ and TNF-α may drive tissue chemokine production and inflammation [90, 91].

Exacerbated production of inflammatory cytokines [46, 79, 92, 93] and NO [85] are also associated with tissue damage in human and experimental Chagas disease, as is known to occur in patients with heart failure [94, 95]. Modulatory cytokines such as IL-4, IL-10 and TGF-β are essential to control the production of inflammatory cytokines. In *T. cruzi* infection, IL-10 and IL-4 modulate the production of proinflammatory cytokines [96, 97], NO [84] and chemokines [90]. The latter is also regulated by transforming growth factor (TGF)-β [90]. *In vitro* studies with isolated cardiomyocytes [98] as well as trials in chronic heart failure [99, 100] have strengthened the notion that disturbances in the balance between proinflammatory mediators and modulatory cytokines could better explain the cytokine-associated tissue damage than the increase in proinflammatory cytokines by itself. As heart failure is a feature of chronic Chagasic cardiomyopathy, this kind of imbalance could well contribute to cardiac remodeling. Interestingly, in PMBC and T-cell lines derived from endomyocardial biopsies obtained from patients with Chagasic cardiomyopathy, the production of IL-4 is suppressed or inconstant [78]. In contrast, the higher production of IL-10 by monocytes from patients with the indeterminate form in comparison with those from patients with chronic Chagas-induced cardiomyopathy is consistent with the long-lasting nature of the disease [101].

Cardiomyocytes from *T. cruzi*-infected mice as well as mouse cardiomyocytes cultured with trypomastigotes produce NO by iNOS, some C-C-chemokines and proinflammatory cytokines [82, 102]. Human cardiomyocytes also produce iNOS-derived NO and TNF-α in patients with heart failure not related to Chagas disease [103, 104] or in cardiac remodeling after transplantation [105]. Thus, cardiomyocytes may contribute to the control of parasite proliferation and to increased tissue damage. Table **1** summarizes host and parasite molecules involved in the pathogenesis of Chagas disease.

Table 1. Parasite and Host Molecules Known to Play a Role in the Cellular Phenomena Underlying the Pathogenesis of Chagas Disease

Parasite	Host
• GPI - anchored glycoproteins	• Pro-inflammatory cytokines (IFN-α, TNF-γ, IL-12)
• Ca^{++} signaling glycoproteins	• Regulatory cytokines (IL-4, IL-10, TGF-ß)
• Trans-sialidases	• Nitric oxide derivatives
	• Immunoglobulins
• Parasite products (Thromboxana A2)	• Chemokines
	• Endothelin
Genetic Background	
⇩	
Differential parasite infectivity and tissue tropism	
Persistent parasitism	
Molecular mimicry (auto-immunity)	
Innate and acquired immune response panel	
Tissue damage and remodeling	
Microvascular disorders	
⇩	
Asymptomatic patients (60-70%) Chronic chagasic cardiomyopathy (20-30%)	
Esofagopathy and colopathy (9-14%)	

ENDOTHELINS AND CHAGAS DISEASE

Coronary microvascular disorders associated with myocardial damage and remodeling have been described in patients with chronic Chagas disease cardiomyopathy and in mice during the acute [46, 106] and chronic [107,108] phases of the infection. Among the changes thought to be responsible for heart hypoperfusion are focal vascular constriction, microaneurysm formation, increased intravascular platelet aggregation, thrombosis and endothelial dysfunction [39, 46, 106]. The mechanisms underlying these vascular changes are not completely elucidated. During the chronic phase, *T. cruzi* or its products may not be an essential factor because similar changes occur in other dilated cardiomyopathy [109]. However, endothelial cells from human umbilical vein (HUVEC) cultured with *T. cruzi* produce increased amounts of ET-1 [110]. Also, infection of HUVEC with *T. cruzi* activates the endothelial NF-kB, a major component of inflammatory response, and induces the expression of vascular adhesion molecules [111]. Thus, endothelial activation caused by the parasite or their products cannot be discarded, at least during the murine acute phase in which high parasitemia is observed. Inflammatory cells may contribute to the vascular changes, through the release of cytokines that are thought to influence endothelial cells [112].

In the cardiovascular system, endothelins have several beneficial roles such as maintenance of basal vascular tonus, positive inotropy, myocardial contractile efficiency, compensatory left ventricle hypertrophy, and cardiac tissue repair after ischemia [2, 26]. However, endothelin overproduction is thought to contribute to or cause vascular dysfunction leading to hypoperfusion and tissue damage observed in several cardiovascular diseases [2, 26, 27]. In the last decade, Tanowitz's group has obtained a bulk of evidence supporting the participation ET-1 in Chagas disease pathogenesis [107, 110, 111, 113-116]. Accordingly, patients with chronic Chagasic cardiomyopathy have elevated plasma levels of ET-1 [117]. Unfortunately, endothelial dysfunction or endothelin levels have not yet been studied during the human acute and indeterminate form of the chronic phase. As patients with chronic Chagasic cardiomyopathy also suffer some degree of heart failure, it is unclear whether the elevation of endothelin plasma levels in such patients is due to the infection or the state of congestive heart failure.

Impaired production of NO or an increase in its degradation is thought to contribute to the endothelial dysfunction in heart failure and other cardiovascular diseases. A lapse in the constitutive production of the vasodilator NO by eNOS exacerbates the ET-1 effects on the vasculature. Several factors

modulate eNOS expression or activity [118]. Among them are the NOS cofactor, tetrahydrobiopterin (BH4), and an endogenous NOS inhibitor, the asymmetric dimethyl arginine (ADMA). The notion that dysfunctional eNOS may be in part due to deficiency in BH4 has been supported by recent studies [119]. Elevated plasma levels of ADMA are found in various clinical conditions, including heart failure [120, 121]. Unfortunately, the modulators of eNOS have not been studied in Chagas disease to determine how much it differs from other cardiovascular syndromes.

In the murine model of the disease, the elevation of ET-1 occurs during a short period of the acute phase [115], suggesting a possible ET beneficial effect specific for this phase. In *T. cruzi* infected rats, endothelial dysfunction demonstrated by attenuation of the endothelium-dependent vasodilatation occurs at the end of the acute phase. Treatment with an endothelin ET_A receptor antagonist reversed this vascular dysfunction, but increased tissue parasitism and/or inflammation in the heart and skeletal muscle. It was hypothesized that ET_A receptor activation contributes to the vascular dysfunction in the acute phase of the infection probably because endothelins have a role in the cascade of events that leads to parasitism control [122]. Indeed, it seems unlikely that ET elevates during the acute phase merely in order to cause deleterious effects. The delay in parasite clearance caused by blockage of ET_A receptors in *T. cruzi*-infected rats could involve disturbance in the expression of chemokines, iNOS, and/or cytokines that are known to contribute to the control of *T. cruzi*-induced acute phase, as already discussed [40, 75-91]. This possibility was addressed in rats under pharmacological blockage of both ET receptors by bosentan [88]. Bosentan treatment increased significantly the number of circulating parasites, in accordance with a higher tissue inflammation (heart) or parasitism (diaphragm). However, bosentan treatment did not prevent the infection-induced elevation of cardiac levels of two chemokines, CCL2 and CCL5 that are known to be involved in the recruitment of macrophages and lymphocytes. As expected, greater inflammation occurs in the hearts of bosentan-treated animals at the middle of the acute phase. Also, bosentan treatment failed to inhibit the *T. cruzi*-induced increase in cardiac levels of IFN-γ and TNF-α. Actually, the cardiac levels of TNF-α in bosentan-treated rats were slightly but significantly higher than in vehicle-treated rats at the moment of greatest inflammatory response in the heart. Conversely, the cardiac IL-10 levels were lower in bosentan-treated rats some days before, a condition favorable to higher elevation of TNF- α levels. Finally, the plasma levels of nitrite/ nitrate (NOx), the NO derivatives, were significantly lower in Bosentan-treated rats [88]. ET is able to increase the expression of iNOS in vascular tissues [123] and macrophages [124]. Also, serum levels of NOx correlate with iNOS activation in *T. cruzi*-infected rats [125]. Thus, it is reasonable to hypothesize that the higher parasitemia caused by bosentan treatment in *T. cruzi*-infected rats could be due to impairment of NO synthesis catalyzed by iNOS. However, further studies are necessary to confirm this hypothesis.

ENDOTHELINS AND OTHER INFECTIONS

We believe that the higher parasitemia in *T. cruzi*-infected rats treated with bosentan occurred because endothelins participate in the cascade of events aiming at an early control of parasitism, probably because of their proinflammatory effects. This hypothesis would be reinforced if endothelins could contribute to the control of other infections.

ET-l is produced in the airways and has a powerful bronchoconstrictor effect. It has been implicated in the pathogenesis of asthma and virus-mediated airway inflammation, and may have detrimental effects in chronic obstructive pulmonary disease. In patients with obstructive pulmonary disease, sputum shows increased levels of ET-1 that correlates with the increase in plasma ET-1 levels and sputum IL-6 levels [126]. *In vitro* studies have showed that viruses or virus-derived molecules are able to increase ET-1 production by endothelial cell lines [127, 128], macrophages [6] and a bronchial epithelial cell line [129]. Accordingly, intranasal infection of mice with an *Influenza* virus causes a marked increase in the intensity and distribution of immunoreactive ET in intrapulmonary airway epithelial cells and in pockets of inflammatory mononuclear cells [130]. In myocarditis caused by inoculation of encephalomyocarditis virus, the levels of heart ET converting enzyme-1 (ECE-1) and preproET-1 and ET-1 are significantly increased, as well as the plasma levels of ET-1. Immunohistochemical analysis showed that not only endothelial cells and myocytes but also infiltrating mononuclear cells produce ET-1 protein. Treatment with bosentan had a cardioprotective effect without modifying viral replication [131]. Interestingly, circulating monocytes from HIV-infected individuals express endothelin-1 gene in contrast to those from healthy controls, indicating chronic activation of this gene in HIV-infection. In addition, cerebral macrophages in patients with HIV-encephalopathy were strongly positive for endothelin [6]. Unfortunately, these studies addressing ET production in viral infectious emphasize the pathogenic effects of elevated expression of ET-1.

ET-1 appears to have a key role in inflammatory processes associated with bacterial infection, as will be exemplified. Human, rat and guinea pig macrophages are able to produce ET-1 in response to a variety of stimuli such as the bacterial LPS and forbol ester [5, 7]. Acting *via* ET_A receptors, endothelins seem to play an important role in early cytokine/chemokine production and on granulocyte and lymphocyte mobilization in LPS-induced pleurisy [30]. Infection of a human monocytic cell line with the bacteria *Chlamydia pneumonia* induces the expression of several genes associated with acute and chronic inflammation and tissue remodeling, including ET-1 [132].

Among the pathophysiological conditions known to involve the endothelin system, sepsis shows the highest plasma levels of endothelins. ET-1 is thought to contribute to dysfunction in several vital organ systems in septic shock. Indeed, there is a strong correlation between ET-1 plasma levels and morbidity and mortality in septic patients [133]. However, there is evidence indicating that the dramatic increase in plasma ET-1 in patients with sepsis or endotoxemia is caused primarily by monocytes/macrophage-derived ET-1 rather than by endothelial cells [134]. Accordingly, peripheral blood monocytes from septic patients express significantly higher levels of ET-1 mRNA than those of healthy control individuals [135]. Recently, an interesting study

demonstrated the production of ET-1 by murine macrophages in response to gram-positive and gram-negative bacteria. Interaction of LPS to toll-like receptor 4 is sufficient to induce ET-1 production in macrophages. Pharmacological inhibition of the transcription factor NF-kB suppresses the LPS-induced ET-1 production. The authors emphasize that these findings support the notion that ET-1 production is part of the characteristic macrophage response to microbial challenge and may be a key source of ET-1 during inflammatory conditions induced by microbial infections [136].

Incubation of macrophages with yeast (*Candida albicans* and *Saccharomyces cerevisiae*) or the protozoan parasite *Leishmania major* has little or no effect on the production of ET-1 [136]. The authors do not comment on why these eukaryotic microbes were unable to induce ET-1 release by macrophage. Interestingly, *Leishmania* parasites belong to the *Trypanosomatidae* family and are the agents of a spectrum of important illnesses ranging from self-healing lesions to non-healing mucocutaneous and visceral diseases. In mammalian hosts, *Leishmania* species infect cells of the monocytes/macrophage lineage in which they proliferate within phagolysosomes. This intracellular pathogen prevents the activation of an effective immune response by inhibiting the production of a number of cytokines, particularly those involved in the inflammatory response (IL-1, TNF-α) or in T cell activation as well as the production of deadly antimicrobial agents such as nitric oxide [137]. It is exciting that an intracellular pathogen that escapes the host's immune response would fail to induce ET-1 production by murine macrophages. As far as we know, there is no other study on endothelin expression in infections by other members of the *Trypanosomatidae* family, excepting *T. cruzi*.

Among other diseases caused by pathogenic protozoa, only a few studies about malaria were found [138-140]. Patients with complicated *Plasmodium falciparum* malaria have elevated plasma ET-1 levels that correlate with levels of TNF-α. [138]. In a murine model of cerebral malaria, a deadly complication of *Plasmodium falciparum* infection, there is a striking reduction in cerebral blood flow, and large increase in the expression of ET-1 and ECE-1 mRNAs in the brain. Also, there is increased expression in mRNA of ET_A and ET_B receptors, neuronal lesion and signs of microglial cell activation [139]. Both studies reinforce a role for ET-1 in vasculopathy and malarial pathology. The cell types responsible for the increase in ET-1 levels have not been addressed by these works. Conversely, cytoadherence of *P. falciparum* parasitized erythrocytes (pRBC) to vascular endothelium is thought to contribute to the pathogenesis of severe malaria by causing microcirculatory obstruction and subsequent tissue hypoxia. IL-1 beta and hypoxia are able to increase the production of ET-1 by endothelial cell lines. Coculture of these cell lines with different strains of *P. falciparum* pRBC decrease the constitutive and IL-1- or hypoxia-induced production of ET-1 [140]. This *in vitro* modulation of ET-1 production suggested that other cell types could be involved in the enhancement of ET-1 level observed in human natural and experimental malaria.

To sum up, the role of endothelins in infectious diseases deserves more studies aiming at finding ET's beneficial effects, mainly in the early acute phase.

CONCLUDING REMARKS

The detrimental effects of endothelins in several cardiovascular diseases and some infectious diseases are well documented. However, their possible beneficial roles remain to be completely elucidated. It would be worth investigating possible endothelin roles in infections that are successfully controlled by the immune response. Chagas disease infection in rats is a good example of a successful strategy that allows the persistence of *T. cruzi* without the progressive tissue damage and fibrosis, as occur during the indeterminate form of human chronic phase. In human Chagas disease it would be important to investigate the ET-1 levels during the distinct forms of the chronic phase and early acute phase.

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