Endothelin: Physiology and Pharmacology[1]

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ABSTRACT

Endothelins are peptides that have receptors and actions in a variety of organs. Endothelin causes veins and arteries to contract and elevates blood pressure. Endothelins are generally balanced by other systems, but when they are overexpressed, they lead to high blood pressure (hypertension), heart disease, and maybe other disorders. Endothelins are 21-amino acid vasoconstricting peptides that are largely synthesized in the endothelium and play an important role in vascular homeostasis. Endothelins have been linked to vascular illnesses in a variety of organ systems, including the heart, lungs, kidneys, and brain. Endothelins are still the subject of substantial scientific and clinical study to establish their roles in many organ systems. In this review, we focus on the physiology and pharmacology of endothelin.

Keywords: *endothelin, endothelin inhibitor, endothelin converting enzyme.*

INTRODUCTION

Endothelin-1 is the foremost strong vasoconstrictor biogenic molecule right now distinguished, and it was initially confined and demonstrated from the laboratory-based culture media of endothelial cells collected from the aorta in 1985 [1, 2]. Some factors stimulate endothelin production, such as inflammatory mediators, thrombin, cyclosporine, insulin, cortisol, hypoxia, epinephrine, angiotensin II & vascular shear stress [2-10]. Some other factors are inhibitory for endothelin production including nitric oxide, prostanoids, and natriuretic peptides. The complete structure of endothelin has fully demonstrated in 1988-1994[2, 3], and has been described as a potent remarkable vasoconstrictor for vascular smooth muscle. This highlight has been confirmed by in vivo sustained elevation of blood pressure in anaesthetized laboratory administration following administration of IV of ET [1,2]. Sarafotoxins has been identified in snake venom and show structural similarity to ET and similarity in action [1,2]. Variation in response between rabbit aorta and rat artery has been later demonstrated suggesting splice variants; which has been shortly later on investigated that there is different ET isoform and distinct receptor subtypes. A few years later on a structural sequence of 21 amino acids assembling ET has been described [11,12]. Antagonist and agonist for research purposes have been jointly identified and used for research purposes [13-15].

Pharmacological researchers attempt to identify antagonists at receptors to block vasoconstriction and ensure reduction in peripheral resistance for therapeutic purposes in cardiac diseases[16]. The introduction of ambrisentan as an active agent for clinical use has revolutionized the field and later on a selective antagonist was introduced [17-20].; sitaxentan, which

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has been withdrawn shortly after postmarketing due to idiosyncratic adverse reaction resulting in death due to liver disorder [21].

SYNTHESIS OF ENDOTHELIN

The synthesis of ET is a stepwise process involving gene encoding synthesis of preproET, followed by partial removal of some amino acids by peptidase enzyme resulting in proET production followed by cleavage step catalysed by furin and convertase enzyme yielding an ET (Figure 1)[22]. Once synthesized, ET is stored in vesicles and continuously released to maintain vascular tone. Once these vesicles receive physiological or pathological stimuli; they degranulate releasing ET to the vicinity inducing vascular action. These degranulation processes are under the control of the endothelin converting enzyme (ECE). The action of this enzyme is upregulated in atherosclerotic injurious tissues [23-26].

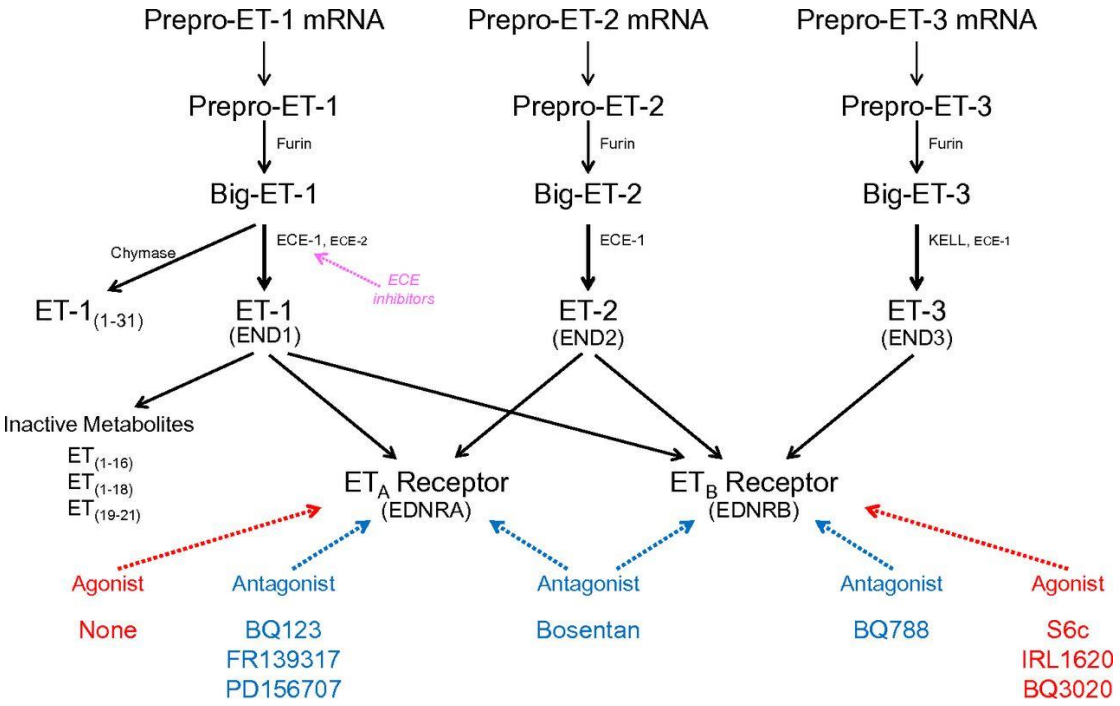

Figure 1. Endothelin synthesis steps [22].

ENDOTHELIN

Endothelin converting enzyme (ECE) and inhibitors:

Initially isolated and purified from aortic endothelial cells, the activity of which was shown to be inhibited by phosphoramidon (neutral endopeptidase inhibitor). ECE is responsible for elevated plasma ET levels in diabetic patients confirming a positive correlation between high plasma glucose levels and activation of ECE. Pharmacological targeting ECE is difficult to interpret due to compensation by alternative vasoactive pathways which might be reciprocally modulated due to the presence of ECE inhibitors. Additionally, it has been speculated that ECE is involved in the angiotensin system and bradykinin inactivation [27-37]. Phosphoramidon is considered a non-selective inhibitor of ET because it has been supplied by the manufacturer as an endopeptidase inhibitor and as a stimulator for atrial natriuretic peptide and inactivator for other peptides (enkephalins and tachykinins). Thiorphan has been experimentally introduced as an alternative for phosphoramidon but the latter was shown to be more effective than the former, hence thiorphan use was obsolete and solely hold for research use. Unlike Thiorphan, phosphoramidon doesn't cross the plasma membrane hence no action was achieved against ET synthesis which means that only extracellular ET was affected[26,27,38].

On the other hand, daglutril is been introduced as a potential ECE inhibitor, introduced as a small molecule to be used clinically because it lacks some side effects

associated with ET receptor blockers such as hepatotoxicity and oedema. Moreover, it has been considered as a comparable molecule to captopril and other ACE inhibitors in reducing proteinuria and providing protection against nephrotoxicity. However, in comparison to ACE inhibitors whose efficacy is reduced as renal insufficiency advances, daglutril retains its activity even upon advanced disease conditions, this could be a promising clue for targeting ET as a potential renal disease therapeutic approach [39,40].

Endothelin receptor (ET-R)

ET-R is a seven-transmembrane G protein-coupled receptor. ET-R are distributed in distinct tissues and organs of our body. Most important is their abundant presence in the vascular system which upon activation produce vasoconstriction resulting in modulation of normal vascular physiology. The underlying mechanism is that activation of ET-R results in adenylyl cyclase stimulation resulting in increased cAMP and subsequent vasoconstriction. ET activate ET-R (G protein-coupled 7 transmembrane spanning domains receptors); this receptor is only present in invertebrates. The receptor showed structural similarities between vertebrates (sheep (95%), rat (93%), pig (95%), dog (95%), and mouse (92%). Moreover, the differences are mainly is in the non-binding sites (N-terminus) indicating cross-similarities between the aforementioned species concerning humans [41]. These claims have been confirmed by terminal mutation of some aminoacids which induce no changes when compared with core mutation amino acids shown great mutation. Additionally, ET-receptors showed splice variances (in the aorta, atrium, and lung), however, the splice variant showed no significant physiological or pathological differences. The extracellular spanning domain is involved in ligand binding while immersed domain and externally spanned are of great interest clinically and being mutated inducing different diseases including skin diseases (hyperpigmentation) and sensorineural deficit and aganglionic megacolon [42,43]. Stimulation or inhibition plays a great role in vasoconstriction or vasodilation. The distribution of endothelin seems to be ubiquitous whenever and wherever a blood supply has arrived. CNS contain abundant ET receptor and play a great role in haemorrhagic stroke by reflex vasospasms. ET binding to receptors in the myocardium induces positive inotropic effects. However, recent reports confirmed that ET presents in 2 isoforms Et_A and E_{TB} showing a contrasting activity at ET receptors with more abundant ET_A receptors in muscular tissues. ET play a major role in most if not all vascular system in our body. In pathology, the production of ET is highly increased resulting in a wide range of contraction areas and the diseased conditions were further exacerbated due to the absence of naturally produced vasodilators (Nitric oxide and prostacyclin). ET bind strongly and irreversibly to its receptor resulting in allosteric modulation of receptors resulting in complete receptor agonistic activity which can't even be reversed by any antagonists. Surprisingly, a low level of ET promotes vasodilatation while a high concentration promotes vascular resistance which might be due to overall modulation in receptor density. Despite the highest density of the receptor in CNS, they seem that the receptor also presents in peripheral tissues especially in lungs tissue more specifically localized in arteries and veins. The ET level increased in patients with pulmonary arterial hypertension and correlated with disease condition and its prognosis. The receptors are also expressed in the heart (atrium, ventricles, and septum). ET is characterized by having strong positive inotropic effects on the cardiac muscle. Isolated human coronary arteries have been investigated to show the difference between normal and atherosclerotic diseased arteries following exposure to sarafotoxins; the result has shown that response was weaker to ET in diseased arteries compared to normal ones. However, there was no difference between maximum response and receptor density between normal and diseased tissues [44-49].

ENDOTHELIN ROLE IN DISEASE CONDITIONS

Pulmonary hypertension

ET is involved in the pathology of pulmonary hypertension and the circulating level of ET has been demonstrated to be much higher than the counterpart normal individual. Evidence confirmed that smooth muscle cells and endothelial cells of lung vessels produce ET when activated by cytokines. This condition mimics patients with pulmonary hypertension concerning ET gene expression and protein production. These patients have shown a close correlation between measured parameters including (pulmonary vascular resistance, atrial pressure, and level of oxygen saturation) [50, 51].

Systemic hypertension

Recently, it has been discovered that endothelin is a vasoconstrictor and its production is mainly through the endothelium of blood vessels during normal and pathological conditions. This discovery has been taken as proof of the involvement of endothelin in the pathology of hypertension. This link has been further confirmed the following reduction in blood pressure after surgical treatment of hemangioendothelioma patients; which showed a great elevation of blood before surgery. Furthermore, studies have confirmed that endothelin plasma concentrations were normal in a patient with essential hypertension despite elevated local vascular endothelin levels. Further studies have confirmed that endothelin receptor blockage is essentially more important in reducing blood pressure than salt intake or angiotensin system. Moreover, ET role has been confirmed in cardiac remodelling and associated with changes of myocardial infarction and biochemical changes of atherosclerotic diseases [52-55].

Heart failure

The stage of heart failure has been linked to a great extent to circulating endothelin and is responsible for raising vascular resistance, remodelling of the smooth muscle of vascular and ventricular tissues, promoting inflammatory reactions and arrhythmic signalling in animal models of heart failure [56-61].

Ovarian cancer

ET is characterised by mitogenic effects that are characterised by stimulation of vascular/ non-vascular proto-oncogene expression. Several types of tumours (ovarian, prostate, colorectal, lung carcinomas, bladder, and breast) is associated with higher plasma ET concentration. Activation of ET-receptors results in stimulation of proliferation, modulation in apoptosis, stimulation of angiogenesis, neovascularisation, cellar migration and invasion [62-64].

CONCLUSION

Endothelin plays important role in health and diseases and focusing on the different research aspects of endothelin could lead to the discovery of a new approach for the treatment of diseases.

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REFERENCES

1. Sokolovsky, Mordechai. "Endothelins and sarafotoxins: receptor heterogeneity." *The International journal of biochemistry* 26.3 (1994): 335-340.
2. Takasaki, Chikahisa, et al. "Sarafotoxins S6: several mycotoxins from Atractaspis engaddensis (burrowing asp) venom that affect the heart." *Toxicon* 26.6 (1988): 543-548.
3. Westby CM, Weil BR, Greiner JJ, Stauffer BL, and DeSouza CA (2011) Endothelin-1 vasoconstriction and the age-related decline in endothelium-dependent vasodilatation in men. Clin Sci (Lond) 120:485–491.
4. Whyteside AR, Turner AJ, and Lambert DW (2014) Endothelin-converting enzyme-1 (ECE-1) is post-transcriptionally regulated by alternative polyadenylation. PLoSOne 9:e83260.
5. Wiley KE and Davenport AP (2000) Novel nitric oxide donors reverse endothelin-1-mediated constriction in human blood vessels. J Cardiovasc Pharmacol 36(5, Suppl 1)S151–S152.
6. Wiley KE and Davenport AP (2001a) Physiological antagonism of endothelin-1 in human conductance and resistance coronary artery. Br J Pharmacol 133:568–574.
7. Wiley KE and Davenport AP (2001b) Nitric oxide-mediated modulation of the endothelin-1 signalling pathway in the human cardiovascular system. Br J Pharmacol 132:213–220.
8. Wiley KE and Davenport AP (2002) Comparison of the effects of atherosclerosis and nitrate therapy on responses to nitric oxide and endothelin-1 in human arteries in vitro. Clin Sci (Lond) 103 (Suppl 48):124S–127S.
9. Heringlake, M., and A. Roth-lsigkeit. "Variations of atrial natriuretic peptide, cortisol and endothelin during different body positions." *Critical Care*. Vol. 1. No. 1. BioMed Central, 1997.

10. Arai H, Hori S, Aramori I, Ohkubo H, and Nakanishi S (1990) Cloning and expression of a cDNA encoding an endothelin receptor. Nature 348:730–732.
11. Ito S, Juncos LA, Nushiro N, Johnson CS, and Carretero OA (1991) Endothelium-derived relaxing factor modulates endothelin action in afferent arterioles. Hypertension 17:1052–1056.
12. Fukuroda T, Kobayashi M, Ozaki S, Yano M, Miyauchi T, Onizuka M, Sugishita Y, Goto K, and Nishikibe M (1994a) Endothelin receptor subtypes in human versus rabbit pulmonary arteries. J Appl Physiol 76:1976–1982.
13. Carducci MA, Saad F, Abrahamsson PA, Dearnaley DP, Schulman CC, North SA, Sleep DJ, Isaacson JD, and Nelson JB; Atrasentan Phase III Study Group Institutions (2007) A phase 3 randomized controlled trial of the efficacy and safety of atrasentan in men with metastatic hormone-refractory prostate cancer. Cancer 110:1959–1966.
14. James ND, Caty A, Payne H, Borre M, Zonnenberg BA, Beuzeboc P, McIntosh S, Morris T, Phung D, and Dawson NA (2010) Final safety and efficacy analysis of the specific endothelin A receptor antagonist zibotentan (ZD4054) in patients with metastatic castration-resistant prostate cancer and bone metastases who were pain-free or mildly symptomatic for pain: a double-blind, placebo-controlled, randomized Phase II trial. BJU Int 106:966–973.
15. Kefford R, Beith JM, Van Hazel GA, Millward M, Trotter JM, Wyld DK, Kusic R, Shreeniwas R, Morganti A, and Ballmer A, et al. (2007) A phase II study of bosentan, a dual endothelin receptor antagonist, as monotherapy in patients with stage IV metastatic melanoma. Invest New Drugs 25:247–252.
16. Inoue A, Yanagisawa M, Takuwa Y, Mitsui Y, Kobayashi M, and Masaki T (1989) The human preproendothelin-1 gene. Complete nucleotide sequence and regulation of expression. J Biol Chem 264:14954–14959.
17. Barst RJ (2007) A review of pulmonary arterial hypertension: role of ambrisentan. Vasc Health Risk Manag 3:11–22.
18. Spence R, Mandagere A, Dufton C, and Venitz J (2008) Pharmacokinetics and safety of ambrisentan in combination with sildenafil in healthy volunteers. J Clin Pharmacol 48:1451–1459.
19. Vatter H and Seifert V (2006) Ambrisentan, a non-peptide endothelin receptor antagonist. Cardiovasc Drug Rev 24:63–76.
20. Vizza CD, Fedele F, Pezzuto B, and Rubin LJ (2012) Safety and efficacy evaluation of ambrisentan in pulmonary hypertension. Expert Opin Drug Saf 11:1003–1011.
21. Don GW, Joseph F, Celermajer DS, and Corte TJ (2012) Ironic case of hepatic dysfunction following the global withdrawal of sitaxentan. Intern Med J 42: 1351–1354.
22. Davenport AP, Hyndman KA, Dhaun N, Southan C, Kohan DE, Pollock JS, Pollock DM, Webb DJ, Maguire JJ. Endothelin. Pharmacological reviews. 2016 Apr 1;68(2):357-418.
23. Yorimitsu K, Moroi K, Inagaki N, Saito T, Masuda Y, Masaki T, Seino S, and Kimura S (1995) Cloning and sequencing of a human endothelin converting enzyme in renal adenocarcinoma (ACHN) cells producing endothelin-2. Biochem Biophys Res Commun 208:721–727.
24. Yorimitsu K, Shinmi O, Nishiyama M, Moroi K, Sugita Y, Saito T, Inagaki Y, Masaki T, and Kimura S (1992) Effect of phosphoramidon on big endothelin-2 conversion into endothelin-2 in human renal adenocarcinoma (ACHN) cells. Analysis of endothelin-2 biosynthetic pathway. FEBS Lett 314:395–398.
25. Shinmi O, Yorimitsu K, Moroi K, Nishiyama M, Sugita Y, Saito T, Inagaki Y, Masaki T, and Kimura S (1993) Endothelin-2-converting enzyme from human renal adenocarcinoma cells is a phosphoramidon-sensitive, membrane-bound metalloprotease. J Cardiovasc Pharmacol 22 (Suppl 8): S61–S64.
26. Gardiner SM, Kemp PA, and Bennett T (1992a) Inhibition by phosphoramidon of the regional haemodynamic effects of proendothelin-2 and -3 in conscious rats. Br J Pharmacol 107:584–590.
27. Mattera GG, Eglezos A, Renzetti AR, and Mizrahi J (1993) Comparison of the cardiovascular and neural activity of endothelin-1, -2, -3 and respective proendothelins: effects of phosphoramidon and thiorphan. Br J Pharmacol 110:331–337.
28. Ahn K, Sisneros AM, Herman SB, Pan SM, Hupe D, Lee C, Nikam S, Cheng XM, Doherty AM, and Schroeder RL, et al. (1998) Novel selective quinazoline inhibitors of endothelin converting enzyme-1. Biochem Biophys Res Commun 243:184–190.

29. Davenport AP and Kuc RE (2000) Cellular expression of isoforms of endothelinconverting enzyme-1 (ECE-1c, ECE-1b and ECE-1a) and endothelin-converting enzyme-2. J Cardiovasc Pharmacol 36(5, Suppl 1)S12–S14.
30. Davenport AP, Kuc RE, Plumpton C, Mockridge JW, Barker PJ, and Huskisson NS (1998) Endothelin-converting enzyme in human tissues. Histochem J 30:359–374.
31. Dickstein K, De Voogd HJ, Miric MP, Willenbrock R, Mitrovic V, Pacher R, and Koopman PA (2004) Effect of single doses of SLV306, an inhibitor of both neutral endopeptidase and endothelin-converting enzyme, on pulmonary pressures in congestive heart failure. Am J Cardiol 94:237–239.
32. Emoto N and Yanagisawa M (1995) Endothelin-converting enzyme-2 is a membrane bound, phosphoramidon-sensitive metalloprotease with acidic pH optimum. J Biol Chem 270:15262–15268.
33. Johnson GD, Stevenson T, and Ahn K (1999) Hydrolysis of peptide hormones by endothelin-converting enzyme-1. A comparison with neprilysin. J Biol Chem 274: 4053–4058.
34. Kalk P, Sharkovska Y, Kashina E, von Websky K, Relle K, Pfab T, Alter M, Guillaume P, Provost D, and Hoffmann K, et al. (2011) Endothelin-converting enzyme/neutral endopeptidase inhibitor SLV338 prevents hypertensive cardiac remodeling in a blood pressure-independent manner. Hypertension 57:755–763.
35. Kuruppu S, Rajapakse NW, Dunstan RA, and Smith AI (2014) Nitric oxide inhibits the production of soluble endothelin converting enzyme-1. Mol Cell Biochem 396: 49–54.
36. Lorenzo MN, Khan RY, Wang Y, Tai SC, Chan GC, Cheung AH, and Marsden PA (2001) Human endothelin converting enzyme-2 (ECE2): characterization of mRNA species and chromosomal localization. Biochim Biophys Acta 1522:46–52.
37. Maguire JJ and Davenport AP (1998) Increased response to big endothelin-1 in atherosclerotic human coronary artery: functional evidence for up-regulation of endothelin-converting enzyme activity in disease. British journal of pharmacology 125:238–240.
38. Emoto N and Yanagisawa M (1995) Endothelin-converting enzyme-2 is a membranebound, phosphoramidon-sensitive metalloprotease with acidic pH optimum. J Biol Chem 270:15262–15268.
39. Parvanova A, van der Meer IM, Iliev I, Perna A, Gaspari F, Trevisan R, Bossi A, Remuzzi G, Benigni A, and Ruggenenti P; Daglutril in Diabetic Nephropathy Study Group (2013) Effect on blood pressure of combined inhibition of endothelin converting enzyme and neutral endopeptidase with daglutril in patients with type 2 diabetes who have albuminuria: a randomised, crossover, double-blind, placebocontrolled trial. Lancet Diabetes Endocrinol 1:19–27.
40. Seed A, Kuc RE, Maguire JJ, Hillier C, Johnston F, Essers H, de Voogd HJ, McMurray J, and Davenport AP (2012) The dual endothelin converting enzyme/neutral endopeptidase inhibitor SLV-306 (daglutril), inhibits systemic conversion of big endothelin-1 in humans. Life Sci 91:743–748.
41. Isberg V, Vroling B, van der Kant R, Li K, Vriend G, and Gloriam D (2014) GPCRDB: an information system for G protein-coupled receptors. Nucleic Acids Res 42: D422–D425.
42. Schweizer A, Valdenaire O, Nelböck P, Deuschle U, Dumas Milne Edwards JB, Stumpf JG, and Löffler BM (1997) Human endothelin-converting enzyme (ECE-1): three isoforms with distinct subcellular localizations. Biochem J 328:871–877.
43. Valdenaire O, Lepailleur-Enouf D, Egidy G, Thouard A, Barret A, Vranckx R, Tougard C, and Michel JB (1999) A fourth isoform of endothelin-converting enzyme (ECE-1) is generated from an additional promoter molecular cloning and characterization. Eur J Biochem 264:341–349.
44. Russell FD and Davenport AP (1995) Characterization of endothelin receptors in the human pulmonary vasculature using bosentan, SB209670, and 97-139. J Cardiovasc Pharmacol 26 (Suppl 3):S346–S347.
45. Russell FD and Davenport AP (1996) Characterization of the binding of endothelin ETB selective ligands in human and rat heart. Br J Pharmacol 119:631–636.
46. Russell FD and Davenport AP (1999a) Secretory pathways in endothelin synthesis. Br J Pharmacol 126:391–398.
47. Russell FD and Davenport AP (1999b) Evidence for intracellular endothelin converting enzyme-2 expression in cultured human vascular endothelial cells. Circ Res 84:891–896.
48. Russell FD, Coppell AL, and Davenport AP (1998) In vitro enzymatic processing of radiolabelled big ET-1 in human kidney. Biochem Pharmacol 55:697–701.

49. Russell FD, Skepper JN, and Davenport AP (1997) Detection of endothelin receptors in human coronary artery vascular smooth muscle cells but not endothelial cells by using electron microscope autoradiography. J Cardiovasc Pharmacol 29:820–826.
50. Cody RJ, Haas GJ, Binkley PF, Capers Q, and Kelley R (1992) Plasma endothelin correlates with the extent of pulmonary hypertension in patients with chronic congestive heart failure. Circulation 85:504–509.
51. Giaid A, Yanagisawa M, Langleben D, Michel RP, Levy R, Shennib H, Kimura S, Masaki T, Duguid WP, and Stewart DJ (1993) Expression of endothelin-1 in the lungs of patients with pulmonary hypertension. N Engl J Med 328:1732–1739.
52. Weber MA, Black H, Bakris G, Krum H, Linas S, Weiss R, Linseman JV, Wiens BL, Warren MS, and Lindholm LH (2009) A selective endothelin-receptor antagonist to reduce blood pressure in patients with treatment-resistant hypertension: a randomised, double-blind, placebo-controlled trial. Lancet 374:1423–1431.
53. Black HR, Bakris GL, Weber MA, Weiss R, Shahawy ME, Marple R, Tannoury G, Linas S, Wiens BL, and Linseman JV, et al. (2007) Efficacy and safety of darusentan in patients with resistant hypertension: results from a randomized, double-blind, placebo-controlled dose-ranging study. J Clin Hypertens (Greenwich) 9:760–769.
54. Bakris GL, Lindholm LH, Black HR, Krum H, Linas S, Linseman JV, Arterburn S, Sager P, and Weber M (2010) Divergent results using clinic and ambulatory blood pressures: report of a darusentan-resistant hypertension trial. Hypertension 56: 824–830.
55. Webb DJ (2010) DORADO: opportunity postponed: lessons from studies of endothelin receptor antagonists in treatment-resistant hypertension. Hypertension 56:806–807.
56. Sakai S, Miyauchi T, Sakurai T, Kasuya Y, Ihara M, Yamaguchi I, Goto K, and Sugishita Y (1996) Endogenous endothelin-1 participates in the maintenance of cardiac function in rats with congestive heart failure. Marked increase in endothelin-1 production in the failing heart. Circulation 93:1214–1222.
57. Kobayashi T, Miyauchi T, Sakai S, Kobayashi M, Yamaguchi I, Goto K, and Sugishita Y (1999) Expression of endothelin-1, ETA and ETB receptors, and ECE and distribution of endothelin-1 in failing rat heart. Am J Physiol 276:H1197–H1206.
58. Pieske B, Beyermann B, Breu V, Löffler BM, Schlotthauer K, Maier LS, Schmidt-Schweda S, Just H, and Hasenfuss G (1999) Functional effects of endothelin and regulation of endothelin receptors in isolated human nonfailing and failing myocardium. Circulation 99:1802–1809.
59. Motte S, McEntee K, and Naeije R (2006) Endothelin receptor antagonists. Pharmacol Ther 110:386–414.
60. Kiowski W, Sütsch G, Hunziker P, Müller P, Kim J, Oechslin E, Schmitt R, Jones R, and Bertel O (1995) Evidence for endothelin-1-mediated vasoconstriction in severe chronic heart failure. Lancet 346:732–736.
61. Cowburn PJ, Cleland JG, McDonagh TA, McArthur JD, Dargie HJ, and Morton JJ (2005) Comparison of selective ET(A) and ET(B) receptor antagonists in patients with chronic heart failure. Eur J Heart Fail 7:37–42.
62. Cianfrocca R, Tocci P, Semprucci E, Spinella F, Di Castro V, Bagnato A, and Rosanò L (2014) b-Arrestin 1 is required for endothelin-1-induced NF-kB activation in ovarian cancer cells. Life Sci 118:179–184.
63. Cognetti F, Bagnato A, Colombo N, Savarese A, Scambia G, Sehouli J, Wimberger P, Sorio R, Harter P, and Mari E, et al. (2013) A Phase II, randomized, double-blind study of zibotentan (ZD4054) in combination with carboplatin/paclitaxel versus placebo in combination with carboplatin/paclitaxel in patients with advanced ovarian cancer sensitive to platinum-based chemotherapy. Gynecol Oncol 130:31–37.
64. Rosanò L, Cianfrocca R, Masi S, Spinella F, Di Castro V, Biroccio A, Salvati E, Nicotra MR, Natali PG, and Bagnato A (2009) Beta-arrestin links endothelin A receptor to beta-catenin signaling to induce ovarian cancer cell invasion and metastasis. Proc Natl Acad Sci USA 106:2806–2811.