We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,300

Open access books available

172,000

International authors and editors

190M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

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

Maria das Graças Muller de Oliveira Henriques

Additional information is available at the end of the chapter

<http://dx.doi.org/10.5772/53738>

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 joint 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)B₄ [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]

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, Plasma 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 synovio-cyte 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 TGF α , 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-1 β 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/	[53, 73, 85, 94]
	Cytokine production	
knee-joint inflammation	Hyperalgesia/edema	[95-100]
surgical osteoarthritis	nociception	[95]

Table 4. Endothelins in Vascular Permeability and Pain.

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 S_{6c} (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 14 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 PGE₂ 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].

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 A₄ was described as exerting anti-inflammatory effects on articular inflammation, inhibiting oedema and neutrophil influx and the levels of preproET-1 mRNA, KC/CXCL1, LTB₄ and TNF- α through a mechanism that involved the inhibition of ET-1 expression and its effects. Likewise, lipoxin A₄ 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-1 β , 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-1 β 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-1 β 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

Acknowledgements

The author wish to thank the support of CNPq; CAPES and FAPERJ.

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

References

- [1] Arend WP. The innate immune system in rheumatoid arthritis. *Arthritis Rheum.* 2001 Oct;44(10):2224-34. PubMed PMID: 11665962. eng.
- [2] Yamamura Y, Gupta R, Morita Y, He X, Pai R, Endres J, et al. Effector function of resting T cells: activation of synovial fibroblasts. *J Immunol.* 2001 Feb;166(4):2270-5. PubMed PMID: 11160281. eng.
- [3] Maini RN, Taylor PC, Paleolog E, Charles P, Ballara S, Brennan FM, et al. Anti-tumour necrosis factor specific antibody (infliximab) treatment provides insights into the pathophysiology of rheumatoid arthritis. *Ann Rheum Dis.* 1999 Nov;58 Suppl 1:I56-60. PubMed PMID: 10577974. Pubmed Central PMCID: PMC1766574. eng.
- [4] Feldmann M, Bondeson J, Brennan FM, Foxwell BM, Maini RN. The rationale for the current boom in anti-TNFalpha treatment. Is there an effective means to define therapeutic targets for drugs that provide all the benefits of anti-TNFalpha and minimise hazards? *Ann Rheum Dis.* 1999 Nov;58 Suppl 1:I27-31. PubMed PMID: 10577970. Pubmed Central PMCID: PMC1766587. eng.
- [5] Lajas C, Abasolo L, Bellajdel B, Hernández-García C, Carmona L, Vargas E, et al. Costs and predictors of costs in rheumatoid arthritis: a prevalence-based study. *Arthritis Rheum.* 2003 Feb;49(1):64-70. PubMed PMID: 12579595. eng.
- [6] Usuki S, Saitoh T, Sawamura T, Suzuki N, Shigemitsu S, Yanagisawa M, et al. Increased maternal plasma concentration of endothelin-1 during labor pain or on delivery and the existence of a large amount of endothelin-1 in amniotic fluid. *Gynecol Endocrinol.* 1990 Jun;4(2):85-97. PubMed PMID: 2204252. eng.

- [7] Iglarz M, Clozel M. At the heart of tissue: endothelin system and end-organ damage. *Clin Sci (Lond)*. 2010 Dec;119(11):453-63. PubMed PMID: 20712600. eng.
- [8] Masaki T. Historical review: Endothelin. *Trends Pharmacol Sci*. 2004 Apr;25(4):219-24. PubMed PMID: 15063086. eng.
- [9] Dhaun N, Pollock DM, Goddard J, Webb DJ. Selective and mixed endothelin receptor antagonism in cardiovascular disease. *Trends Pharmacol Sci*. 2007 Nov;28(11):573-9. PubMed PMID: 17950470. eng.
- [10] Khodorova A, Zou S, Ren K, Dubner R, Davar G, Strichartz G. Dual Roles for Endothelin-B Receptors in Modulating Adjuvant-Induced Inflammatory Hyperalgesia in Rats. *Open Pain J*. 2009;2:30-40. PubMed PMID: 20559459. Pubmed Central PMCID: PMC2886510. ENG.
- [11] Rae, G.A. & Henriques, MG. Endothelins in inflammation Dekker M, editor. New York 1998. 163-202 p.
- [12] Wagner OF, Christ G, Wojta J, Vierhapper H, Parzer S, Nowotny PJ, et al. Polar secretion of endothelin-1 by cultured endothelial cells. *J Biol Chem*. 1992 Aug;267(23):16066-8. PubMed PMID: 1644793. eng.
- [13] Hickey KA, Rubanyi G, Paul RJ, Highsmith RF. Characterization of a coronary vasoconstrictor produced by cultured endothelial cells. *Am J Physiol*. 1985 May;248(5 Pt 1):C550-6. PubMed PMID: 3993773. eng.
- [14] Yanagisawa M, Kurihara H, Kimura S, Goto K, Masaki T. A novel peptide vasoconstrictor, endothelin, is produced by vascular endothelium and modulates smooth muscle Ca^{2+} channels. *J Hypertens Suppl*. 1988 Dec;6(4):S188-91. PubMed PMID: 2853725. eng.
- [15] Markewitz BA, Kohan DE, Michael JR. Endothelin-1 synthesis, receptors, and signal transduction in alveolar epithelium: evidence for an autocrine role. *Am J Physiol*. 1995 Feb;268(2 Pt 1):L192-200. PubMed PMID: 7864140. eng.
- [16] Sun G, De Angelis G, Nucci F, Ackerman V, Bellini A, Mattoli S. Functional analysis of the preproendothelin-1 gene promoter in pulmonary epithelial cells and monocytes. *Biochem Biophys Res Commun*. 1996 Apr;221(3):647-52. PubMed PMID: 8630015. eng.
- [17] Odoux C, Crestani B, Lebrun G, Rolland C, Aubin P, Seta N, et al. Endothelin-1 secretion by alveolar macrophages in systemic sclerosis. *Am J Respir Crit Care Med*. 1997 Nov;156(5):1429-35. PubMed PMID: 9372656. eng.
- [18] Gandhi CR, Harvey SA, Olson MS. Hepatic effects of endothelin: metabolism of (125I)endothelin-1 by liver-derived cells. *Arch Biochem Biophys*. 1993 Aug;305(1):38-46. PubMed PMID: 8342954. eng.
- [19] Kawaguchi Y, Suzuki K, Hara M, Hidaka T, Ishizuka T, Kawagoe M, et al. Increased endothelin-1 production in fibroblasts derived from patients with systemic sclerosis.

- Ann Rheum Dis. 1994 Aug;53(8):506-10. PubMed PMID: 7944634. Pubmed Central PMCID: PMC1005389. eng.
- [20] Brenner M, Degitz K, Besch R, Berking C. Differential expression of melanoma-associated growth factors in keratinocytes and fibroblasts by ultraviolet A and ultraviolet B radiation. *Br J Dermatol*. 2005 Oct;153(4):733-9. PubMed PMID: 16181453. eng.
- [21] Yoshida H, Ohhara M, Ohsumi K. Production of endothelin-1 by cultured human synoviocytes. *Clin Chim Acta*. 1997 Mar;259(1-2):187-9. PubMed PMID: 9086307. eng.
- [22] Yoshida H, Imafuku Y, Ohhara M, Miyata M, Kasukawa R, Ohsumi K, et al. Endothelin-1 production by human synoviocytes. *Ann Clin Biochem*. 1998 Mar;35 (Pt 2):290-4. PubMed PMID: 9547903. eng.
- [23] Amedeo Modesti P, Zecchi-Orlandini S, Vanni S, Polidori G, Bertolozzi I, Perna AM, et al. Release of preformed Ang II from myocytes mediates angiotensinogen and ET-1 gene overexpression in vivo via AT1 receptor. *J Mol Cell Cardiol*. 2002 Nov;34(11):1491-500. PubMed PMID: 12431448. eng.
- [24] Rubanyi GM, Polokoff MA. Endothelins: molecular biology, biochemistry, pharmacology, physiology, and pathophysiology. *Pharmacol Rev*. 1994 Sep;46(3):325-415. PubMed PMID: 7831383. eng.
- [25] Kedzierski RM, Yanagisawa M. Endothelin system: the double-edged sword in health and disease. *Annu Rev Pharmacol Toxicol*. 2001;41:851-76. PubMed PMID: 11264479. eng.
- [26] Inoue A, Yanagisawa M, Takuwa Y, Mitsui Y, Kobayashi M, Masaki T. The human preproendothelin-1 gene. Complete nucleotide sequence and regulation of expression. *J Biol Chem*. 1989 Sep;264(25):14954-9. PubMed PMID: 2670930. eng.
- [27] Yanagisawa M, Inoue A, Takuwa Y, Mitsui Y, Kobayashi M, Masaki T. The human preproendothelin-1 gene: possible regulation by endothelial phosphoinositide turnover signaling. *J Cardiovasc Pharmacol*. 1989;13 Suppl 5:S13-7; discussion S8. PubMed PMID: 2473287. eng.
- [28] Xu D, Emoto N, Giaid A, Slaughter C, Kaw S, deWit D, et al. ECE-1: a membrane-bound metalloprotease that catalyzes the proteolytic activation of big endothelin-1. *Cell*. 1994 Aug;78(3):473-85. PubMed PMID: 8062389. eng.
- [29] McMahon EG, Palomo MA, Moore WM, McDonald JF, Stern MK. Phosphoramidon blocks the pressor activity of porcine big endothelin-1-(1-39) in vivo and conversion of big endothelin-1-(1-39) to endothelin-1-(1-21) in vitro. *Proc Natl Acad Sci U S A*. 1991 Feb;88(3):703-7. PubMed PMID: 1992461. Pubmed Central PMCID: PMC50881. eng.
- [30] D'Orléans-Juste P, Plante M, Honoré JC, Carrier E, Labonté J. Synthesis and degradation of endothelin-1. *Can J Physiol Pharmacol*. 2003 Jun;81(6):503-10. PubMed PMID: 12839262. eng.

- [31] Valdenaire O, Rohrbacher E, Mattei MG. Organization of the gene encoding the human endothelin-converting enzyme (ECE-1). *J Biol Chem*. 1995 Dec;270(50):29794-8. PubMed PMID: 8530372. eng.
- [32] Hayasaki-Kajiwara Y, Naya N, Shimamura T, Iwasaki T, Nakajima M. Endothelin generating pathway through endothelin1-31 in human cultured bronchial smooth muscle cells. *Br J Pharmacol*. 1999 Jul;127(6):1415-21. PubMed PMID: 10455291. Pubmed Central PMCID: PMC1760661. eng.
- [33] D'Orléans-Juste P, Houde M, Rae GA, Bkaily G, Carrier E, Simard E. Endothelin-1 (1-31): from chymase-dependent synthesis to cardiovascular pathologies. *Vascul Pharmacol*. 2008 Aug-Sep;49(2-3):51-62. PubMed PMID: 18675382. eng.
- [34] Arai H, Hori S, Aramori I, Ohkubo H, Nakanishi S. Cloning and expression of a cDNA encoding an endothelin receptor. *Nature*. 1990 Dec 20-27;348(6303):730-2. PubMed PMID: 2175396. eng.
- [35] Sakurai T, Yanagisawa M, Takuwa Y, Miyazaki H, Kimura S, Goto K, et al. Cloning of a cDNA encoding a non-isopeptide-selective subtype of the endothelin receptor. *Nature*. 1990 Dec 20-27;348(6303):732-5. PubMed PMID: 2175397. eng.
- [36] Huggins JP, Pelton JT, Miller RC. The structure and specificity of endothelin receptors: their importance in physiology and medicine. *Pharmacol Ther*. 1993;59(1):55-123. PubMed PMID: 8259382. eng.
- [37] Simonson MS, Dunn MJ. Cellular signaling by peptides of the endothelin gene family. *FASEB J*. 1990 Sep;4(12):2989-3000. PubMed PMID: 2168326. eng.
- [38] Simonson MS, Osanai T, Dunn MJ. Endothelin isopeptides evoke Ca^{2+} signaling and oscillations of cytosolic free (Ca^{2+}) in human mesangial cells. *Biochim Biophys Acta*. 1990 Oct;1055(1):63-8. PubMed PMID: 2171677. eng.
- [39] Simonson MS, Dunn MJ. Endothelin. Pathways of transmembrane signaling. *Hypertension*. 1990 Feb;15(2 Suppl):I5-12. PubMed PMID: 2153630. eng.
- [40] Abdel-Latif AA, Yousufzai SY, el-Mowafy AM, Ye Z. Prostaglandins mediate the stimulatory effects of endothelin-1 on cyclic adenosine monophosphate accumulation in ciliary smooth muscle isolated from bovine, cat, and other mammalian species. *Invest Ophthalmol Vis Sci*. 1996 Feb;37(2):328-38. PubMed PMID: 8603837. eng.
- [41] Suzuki Y, Tanoi C, Shibuya M, Sugita K, Masuzawa-Ito K, Asano M. Different utilization of Ca^{2+} in the contractile action of endothelin-1 on cerebral, coronary and mesenteric arteries of the dog. *Eur J Pharmacol*. 1992 Sep;219(3):401-8. PubMed PMID: 1425968. eng.
- [42] Verri W, Cunha T, Parada C, Wei X, Ferreira S, Liew F, et al. IL-15 mediates immune inflammatory hypernociception by triggering a sequential release of IFN-gamma, endothelin, and prostaglandin. *Proceedings of the National Academy of Sciences of the*

United States of America. 2006 JUN 20 2006;103(25):9721-5. PubMed PMID: WOS:000238660400060. English.

- [43] Suzuki S, Suzuki A, Kajikuri J, Itoh T. Endothelin-1-induced prostaglandin E2 production: modulation of contractile response to endothelin-1 in porcine coronary artery. *Eur J Pharmacol.* 1992 Jun;217(1):97-100. PubMed PMID: 1397025. eng.
- [44] Nelson J, Bagnato A, Battistini B, Nisen P. The endothelin axis: emerging role in cancer. *Nat Rev Cancer.* 2003 Feb;3(2):110-6. PubMed PMID: 12563310. eng.
- [45] Albrecht EW, Stegeman CA, Heeringa P, Henning RH, van Goor H. Protective role of endothelial nitric oxide synthase. *J Pathol.* 2003 Jan;199(1):8-17. PubMed PMID: 12474221. eng.
- [46] Liu S, Premont RT, Kontos CD, Huang J, Rockey DC. Endothelin-1 activates endothelial cell nitric-oxide synthase via heterotrimeric G-protein betagamma subunit signaling to protein kinase B/Akt. *J Biol Chem.* 2003 Dec;278(50):49929-35. PubMed PMID: 14523027. eng.
- [47] Herrera M, Hong NJ, Ortiz PA, Garvin JL. Endothelin-1 inhibits thick ascending limb transport via Akt-stimulated nitric oxide production. *J Biol Chem.* 2009 Jan;284(3):1454-60. PubMed PMID: 19033447. Pubmed Central PMCID: PMC2615526. eng.
- [48] Alonso D, Radomski MW. The nitric oxide-endothelin-1 connection. *Heart Fail Rev.* 2003 Jan;8(1):107-15. PubMed PMID: 12652164. eng.
- [49] Shah R. Endothelins in health and disease. *Eur J Intern Med.* 2007 Jul;18(4):272-82. PubMed PMID: 17574100. eng.
- [50] Ferreira SH, Romitelli M, de Nucci G. Endothelin-1 participation in overt and inflammatory pain. *J Cardiovasc Pharmacol.* 1989;13 Suppl 5:S220-2. PubMed PMID: 2473319. eng.
- [51] Sirois MG, Filep JG, Rousseau A, Fournier A, Plante GE, Sirois P. Endothelin-1 enhances vascular permeability in conscious rats: role of thromboxane A2. *Eur J Pharmacol.* 1992 Apr;214(2-3):119-25. PubMed PMID: 1516634. eng.
- [52] SAMPAIO A, RAE G, DORLEANSJUSTE P, HENRIQUES M. ET(A) RECEPTOR ANTAGONISTS INHIBIT ALLERGIC INFLAMMATION IN THE MOUSE. *Journal of Cardiovascular Pharmacology.* 1995 1995;26:S416-S8. PubMed PMID: WOS:A1995TH91200122. English.
- [53] Sampaio A, Rae G, Henriques M. Participation of endogenous endothelins in delayed eosinophil and neutrophil recruitment in mouse pleurisy. *Inflammation Research.* 2000 APR 2000;49(4):170-6. PubMed PMID: WOS:000087042300006. English.
- [54] Zouki C, Baron C, Fournier A, Filep JG. Endothelin-1 enhances neutrophil adhesion to human coronary artery endothelial cells: role of ET(A) receptors and platelet-acti-

- vating factor. *Br J Pharmacol*. 1999 Jun;127(4):969-79. PubMed PMID: 10433505. Pubmed Central PMCID: PMC1566081. eng.
- [55] Haq A, El-Ramahi K, Al-Dalaan A, Al-Sedairy ST. Serum and synovial fluid concentrations of endothelin-1 in patients with rheumatoid arthritis. *J Med*. 1999;30(1-2): 51-60. PubMed PMID: 10515240. eng.
- [56] Miyasaka N, Hirata Y, Ando K, Sato K, Morita H, Shichiri M, et al. Increased production of endothelin-1 in patients with inflammatory arthritides. *Arthritis Rheum*. 1992 Apr;35(4):397-400. PubMed PMID: 1567488. eng.
- [57] Wharton J, Rutherford RA, Walsh DA, Mapp PI, Knock GA, Blake DR, et al. Autoradiographic localization and analysis of endothelin-1 binding sites in human synovial tissue. *Arthritis Rheum*. 1992 Aug;35(8):894-9. PubMed PMID: 1642655. eng.
- [58] Lebedeva MV, Stakhova TI, Zaitseva LI, Selivanova OI, Severova MM. (Antihypertensive therapy optimization and endothelial function in patients with gout and chronic urate tubulointerstitial nephritis). *Ter Arkh*. 2010;82(6):43-6. PubMed PMID: 20731110. rus.
- [59] Panoulas VF, Douglas KM, Smith JP, Taffé P, Stavropoulos-Kalinoglou A, Toms TE, et al. Polymorphisms of the endothelin-1 gene associate with hypertension in patients with rheumatoid arthritis. *Endothelium*. 2008 Jul-Aug;15(4):203-12. PubMed PMID: 18663623. eng.
- [60] Pache M, Schwarz HA, Kaiser HJ, Wüest P, Klöti M, Dubler B, et al. Elevated plasma endothelin-1 levels and vascular dysregulation in patients with rheumatoid arthritis. *Med Sci Monit*. 2002 Sep;8(9):CR616-9. PubMed PMID: 12218941. eng.
- [61] Ikonomidis I, Lekakis JP, Nikolaou M, Paraskevaidis I, Andreadou I, Kaplanoglou T, et al. Inhibition of interleukin-1 by anakinra improves vascular and left ventricular function in patients with rheumatoid arthritis. *Circulation*. 2008 May;117(20):2662-9. PubMed PMID: 18474811. eng.
- [62] Silveri F, De Angelis R, Argentati F, Brecciaroli D, Muti S, Cervini C. Hypertrophic osteoarthropathy: endothelium and platelet function. *Clin Rheumatol*. 1996 Sep; 15(5):435-9. PubMed PMID: 8894355. eng.
- [63] Fonseca C, Abraham D, Renzoni EA. Endothelin in pulmonary fibrosis. *Am J Respir Cell Mol Biol*. 2011 Jan;44(1):1-10. PubMed PMID: 20448055. eng.
- [64] Khimji AK, Rockey DC. Endothelin--biology and disease. *Cell Signal*. 2010 Nov; 22(11):1615-25. PubMed PMID: 20466059. eng.
- [65] Schwarting A, Schlaak J, Lotz J, Pfers I, Meyer zum Büschenfelde KH, Mayet WJ. Endothelin-1 modulates the expression of adhesion molecules on fibroblast-like synovial cells (FLS). *Scand J Rheumatol*. 1996;25(4):246-56. PubMed PMID: 8792802. eng.
- [66] Khatib AM, Ribault D, Quintero M, Barbara A, Fiet J, Mitrovic DR. The mechanism of inhibition of endothelin-1-induced stimulation of DNA synthesis in rat articular

- chondrocytes. *Mol Cell Endocrinol.* 1997 Sep;132(1-2):25-31. PubMed PMID: 9324043. eng.
- [67] Appleton CT, McErlain DD, Henry JL, Holdsworth DW, Beier F. Molecular and histological analysis of a new rat model of experimental knee osteoarthritis. *Ann N Y Acad Sci.* 2007 Nov;1117:165-74. PubMed PMID: 17646269. eng.
- [68] Usmani SE, Appleton CT, Beier F. Transforming growth factor-alpha induces endothelin receptor A expression in osteoarthritis. *J Orthop Res.* 2012 Sep;30(9):1391-7. PubMed PMID: 22407503. eng.
- [69] Khatib AM, Lomri A, Mitrovic RD, Moldovan F. Articular chondrocyte aging and endothelin-1. *Cytokine.* 2007 Jan;37(1):6-13. PubMed PMID: 17382552. eng.
- [70] Vallender TW, Lahn BT. Localized methylation in the key regulator gene endothelin-1 is associated with cell type-specific transcriptional silencing. *FEBS Lett.* 2006 Aug;580(18):4560-6. PubMed PMID: 16870175. eng.
- [71] Gutierrez S, Palacios I, Egido J, Gómez-Garre D, Hernández P, González E, et al. Endothelin-1 induces loss of proteoglycans and enhances fibronectin and collagen production in cultured rabbit synovial cells. *Eur J Pharmacol.* 1996 Apr;302(1-3):191-7. PubMed PMID: 8791007. eng.
- [72] Speciale L, Roda K, Saresella M, Taramelli D, Ferrante P. Different endothelins stimulate cytokine production by peritoneal macrophages and microglial cell line. *Immunology.* 1998 Jan;93(1):109-14. PubMed PMID: 9536126. Pubmed Central PMCID: PMC1364113. eng.
- [73] Sampaio A, Rae G, Henriques M. Role of endothelins on lymphocyte accumulation in allergic pleurisy. *Journal of Leukocyte Biology.* 2000 FEB 2000;67(2):189-95. PubMed PMID: WOS:000086630800007. English.
- [74] Sampaio A, Rae G, das Gracas M, Henriques M. Effects of endothelin ETA receptor antagonism on granulocyte and lymphocyte accumulation in LPS-induced inflammation. *Journal of Leukocyte Biology.* 2004 JUL 2004;76(1):210-6. PubMed PMID: WOS:000222283400026. English.
- [75] Stojilkovic SS, Vukicevic S, Luyten FP. Calcium signaling in endothelin- and platelet-derived growth factor-stimulated chondrocytes. *J Bone Miner Res.* 1994 May;9(5):705-14. PubMed PMID: 8053400. eng.
- [76] Khatib AM, Lomri A, Moldovan F, Soliman H, Fiet J, Mitrovic DR. Endothelin 1 receptors, signal transduction and effects on DNA and proteoglycan synthesis in rat articular chondrocytes. *Cytokine.* 1998 Sep;10(9):669-79. PubMed PMID: 9770328. eng.
- [77] Messai H, Panasyuk A, Khatib A, Barbara A, Mitrovic DR. Endothelin-1 receptors on cultured rat articular chondrocytes: regulation by age, growth factors, and cytokines, and effect on cAMP production. *Mech Ageing Dev.* 2001 May;122(6):519-31. PubMed PMID: 11295169. eng.

- [78] Manacu C, Martel-Pelletier J, Roy-Beaudry M, Pelletier J, Fernandes J, Shipkolye F, et al. Endothelin-1 in osteoarthritic chondrocytes triggers nitric oxide production and upregulates collagenase production. *Arthritis Research & Therapy*. 2005 2005;7(2):R324-R32. PubMed PMID: WOS:000227579900023. English.
- [79] Kinoshita A, Tamura T, Aoki C, Nakanishi T, Sobue S, Suzuki F, et al. Demonstration of endothelin (ET) receptors on cultured rabbit chondrocytes and stimulation of DNA synthesis and calcium influx by ET-1 via its receptors. *Cell Biol Int*. 1995 Aug; 19(8):647-54. PubMed PMID: 7550073. eng.
- [80] Khatib AM, Siegfried G, Messai H, Moldovan F, Mitrovic DR. Mechanism of inhibition of endothelin-1-stimulated proteoglycan and collagen synthesis in rat articular chondrocytes. *Cytokine*. 2002 Mar;17(5):254-61. PubMed PMID: 12027406. eng.
- [81] Roy-Beaudry M, Martel-Pelletier J, Pelletier JP, M'Barek KN, Christgau S, Shipkolye F, et al. Endothelin 1 promotes osteoarthritic cartilage degradation via matrix metalloprotease 1 and matrix metalloprotease 13 induction. *Arthritis Rheum*. 2003 Oct; 48(10):2855-64. PubMed PMID: 14558091. eng.
- [82] Firestein GS. Evolving concepts of rheumatoid arthritis. *Nature*. 2003 May;423(6937): 356-61. PubMed PMID: 12748655. eng.
- [83] McDougall JJ. Arthritis and pain. Neurogenic origin of joint pain. *Arthritis Res Ther*. 2006;8(6):220. PubMed PMID: 17118212. Pubmed Central PMCID: PMC1794504. eng.
- [84] Andrade D, Serra R, Svensjö E, Lima AP, Ramos ES, Fortes FS, et al. Trypanosoma cruzi invades host cells through the activation of endothelin and bradykinin receptors: a converging pathway leading to chagasic vasculopathy. *Br J Pharmacol*. 2012 Mar;165(5):1333-47. PubMed PMID: 21797847. Pubmed Central PMCID: PMC3372720. eng.
- [85] Kassuya CA, Rogerio AP, Calixto JB. The role of ET(A) and ET(B) receptor antagonists in acute and allergic inflammation in mice. *Peptides*. 2008 Aug;29(8):1329-37. PubMed PMID: 18632188. eng.
- [86] Piovezan AP, D'Orléans-Juste P, Tonussi CR, Rae GA. Effects of endothelin-1 on capsaicin-induced nociception in mice. *Eur J Pharmacol*. 1998 Jun;351(1):15-22. PubMed PMID: 9698200. eng.
- [87] Piovezan AP, D'Orléans-Juste P, Souza GE, Rae GA. Endothelin-1-induced ET(A) receptor-mediated nociception, hyperalgesia and oedema in the mouse hind-paw: modulation by simultaneous ET(B) receptor activation. *Br J Pharmacol*. 2000 Mar; 129(5):961-8. PubMed PMID: 10696096. Pubmed Central PMCID: PMC1571931. eng.
- [88] Piovezan A, D'Orleans-Juste P, Frighetto M, Souza G, Henriques M, Rae G. Endothelins contribute towards nociception induced by antigen in ovalbumin-sensitised mice. *British Journal of Pharmacology*. 2004 FEB 2004;141(4):755-63. PubMed PMID: WOS:000220379200024. English.

- [89] Piovezan AP, D'Orléans-Juste P, Tonussi CR, Rae GA. Endothelins potentiate formalin-induced nociception and paw edema in mice. *Can J Physiol Pharmacol.* 1997 Jun; 75(6):596-600. PubMed PMID: 9276135. eng.
- [90] Motta EM, Chichorro JG, D'Orléans-Juste P, Rae GA. Roles of endothelin ETA and ETB receptors in nociception and chemical, thermal and mechanical hyperalgesia induced by endothelin-1 in the rat hindpaw. *Peptides.* 2009 May;30(5):918-25. PubMed PMID: 19428770. eng.
- [91] Verri W, Schivo I, Cunha T, Liew F, Ferreira S, Cunha F. Interleukin-18 induces mechanical hypernociception in rats via endothelin acting on ETB receptors in a morphine-sensitive manner. *Journal of Pharmacology and Experimental Therapeutics.* 2004 AUG 2004;310(2):710-7. PubMed PMID: WOS:000222728500035. English.
- [92] Verri W, Cunha T, Parada C, Poole S, Liew F, Ferreira S, et al. Antigen-induced inflammatory mechanical hypernociception in mice is mediated by IL-18. *Brain Behavior and Immunity.* 2007 JUL 2007;21(5):535-43. PubMed PMID: WOS:000247652200004. English.
- [93] Gomes LO, Hara DB, Rae GA. Endothelin-1 induces itch and pain in the mouse cheek model. *Life Sci.* 2012 Mar. PubMed PMID: 22483687. ENG.
- [94] Sampaio AL, Rae GA, Henriques MG. Effects of endothelin ETA receptor antagonism on granulocyte and lymphocyte accumulation in LPS-induced inflammation. *J Leukoc Biol.* 2004 Jul;76(1):210-6. PubMed PMID: 15107459. eng.
- [95] Kaufman GN, Zaouter C, Valteau B, Sirois P, Moldovan F. Nociceptive tolerance is improved by bradykinin receptor B1 antagonism and joint morphology is protected by both endothelin type A and bradykinin receptor B1 antagonism in a surgical model of osteoarthritis. *Arthritis Res Ther.* 2011;13(3):R76. PubMed PMID: 21575197. Pubmed Central PMCID: PMC3218886. eng.
- [96] Daher JB, Souza GE, D'Orléans-Juste P, Rae GA. Endothelin ETB receptors inhibit articular nociception and priming induced by carrageenan in the rat knee-joint. *Eur J Pharmacol.* 2004 Aug;496(1-3):77-85. PubMed PMID: 15288578. eng.
- [97] Verri W, Cunha T, Magro D, Domingues A, Vieira S, Souza G, et al. Role of IL-18 in overt pain-like behaviour in mice. *European Journal of Pharmacology.* 2008 JUL 7 2008;588(2-3):207-12. PubMed PMID: WOS:000257187600010. English.
- [98] De-Melo JD, Tonussi CR, D'Orléans-Juste P, Rae GA. Articular nociception induced by endothelin-1, carrageenan and LPS in naive and previously inflamed knee-joints in the rat: inhibition by endothelin receptor antagonists. *Pain.* 1998 Sep;77(3):261-9. PubMed PMID: 9808351. eng.
- [99] De-Melo JD, Tonussi CR, D'Orléans-Juste P, Rae GA. Effects of endothelin-1 on inflammatory incapacitation of the rat knee joint. *J Cardiovasc Pharmacol.* 1998;31 Suppl 1:S518-20. PubMed PMID: 9595530. eng.

- [100] Pinto LG, Cunha TM, Vieira SM, Lemos HP, Verri WA, Cunha FQ, et al. IL-17 mediates articular hypernociception in antigen-induced arthritis in mice. *Pain*. 2010 Feb; 148(2):247-56. PubMed PMID: 19969421. eng.
- [101] Vemulapalli S, Chiu PJ, Griscti K, Brown A, Kurowski S, Sybertz EJ. Phosphoramidon does not inhibit endogenous endothelin-1 release stimulated by hemorrhage, cytokines and hypoxia in rats. *Eur J Pharmacol*. 1994 May;257(1-2):95-102. PubMed PMID: 8082712. eng.
- [102] Morise Z, Ueda M, Aiura K, Endo M, Kitajima M. Pathophysiologic role of endothelin-1 in renal function in rats with endotoxin shock. *Surgery*. 1994 Feb;115(2):199-204. PubMed PMID: 8310408. eng.
- [103] Nambi P, Pullen M, Slivjak MJ, Ohlstein EH, Storer B, Smith EF. Endotoxin-mediated changes in plasma endothelin concentrations, renal endothelin receptor and renal function. *Pharmacology*. 1994 Mar;48(3):147-56. PubMed PMID: 8153142. eng.
- [104] Pernow J, Hemsén A, Hallén A, Lundberg JM. Release of endothelin-like immunoreactivity in relation to neuropeptide Y and catecholamines during endotoxin shock and asphyxia in the pig. *Acta Physiol Scand*. 1990 Nov;140(3):311-22. PubMed PMID: 2082700. eng.
- [105] Lundberg JM, Ahlborg G, Hemsén A, Nisell H, Lunell NO, Pernow J, et al. Evidence for release of endothelin-1 in pigs and humans. *J Cardiovasc Pharmacol*. 1991;17 Suppl 7:S350-3. PubMed PMID: 1725378. eng.
- [106] Myhre U, Pettersen JT, Risøe C, Giercksky KE. Endothelin-1 and endotoxemia. *J Cardiovasc Pharmacol*. 1993;22 Suppl 8:S291-4. PubMed PMID: 7509968. eng.
- [107] Henriques M, Rae G, Cordeiro R, Williams T. Endothelin-1 Inhibits Paf-Induced paw edema and pleurisy in the mouse. *British Journal of Pharmacology*. 1992 JUL 1992;106(3):579-82. PubMed PMID: WOS:A1992JA35800015. English.
- [108] D'Orléans-Juste P, Claing A, Regoli D, Sirois P, Plante GE. Endothelial and smooth muscle pharmacology of pre- and post-capillary microcirculation: correlation with plasma extravasation. *Prostaglandins Leukot Essent Fatty Acids*. 1996 Jan;54(1):31-7. PubMed PMID: 8992491. eng.
- [109] Dahlöf B, Gustafsson D, Hedner T, Jern S, Hansson L. Regional haemodynamic effects of endothelin-1 in rat and man: unexpected adverse reaction. *J Hypertens*. 1990 Sep;8(9):811-7. PubMed PMID: 2172370. eng.
- [110] Brain SD. The direct observation of arteriolar constriction induced by endothelin in vivo. *Eur J Pharmacol*. 1989 Feb;160(3):401-3. PubMed PMID: 2653847. eng.
- [111] Filep JG, Sirois MG, Rousseau A, Fournier A, Sirois P. Effects of endothelin-1 on vascular permeability in the conscious rat: interactions with platelet-activating factor. *Br J Pharmacol*. 1991 Dec;104(4):797-804. PubMed PMID: 1667286. Pubmed Central PMCID: PMC1908850. eng.

- [112] Filep JG, Fournier A, Földes-Filep E. Endothelin-1-induced myocardial ischaemia and oedema in the rat: involvement of the ETA receptor, platelet-activating factor and thromboxane A₂. *Br J Pharmacol.* 1994 Jul;112(3):963-71. PubMed PMID: 7921626. Pubmed Central PMCID: PMC1910206. eng.
- [113] Lopez-Belmonte J, Whittle BJ. Endothelin-1 induces neutrophil-independent vascular injury in the rat gastric microcirculation. *Eur J Pharmacol.* 1995 May;278(1):R7-9. PubMed PMID: 7664809. eng.
- [114] Filep JG, Clozel M, Fournier A, Földes-Filep E. Characterization of receptors mediating vascular responses to endothelin-1 in the conscious rat. *Br J Pharmacol.* 1994 Nov;113(3):845-52. PubMed PMID: 7858876. Pubmed Central PMCID: PMC1510416. eng.
- [115] Filep JG, Fournier A, Földes-Filep E. Acute pro-inflammatory actions of endothelin-1 in the guinea-pig lung: involvement of ETA and ETB receptors. *Br J Pharmacol.* 1995 May;115(2):227-36. PubMed PMID: 7670725. Pubmed Central PMCID: PMC1908312. eng.
- [116] Kurose I, Miura S, Fukumura D, Tsuchiya M. Mechanisms of endothelin-induced macromolecular leakage in microvascular beds of rat mesentery. *Eur J Pharmacol.* 1993 Nov;250(1):85-94. PubMed PMID: 8119327. eng.
- [117] Conte FeP, Barja-Fidalgo C, Verri WA, Cunha FQ, Rae GA, Penido C, et al. Endothelins modulate inflammatory reaction in zymosan-induced arthritis: participation of LTB₄, TNF- α , and CXCL-1. *J Leukoc Biol.* 2008 Sep;84(3):652-60. PubMed PMID: 18515326. eng.
- [118] Hans G, Deseure K, Robert D, De Hert S. Neurosensory changes in a human model of endothelin-1 induced pain: a behavioral study. *Neurosci Lett.* 2007 May;418(2):117-21. PubMed PMID: 17403578. eng.
- [119] Yuyama H, Koakutsu A, Fujiyasu N, Fujimori A, Sato S, Shibasaki K, et al. Inhibitory effects of a selective endothelin-A receptor antagonist YM598 on endothelin-1-induced potentiation of nociception in formalin-induced and prostate cancer-induced pain models in mice. *J Cardiovasc Pharmacol.* 2004 Nov;44 Suppl 1:S479-82. PubMed PMID: 15838353. eng.
- [120] Yuyama H, Koakutsu A, Fujiyasu N, Tanahashi M, Fujimori A, Sato S, et al. Effects of selective endothelin ET(A) receptor antagonists on endothelin-1-induced potentiation of cancer pain. *Eur J Pharmacol.* 2004 May;492(2-3):177-82. PubMed PMID: 15178362. eng.
- [121] Filep JG. Role for endogenous endothelin in the regulation of plasma volume and albumin escape during endotoxin shock in conscious rats. *Br J Pharmacol.* 2000 Mar;129(5):975-83. PubMed PMID: 10696098. Pubmed Central PMCID: PMC1571901. eng.
- [122] Verri W, Cunha T, Magro D, Guerrero A, Vieira S, Carregaro V, et al. Targeting endothelin ETA and ETB receptors inhibits antigen-induced neutrophil migration and

mechanical hypernociception in mice. *Naunyn-Schmiedeberg's Archives of Pharmacology*. 2009 MAR 2009;379(3):271-9. PubMed PMID: WOS:000263062400007. English.

- [123] Sitbon O, Badesch DB, Channick RN, Frost A, Robbins IM, Simonneau G, et al. Effects of the dual endothelin receptor antagonist bosentan in patients with pulmonary arterial hypertension: a 1-year follow-up study. *Chest*. 2003 Jul;124(1):247-54. PubMed PMID: 12853530. eng.
- [124] Hiramoto Y, Shioyama W, Kuroda T, Masaki M, Sugiyama S, Okamoto K, et al. Effect of bosentan on plasma endothelin-1 concentration in patients with pulmonary arterial hypertension. *Circ J*. 2007 Mar;71(3):367-9. PubMed PMID: 17322637. eng.
- [125] Imhof AK, Glück L, Gajda M, Bräuer R, Schaible HG, Schulz S. Potent anti-inflammatory and antinociceptive activity of the endothelin receptor antagonist bosentan in monoarthritic mice. *Arthritis Res Ther*. 2011;13(3):R97. PubMed PMID: 21689431. Pubmed Central PMCID: PMC3218912. eng.
- [126] Conte F, Menezes-de-Lima O, Verri W, Cunha F, Penido C, Henriques M. Lipoxin A(4) attenuates zymosan-induced arthritis by modulating endothelin-1 and its effects. *British Journal of Pharmacology*. 2010 OCT 2010;161(4):911-24. PubMed PMID: WOS:000282179000015. English.
- [127] Donate P, Cunha T, Verri W, Junta C, Lima F, Vieira S, et al. Bosentan, an endothelin receptor antagonist, ameliorates collagen-induced arthritis: the role of TNF-alpha in the induction of endothelin system genes. *Inflammation Research*. 2012 APR 2012;61(4):337-48. PubMed PMID: WOS:000301778300008. English.

IntechOpen