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Chapter 2

New Therapeutic Targets for the Control of Inflammatory Arthritis: A Pivotal Role for Endothelins

Maria das Graças Muller de Oliveira Henriques

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1. Introduction

Rheumatoid arthritis (RA) is a complex, debilitating, chronic, systemic autoimmune disease characterised by immunological, inflammatory and mesenchymal tissue reactions in the synovium that are accompanied by polyarticular synovitis and ultimately lead to the progressive destruction of articular and periarticular structures [1,2]. A critical factor that contributes to joint damage is the excessive production of inflammatory mediators by resident and/or infiltrating inflammatory cells. Among the main mediators involved in the join damage process are free radicals, extracellular matrix–degrading enzymes, pro-inflammatory cytokines, including interleukin(IL)-6, IL-1 and tumour necrosis factor (TNF)-α, as well as chemokines, such as CXCL1, and lipid mediators, such as leukotriene (LT)B_4 [3,4,5].

Endothelins (ETs) are a family of naturally occurring peptides [6] with well-established growth-promoting, vasoactive, and nociceptive properties that affect the function of a number of tissues and systems [7]. ETs have pathophysiological roles in pulmonary hypertension, arterial hypertension, atherosclerosis, cerebral vasospasm and inflammatory processes [8,9,10,11].

Recently, new evidence has demonstrated that endogenous endothelins (ETs) also play a role in articular inflammation by regulating inflammatory pain, edema formation, leukocyte influx and the production of inflammatory mediators. The present chapter attempts to provide an overview of the evidence accumulated to date, which suggests that ETs play a pivotal role in articular inflammation, and the blockade of these endogenous peptides can represent a promising therapeutic tool for the treatment of RA and other articular inflammatory diseases. To address this issue in a comprehensive manner, however, it is important to briefly provide some fundamental aspects of endothelin biosynthesis and release as well as information about the receptors that they interact with and the modes of action of these peptides.

2. The endothelin system

The endothelin system comprises a family of three highly conserved vasoactive peptides, which bind to two endothelin receptors (endothelin receptor types A [ETA] and B [ETB]), with differing affinities that are determined by the N-terminal domain of the peptide. ET-1 has a higher affinity than ET-2, which, in turn, has a higher affinity than ET-3. In humans, the affinity of ET-1 for the ETA receptor is 1,000-fold higher than that of ET-3 [12] (Fig 1).

ET -1, the most prominent representative of the ET family, was first identified as a potent vasoconstrictor secreted by vascular endothelial cells [13]. Since the initial description of ET-1 [14], it has become evident that in addition to modulating vascular tone, ET peptides are also involved in numerous other pathophysiological processes and are produced not only by endothelial cells but by a wide variety of cells in virtually all organs [7] (Table 1).

Tissue	Cell type	Reference
Lung	Alveolar epithelium	[15-17]
Liver	Hepatocytes	[18]
	Kupffer cells	
Skin	fibroblast	[19, 20]
Synovia	synoviocytes	[21, 22]
Heart	myocytes	[23]

Table 1. Localization of ET system in different cells

Numerous lines of evidence indicate that ET-1 acts locally via both autocrine and paracrine mechanisms in physiological and pathological situations. Contribution of the ET system to disease progression can occur due to either an increase in tissue ET-1 production or an increase in the tissue expression of its receptors. ET-1 is upregulated by angiotensin II, vasopressin, thrombin, lipopolysaccharide, insulin, TGF-β, epithelial growth factor, and EGF-2 and is downregulated by nitric oxide, prostaglandin, and natriuretic hormone [24, 25].

The release of endothelins is regulated both at the gene expression level and at the peptide synthesis level. Preproendothelins are synthesized via the transcriptional activation of the preproendothelin gene, which is regulated by c-fos and c-jun, nuclear factor-1, AP-1 and GATA-2 [26, 27]. The translational product is a 203-amino acid peptide known as preproendothelin, which is cleaved at dibasic sites by furin-like endopeptidases to form big endothelins. These biologically inactive 37- to 41-amino acid intermediates [25] are cleaved at Trp21–Val 22 by a family of endothelin-converting enzymes (ECE) to produce mature ET-1 [28, 29] (Fig 1). Three isoforms of ECE have been reported [30]: ECE-1, ECE-2 and ECE-3. Four variants of ECE-1 have been reported in humans [31], ECE-1a ECE-1b, ECE-1c and ECE-1d, which are the result of alternative splicing of ECE-1 mRNA. Interestingly, chymase, the mast cell-derived serine protease, also hydrolyses big ET-1 [1–38] into the intermediate peptide ET-1 [1–31]

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which is then readily transformed to ET-1 by neutral endopeptidase 24-11 (NEP) in tissue homogenates [32]. Recently, the chymase-dependent production of ET-1 was proposed to play an important role in cardiovascular and pulmonary pathologies [7, 33].

The ETA and ETB receptors belong to the superfamily of G-protein–coupled receptors with seven transmembrane domains and are differentially expressed according to cell type [34, 35]. The ETA receptor is found predominantly in smooth muscle cells and cardiac muscles [36]. Both receptors, however, have a fairly widespread distribution across many cell types (Table 2)

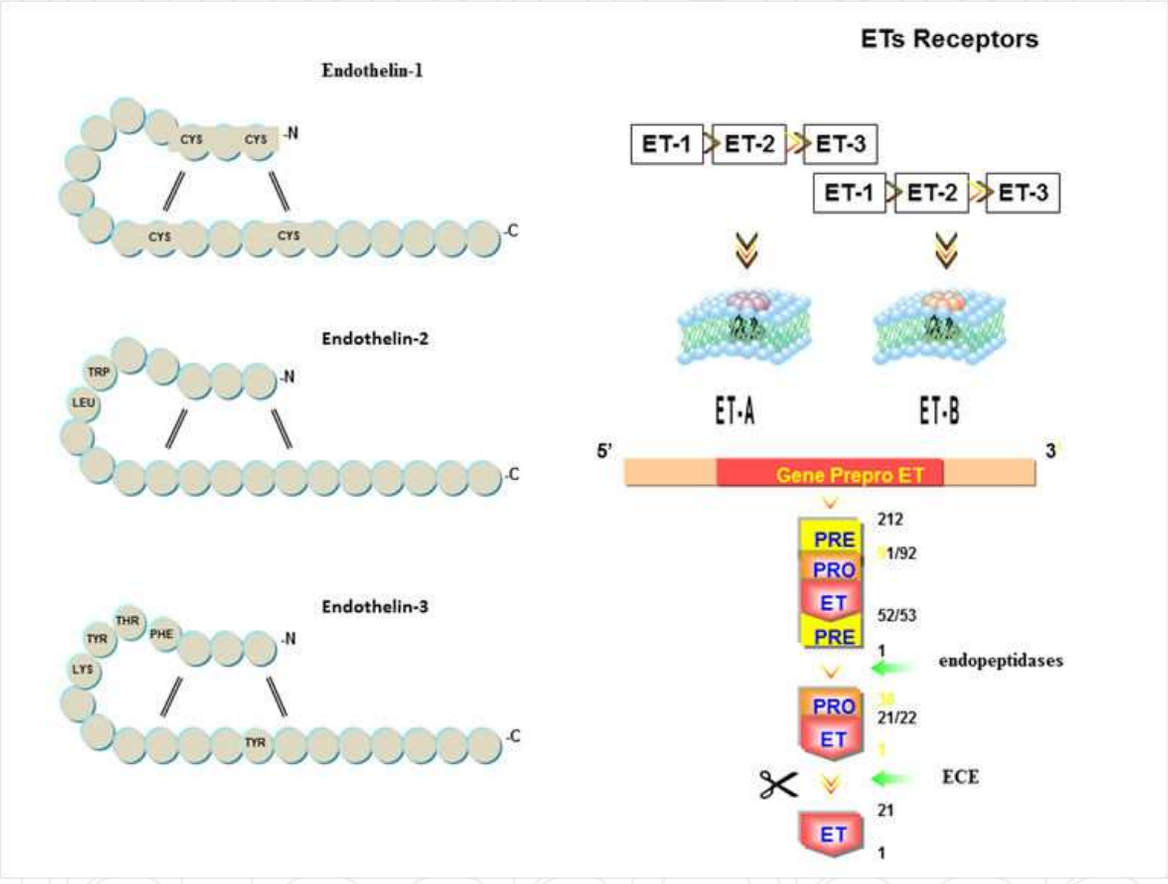

Figure 1. Endothelin structure, receptors and production

3. Endothelin signaling

The detailed mechanism by which ET induces intracellular responses remains unclear. ET receptor activation leads to diverse cellular responses through interaction with a chain of pathways that includes the G-protein-activated cell surface receptor, the coupling of G-proteins and the phospholipase (PLC) pathway as well as other G protein-activated effectors. In one of the canonical signalling pathways, ETA induced activation of phospholipase C leads to the formation of inositol triphosphate and diacylglycerol from phosphatidylinositol. Inositol

1,4,5-triphosphate (IP3] then diffuses to specific receptors on the endoplasmic reticulum and releases stored Ca2+ into the cytosol. This causes a rapid elevation in intracellular Ca2+, which, in turn, causes cellular contraction, followed by vasoconstriction [37-39].

Additionally, ET-1 is known to stimulate arachidonic acid production and prostaglandin release in rabbit iris [40], porcine coronary artery [41] and mouse paw [42]. This occurs as a result of the activation of phospholipase A2 and increased intracellular Ca2+ [43].

In addition to phospholipase activation and prostaglandin production, endothelin-1 also stimulates protein tyrosine kinases (PTK), such as FAK and RAS, in neoplastic cells [44]. The activation of PTKs results in the induction of the RAF/MEK/MAPK pathway, which subsequently stimulates the transcription of proto-oncogenes, such as c-FOS, c-MYC, c-JUN, and, in turn, activates cell growth and metastasis.

Nitric oxide (NO) is a versatile molecule with a multitude of functions, including the regulation of vascular tone, neuronal signalling and host defence [45]. In a classic ET-1 signalling pathway, ET-1 stimulates NO production in endothelial cells by activating endothelial cell NO synthase (eNOS) [46, 47] via PI3-K/Akt activation, which in turn, stimulates the phosphorylation of eNOS and subsequent NO production [47]. Interestingly, NO appears to antagonize ET-1 synthesis by inhibiting preproET-1 transcription [48].

4. Evidence for the involvement of ET-1 in rheumatoid arthritis

ET-1 has been demonstrated to participate in the pathogenesis of a number of diseases, such as sepsis, bronchial asthma and pulmonary hypertension [49]. In addition to their well-recognised vasoconstrictive properties, ETs play an important role in inflammatory reactions modulating hyperalgesia, edema formation [50-52] and cell migration [53, 54]. Considering their pro-inflammatory properties and the presence of ETs in the plasma and synovial fluid from RA patients, the participation of ETs in RA is strongly indicated. These findings will be described in the following sections.

5. Presence of endothelins in plasma and synovial fluid from human RA patients

High levels of ET-1 are detected in the synovial fluid of RA, osteoarthritis (OA), and gout patients. Plasma levels of ET-1 in patients with active RA exceed the values in patients with non-active RA. Moreover, ET-1 is secreted from macrophage-like synoviocytes, and the levels of ET-1-like immunoreactivity in synovial fluid are several times higher than those in plasma [21, 22, 55, 56]. In addition, specific 125I-labeled-ET-1-binding sites that are characteristic of the ETA receptor were localised to the media of the synovial blood vessels in sections of rheumatoid, osteoarthritic, and normal synovium, suggesting that endothelin may act locally to modulate synovial perfusion and exacerbate hypoxia in chronic arthritis.[Table 2].

Disease	Source	Number of patients	References
Gout	Serum	81	[58]
Rheumatoid Arthritis	Serum	20, 397, 23	[55, 59]
	Plasma	12	[60, 61]
	Synovial Fluid	20	[55-57]
Hypertrophic osteoarthropathy	Plasma	20	[62]

Table 2. Presence of ET-1 Serum, Pasma or Synovial Fluid from Patients

6. Evidences from *in vitro* studies

Exogenous ET-1 presents a remarkable variety of inflammatory properties, including the activation of resident and inflammatory cells and the stimulation of cytokine production [11, 63, 64], (table 3).

Accordingly, increased expression of the preproET-1 gene and significant amounts of endothelin-1 are produced by resident cells of the synovia, including endothelial cells of the synovial blood vessels [57], fibroblasts [65], articular chondrocytes [66-70], macrophage-like synoviocyte and fibroblast-like synoviocytes [21, 22].

ET-1 modulates the expression of adhesion molecules on endothelial cells and on fibroblast-like synovial cells [65], stimulates the production of fibronectin and collagen in synoviocytes [65, 71],), stimulates cytokine production on monocytes and macrophages [53, 72, 73], and regulates neutrophil adhesion and migration [9, 53, 74].

Cell Type	Effect
Endothelial cells	Production of reactive oxygen species, TNF-α, IL-1, IL-6, NO, PGE2 Expression of ICAM-1, VCAM-1, E-Selectin
Fibroblasts	Production of reactive oxygen species, proliferation, resistance to apoptosis
Macrophages	Production of TNF-α, IL-1, IL-6, IL-8, GMCSF, reactive oxygen species, Chemotaxis
Mast Cells	Degranulation, release of histamine, production of LTC_4
Neutrophils	Agregation, chemotaxis, release of PAF, elastase

Table 3. Effect of exogenous ET-1 on different cells types

In addition to its pro-inflammatory effects, ET-1 is mitogenic to articular chondrocytes [75] and activates these cells. ET-1 binds to the specific endothelin A or endothelin B receptors

expressed on chondrocytes [76, 77] and triggers a cascade of intracellular events, including phospholipase C activation [75] and the phosphorylation of p38, Akt, p44/42, and SAP/JNK, in a sequential manner [78] thereby inducing an increase in intracellular calcium [75, 79] and prostaglandin production [66]. ET-1 causes the overproduction of nitric oxide (NO) and metalloproteinase (MMP)-1 and -13 in human osteoarthritic chondrocytes [80]. The production of these enzymes seems to occur through the activation of at least two kinases, p38 MAP kinase and PKA [78]. NO seems to be a key molecule that is produced in parallel with the ET-1-induced overproduction of MMPs

Additionally, ET-1 also increases collagenase activity and decreases protein levels of tissue inhibitor of metalloproteinases 1 (TIMP-1), leading to type II collagen breakdown [81]. The endothelin-1 receptors expressed in articular chondrocytes can be up-regulated by the growth factors PDGF, EGF, IGF-1 and TGFα, which are increased in the synovial fluid of RA patients [68, 77].

It is interesting to note the age-related differences in the production of ET-1 and the expression of receptors from chondrocytes. *In vitro* studies have shown that chondrocytes obtained from older donors produce more ET-1 and express more ET-1-specific receptors (as shown by binding assays) both under basal conditions and after challenge with IL-1β or TNF-α, possibly implicating ET-1 in age-related osteoarthritis [69].

Thus, blocking the effects of ET-1 may become a useful therapeutic approach aimed at stopping cartilage destruction in rheumatic conditions such as rheumatoid arthritis and OA

7. Evidence from *in vivo* studies

Active rheumatoid arthritis is characterised by a strong inflammatory reaction and hyperplasia of synovial tissue that is an unremitting and profoundly debilitating consequence of the disease and can lead to substantial loss of function and mobility. [82, 83]. In this regard, ETs are well documented as participating in a wide variety of inflammatory and/or pain-related processes (for summary see table 4).

Animal Model	Effect	References
Paw oedema	Edema	[52, 84, 85]
	Nociception	[86-90]
	Hyperalgesia	[42, 91, 92]
Mouse cheek model	Nociception	[55, 59, 93]
Pleurisy	Cell migration/ Cytokine production	[53, 73, 85, 94]
knee-joint inflammation	Hyperalgesia/edema	[95-100]
surgical osteoarthritis	nociception	[95]

Table 4. Endothelins in Vascular Permeability and Pain.

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8. Effects of exogenous endothelins in vascular permeability and pain

ET-related peptides induce profound effects on the microvasculature *in vivo*, acting as powerful constrictors of arterioles and venules [101-103] and decreasing blood flow in rabbit and human skin [103, 104]. Exogenous ETs exhibit dual effects on vascular permeability that at first glance could be considered to be paradoxical.

Early reports demonstrated a marked inhibitory effect of ET-1 (when administered locally or intradermally) on vascular permeability. ET-1 inhibited plasma extravasation that was induced in rat or rabbit dorsal skin by several stimuli [105, 106]. ET-1 (0.5 pmol/site) also inhibited paw edema and pleural exudation induced by PAF in mice [107]. Notably, the studies that describe the anti-edematogenic effect of ETs have used the local or intradermic administration of low concentrations of ET-1 (between 0.01 pmol to 0.05 pmol). The mechanisms involved in this effect are not clear and may be a consequence of local vasoconstriction or may be explained by the differential effects of ETs on the smooth muscle of arterial and venous vasculature [108]. Nevertheless, the anti-edematogenic effect of exogenous ETs appears to be dependent both on concentration and on the vascular beds.

There are compelling data describing the edematogenic properties of exogenous ET-1. The vasoconstriction effect of ET-1 may actually be masking an edematogenic effect of the peptide because it was also found that ET-1 causes a flare reaction and oedema surrounding the ischaemic area in the human forearm [109, 110]. Accordingly, endothelin-1 (up to 10 pmol) is able to induce ETA receptor mediated oedema in the mouse hind paw [85, 87]. ET-1 markedly enhances extravasation of plasma proteins from the microvasculature in distal organs when administered intravenously [51, 111-113]. This effect is mediated indirectly via the release of PAF and TXA2 in response to ETA receptor activation [112, 114-116]. Endothelin-1 enhances neutrophil adhesion to human coronary artery endothelial cells via ETA receptors [54]. ET-1(1–30 pmol/cavity) or sarafotoxin S6c [0.1–30 pmol/cavity) also triggered edema formation and neutrophil accumulation within 6 h when injected in the synovial cavity [117].

The nociceptive properties of exogenous ET-1 are also well described. Human subjects report a deep burning pain and tenderness following ET-1 injection into the forearm [50, 109]. Recent results confirm that exogenous ET-1 is capable of evoking acute pain in humans. Spontaneous pain was found to develop rapidly after intradermal injection of ET-1 into the volar aspect of the forearm of healthy males at high concentrations (10^{-7} and 10^{-6} M). It decreasing gradually, ending 30 and 60 min after ET-1 administration, respectively [118].

Endothelin-1 triggers ETA receptor-mediated nociception, hyperalgesia and oedema in the mouse hind paw [87]. In mice, ET-1 also causes ETA receptor-mediated enhancement of capsaicin-induced nociception [86], potentiates formalin-induced nociception and paw edema [86, 119] and prostate cancer-induced pain [120].

Endothelin-1 also causes articular nociception as well as hyperalgesia to prostaglandin E2 in dogs [50] and carrageenan in rats [98] when injected into a naive knee-joint. Nociception induced by endothelin-1 in the naive articulation of the rat is mediated largely via ETA

receptors [42, 99], whereas both ETA and ETB receptors underlie its action in the joint primed (pre-inflamed) with carrageenan. Interestingly, ET-1 peptide-induced hypernociception was not altered by the inhibition of neutrophil migration or ET(B) receptor antagonism but rather by ET(A) receptor antagonism. Furthermore, LPS-induced nociception in the carrageenan-primed joint of the rat is largely mediated by endothelin release and the activation of ETB receptors within the joint itself [98]. The pro-nociceptive role of ETB receptors was confirmed by the fact that when its highly selective agonist, sarafotoxin S6c [34], was injected 72 h after priming with carrageenan, pain was increased, indicating incapacitation. Surprisingly, sarafotoxin produced an anti-nociceptive effect when it was given 24 h before either the initial injection of carrageenan into the naive joint or restimulation of the primed joint with carrageenan, ET-1, or S6c [96]. ETB activation exerts an apparent prophylactic action, inhibiting the development of inflammatory (carrageenan-induced) pain. In addition, ETB receptor-operated mechanisms limit the priming effect of carrageenan to nociception evoked by subsequent inflammatory insult. These findings dramatically illustrate the dual pro- and anti-nociceptive roles of the ETB receptors under the same inflammatory conditions. These roles are dependent upon the order in which these stimulus occur.

9. Effects of endogenous endothelins in inflammatory process

Consistent with the observed pro-inflammatory effects of endothelins, the studies with ETA and ETB receptor antagonists have confirmed the role of endothelins in a wide range of inflammatory reactions.

ETA receptor antagonists inhibit allergic paw oedema in mice and plasma extravasation during endotoxin shock in rats [121]. The ETA receptor antagonist BQ-123 inhibits eosinophil migration and lymphocyte accumulation in allergic pleurisy. BQ-123 also inhibited interleukin-5 levels in the exudate and plasma, as well as intracellular staining of interleukin-4, interleukin-5, and interferon-gamma in CD4+ lymphocytes [73]. Endogenous endothelins also participate in delayed eosinophil and neutrophil recruitment in murine pleurisy. Mononuclear and eosinophil accumulation triggered by OVA were reduced by BQ-123 (150 pmol/cavity) or bosentan (by 68 and 43% inhibition of eosinophilia) but were unaffected BQ-788, the ETB receptor antagonist. BQ-123 and bosentan also inhibited LPS-induced increases in neutrophils (by 67 and 40%) and eosinophils (by 63 and 74%) at 24 h [53, 94] and abrogated the increase in tumour necrosis factor alpha, interleukin-6 and keratinocyte-derived chemokine/CXC chemokine ligand 1 4 h after LPS stimulation [74].

Endogenous endothelins contribute to ovalbumin elicited nociceptive responses in the hind paw of sensitised mice, which are mediated locally by IL-15-triggered ETA and ETB receptor mechanisms [42, 88, 122]. Interestingly, ET-1 peptide-induced hypernociception was not altered by the inhibition of neutrophil migration or ET(B) receptor antagonism but rather by ET(A) receptor antagonism. Furthermore, ET(A), but not ET(B), receptor antagonism inhibited antigen-induced PGE[2] production, whereas either the selective or combined blockade of ET(A) and/or ET(B) receptors reduced antigen challenge-induced hypernociception and neutrophil recruitment [122].

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10. Protective effect of the dual ET receptor antagonist on RA in animal models

As indicated above, exogenous ET-1 exhibits well established inflammatory properties and elicits acute nociception. There is also compelling evidence that endogenous endothelins play a role in different aspects of the inflammatory reaction and hyperalgesia. However, the implication of endothelins in the inflammatory process during experimental rheumatoid arthritis was only recently addressed. Most of these studies used the selective ETA receptor antagonist BQ123, the selective ETB receptor antagonist BQ788, or the dual ET receptor antagonist bosentan, which is the prototype sentan-class drug and was first approved by the US Food and Drug Administration (FDA) for human use in pulmonary arterial hypertension [123, 124].

In the murine model of zymosan-induced arthritis, the intra-articular administration of selective ETA or ETB receptor antagonists (BQ-123 and BQ-788, respectively) markedly reduced knee joint edema formation and neutrophil influx into the synovial cavity 6 and 24 h after stimulation. Moreover, increased expression of pre-pro-ET-1 mRNA and the ETA and ETB receptors in knee joint synovial tissue was observed in parallel with the inflammatory process [117]. Likewise, the dual blockade of ETA/ETB with bosentan (10 mg/kg, i.v.) also reduced edema formation and neutrophil counts 6 h after zymosan stimulation. Pretreatment with BQ-123 or BQ-788 (i.a.; 15 pmol/cavity) also decreased zymosan-induced TNF production within 6 h, keratinocyte-derived chemokine/CXCL1 production within 24 h, and leukotriene B4 at both time points. These findings suggest that endogenous ETs contribute to knee joint inflammation, acting through ETA and ETB receptors to modulate edema formation, neutrophil recruitment, and the production of inflammatory mediators [117].

Daily oral administration of bosentan significantly attenuated knee joint swelling and inflammation to an extent that was comparable to dexamethasone in antigen-induced arthritis (AIA). In addition, bosentan reduced inflammatory mechanical hyperalgesia. Chronic bosentan administration also inhibited joint swelling and protected against inflammation and joint destruction during AIA flare-up reactions. Unlike in the zymosan-induced arthritis model, the use of the ETA-selective antagonist ambrisentan failed to promote any detectable anti-inflammatory or antinociceptive activity in the AIA study [125].

Moreover, the lipid anti-inflammatory mediator lipoxin A_4 was described as exerting anti-inflammatory effects on articular inflammation, inhibiting oedema and neutrophil influx and the levels of preproET-1 mRNA, KC/CXCL1, LTB_4 and TNF-α through a mechanism that involved the inhibition of ET-1 expression and its effects. Likewise, lipoxin A_4 treatment also inhibited ET-1-induced oedema formation and neutrophil influx into mouse knee joints [126].

The efficacy of the dual ET receptor antagonist bosentan was described in the collagen-induced arthritis (CIA) model, which is the animal model that best resembles human RA [127]. Oral treatment with bosentan (100 mg/kg) markedly ameliorated the clinical aspects of CIA (visual clinical score, paw swelling and hyperalgesia). Bosentan treatment also reduced joint damage,

leukocyte infiltration and proinflammatory cytokine levels (IL-1β, TNF-α and IL-17) in the joint tissues. Bosentan treatment also inhibited the preproET mRNA expression that is elevated in the lymph nodes of arthritic mice. In this same article, Donate and co-workers [127] demonstrated that pre-pro-ET mRNA expression increased in PBMCs from rheumatoid arthritis (RA) patients but returned to basal levels in PBMCs from patients undergoing anti-TNF therapy. Further supporting the involvement of TNF-α in the upregulation of ET system genes, the authors showed that TNF-α increased the expression of pre-pro-ET-1, ETA and ETB in PBMCs from healthy donors and RA patients. TNF-α also increased the expression of IL-1β mRNA in PBMCs. Interestingly, the effect of TNF-α on the ET system genes was more prominent in cells from RA patients than in cells from healthy donors. However, this effect was not observed for IL-1β expression, suggesting a specific effect of TNF-α on the ET system.

11. Concluding remarks

Taken together, these data highlight the importance of ETs in the context of articular inflammation suggesting a central role for these peptides and represent innovative and promising therapeutic tools for the treatment of RA (Fig 2).

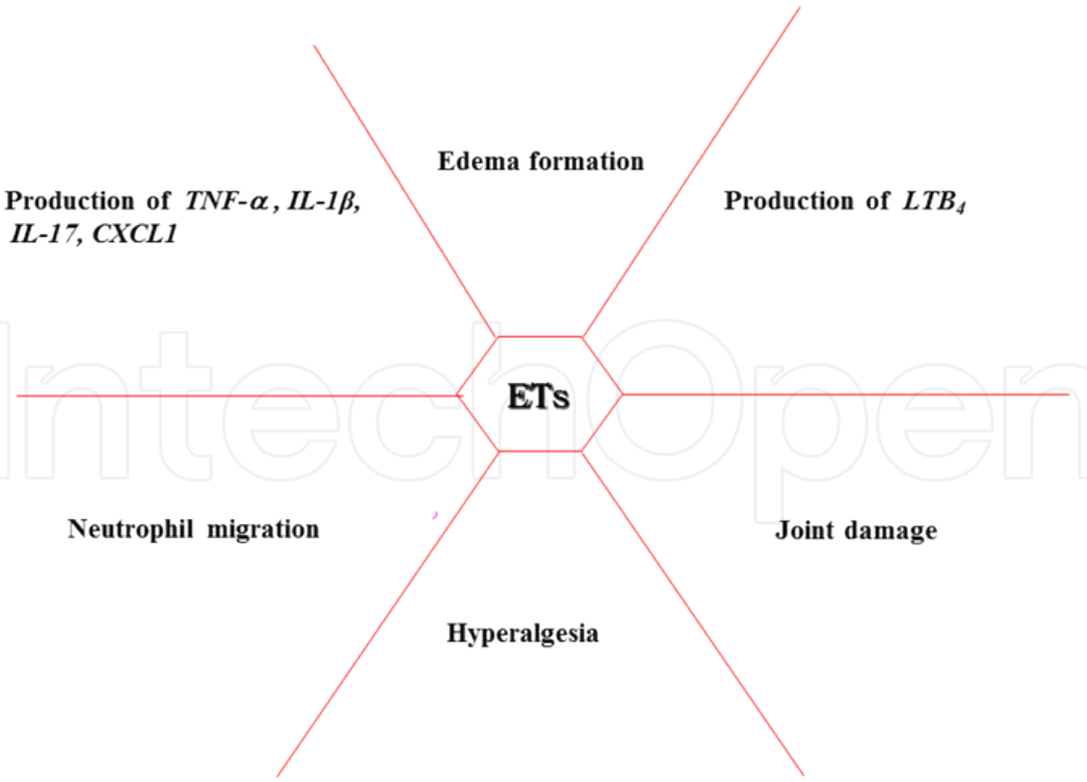

Figure 2. Role of endogenous endothelins in development of RA

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Author details

Maria das Graças Muller de Oliveira Henriques*

Address all correspondence to: gracahenriques@fiocruz.br

Laboratory of Applied Pharmacology, Department of Pharmacolgy, Farmanguinhos, Oswaldo Cruz Foundation (FIOCRUZ), Brazil

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