IN THE NAME OF GOD

Endothelin Receptors,Natriuresis ,Kidney Disease and Hypertension

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Outline:

- What is Endothelin?
- Pathologic and physiologic role of Endotelin
- Pharmacological role and Experimental studies
- Conclusion

INTRODUCTION

- Vascular endothelial cells produce a number of important vasodilator and constrictor substances.
- Prostacyclin and nitric oxide (NO) are potent vasodilators secreted by vascular endothelium.
- The isolation of endothelium-derived vasodilators initiated a search for counterbalancing constricting factors (or EDCFs).
- A long-acting vasoconstrictor substance was isolated from porcine aortic endothelial cells in 1988, and named endothelin.

INTRODUCTION....

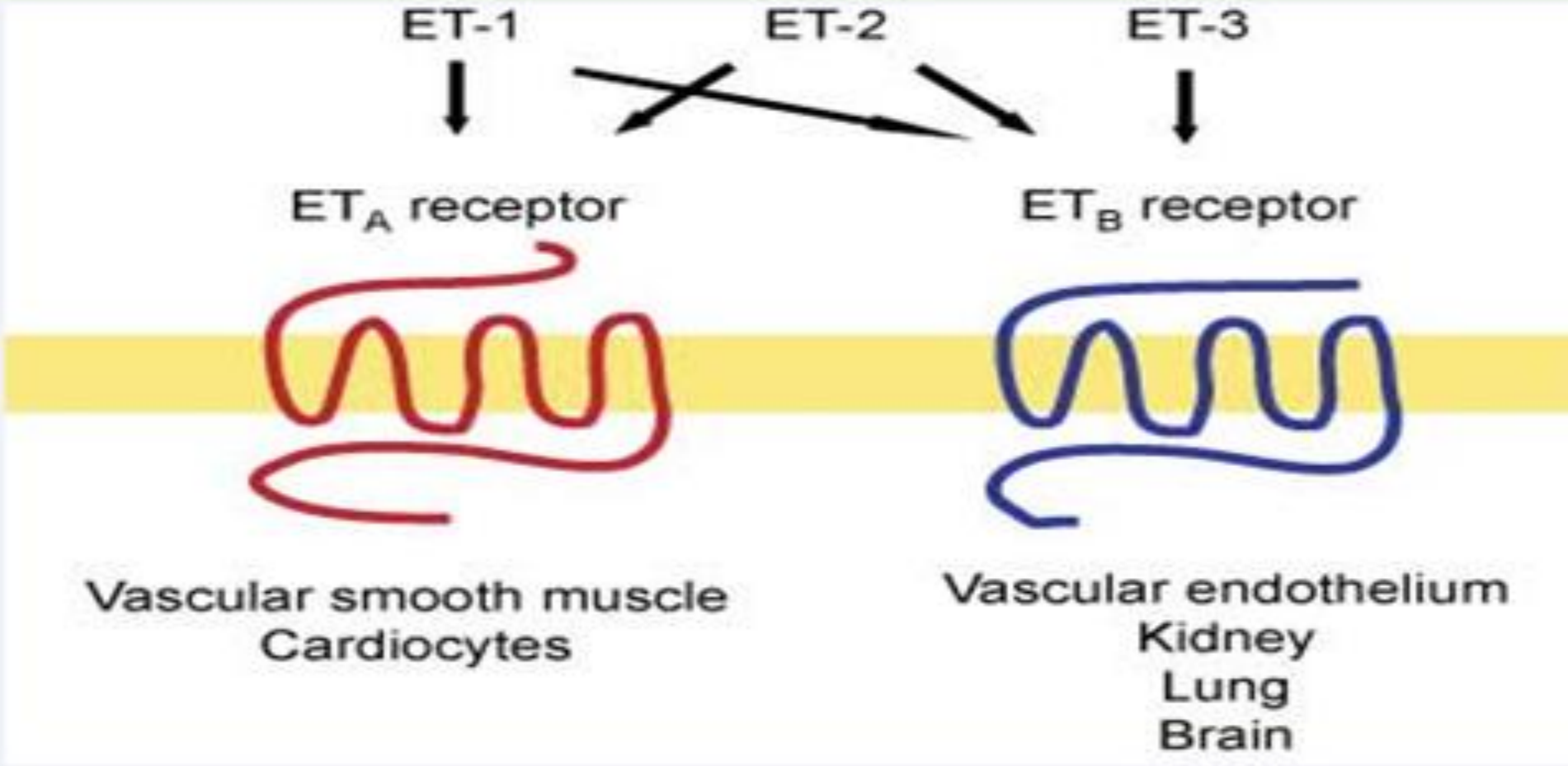
- Most potent and long lasting vasoconstricter
- Endothelin = 100 (noradrenaline)
- Autocrine & Paracrine
- Affects multiple system

ENDOTHELINS

- 21- amino acid peptide
- Three forms :

Type	Source
Endothelin 1	vascular endothelial and smooth muscle cells, airway epithelial cells, macrophages, fibroblasts, cardiac myocytes, brain neurons, and pancreatic islets
Endothelin 2	Ovary Intestinal epithelial cells
Endothelin 3	endothelial cells, brain neurons, renal tubular epithelial cells, intestinal epithelial cells

Endothelins:



ENDOTHELIN RECEPTORS

ET_A RECEPTOR

- G- protein coupled receptor
- Affinity : ET1, ET2 > ET 3
- Primary vasoconstrictor and growth promoting
- Vascular smooth muscle cells

ET_B RECEPTOR

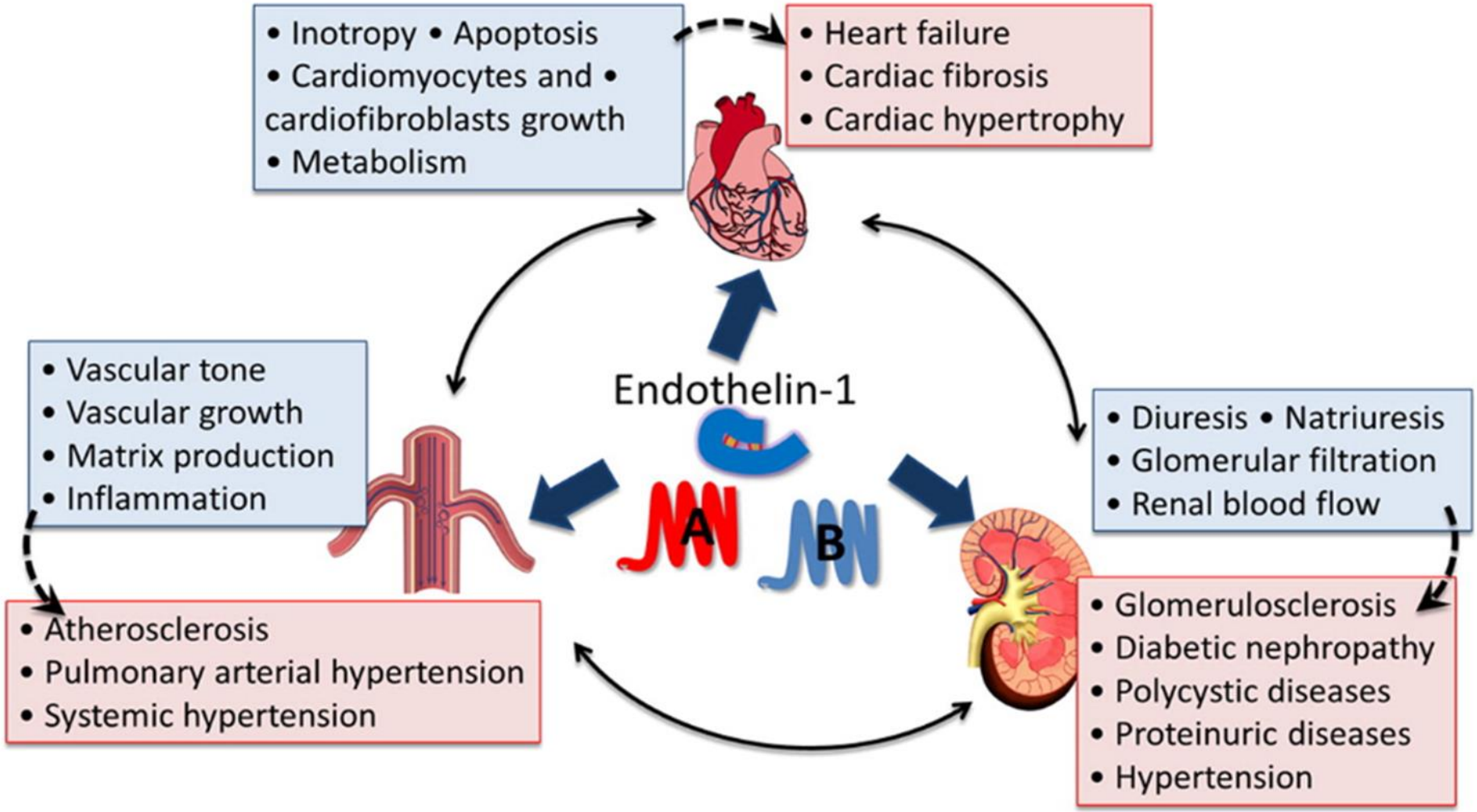
- G- protein coupled receptor
- Affinity : ET1= ET2 = ET 3
- Vasodilator ,Vasoconstrictor, inhibit cell growth
- Vascular smooth muscle cells & endothelial cells
- **"Clearance receptor"**

Endothelins and the kidney

- In the kidney,endothelins have a wide variety of biologic actions.
- Most importantly are :
- Regulation of vascular resistance
- Modulation of fluid and electrolyte transport
- Regulation of cell proliferation and extracellular matrix accumulation.

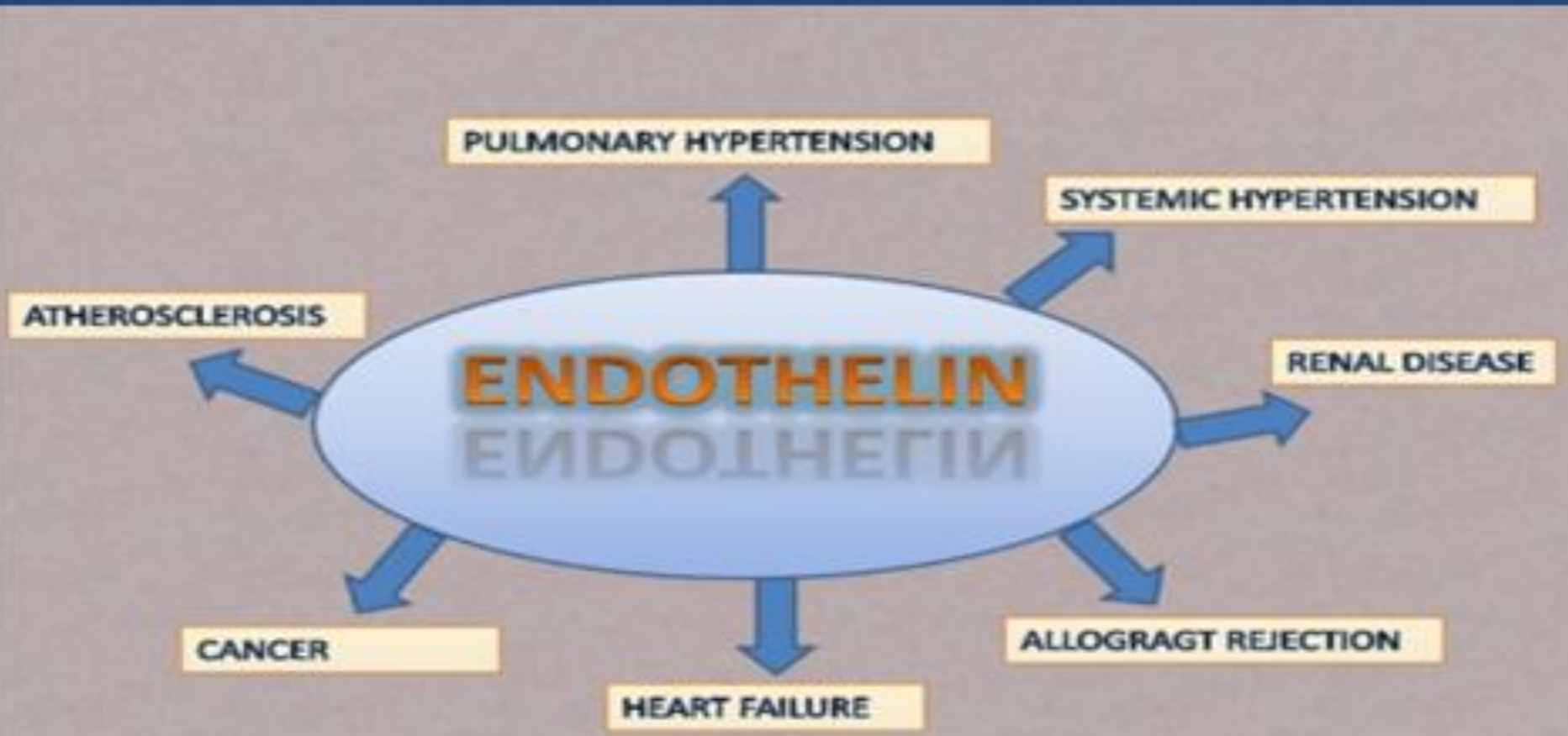
Endothelins regulates cell proliferation and extracellular matrix accumulation

- Cell proliferation and extracellular matrix accumulation are altered by the endothelins. It regulates:
- The release of tissue inhibitor of metalloproteinase
- The release of cytokines that stimulate matrix accumulation
- The production of renal cell fibronectin and collagen



Overview of the physiological effects and pathological processes in which endothelin-1 and its receptors are involved in the renal and cardiovascular systems

Pathologic role of Endothelin



The First Pharmacological role of Endothelin antagonist

PULMONARY HYPERTENSION

- The pharmaceutical industry has extensively studied pulmonary hypertension as a clinical target for ET antagonism
- Randomized clinical trials have demonstrated clear benefits regarding symptoms and quality of life compared with placebo
- The first endothelin receptor antagonist to receive US FDA approval - **Bosentan**

SYSTEMIC HYPERTENSION

- Increasing vascular tone
- Activating the sympathetic nervous system & RAS
- Increasing mitogenesis

Hemangioendothelioma+
ET-1 +hypertension

↓ OPERATED

Normal ET1 & Pressure

Almost all studies animal models of hypertension, hypercholesterolemia,or atherosclerosis was shown chronic treatment with ETA-receptor antagonists was associated with improved endothelium-dependent, NO-mediated vasodilation.

Pharmacological role in HTN

SYSTEMIC HYPERTENSION

- Preclinical data on hypertension have been underscored by clinical studies in humans with essential hypertension
- Nonselective ET-receptor antagonist bosentan or selective ETA-receptor antagonist darusentan substantially reduces arterial blood pressure in patients

HEART FAILURE

Pulmonary hypertension
Coronary artery disease

Chronotropy
Inotropy
Arrhythmia
Contractile function of myocyte
Remodeling

Impaired cardiac function
↓
Pulmonary congestion
↓
Increased level of ET1 & big ET1
↓
Further worsoning of cardiac function

Pharmacological role in Heart failure

HEART FAILURE

- In animals : benefit of chronic endothelin blockade on survival and left ventricular remodelling after myocardial infarction
- Currently no evidence for a protective effect of chronic endothelin antagonism in humans with heart failure
- All long-term clinical trials investigating chronic treatment with endothelin receptor antagonists in patients with acute or chronic congestive heartfailure have been negative

RENAL DISEASE

Regulation of blood flow
Water and sodium transport
Acid base balance

One of the most sensetive vascular bed contracting to endothelin in picomolar range

Glomerulosclerosis
Proteinuria
Salt sensetive hypertension

Podocyte damage

↓

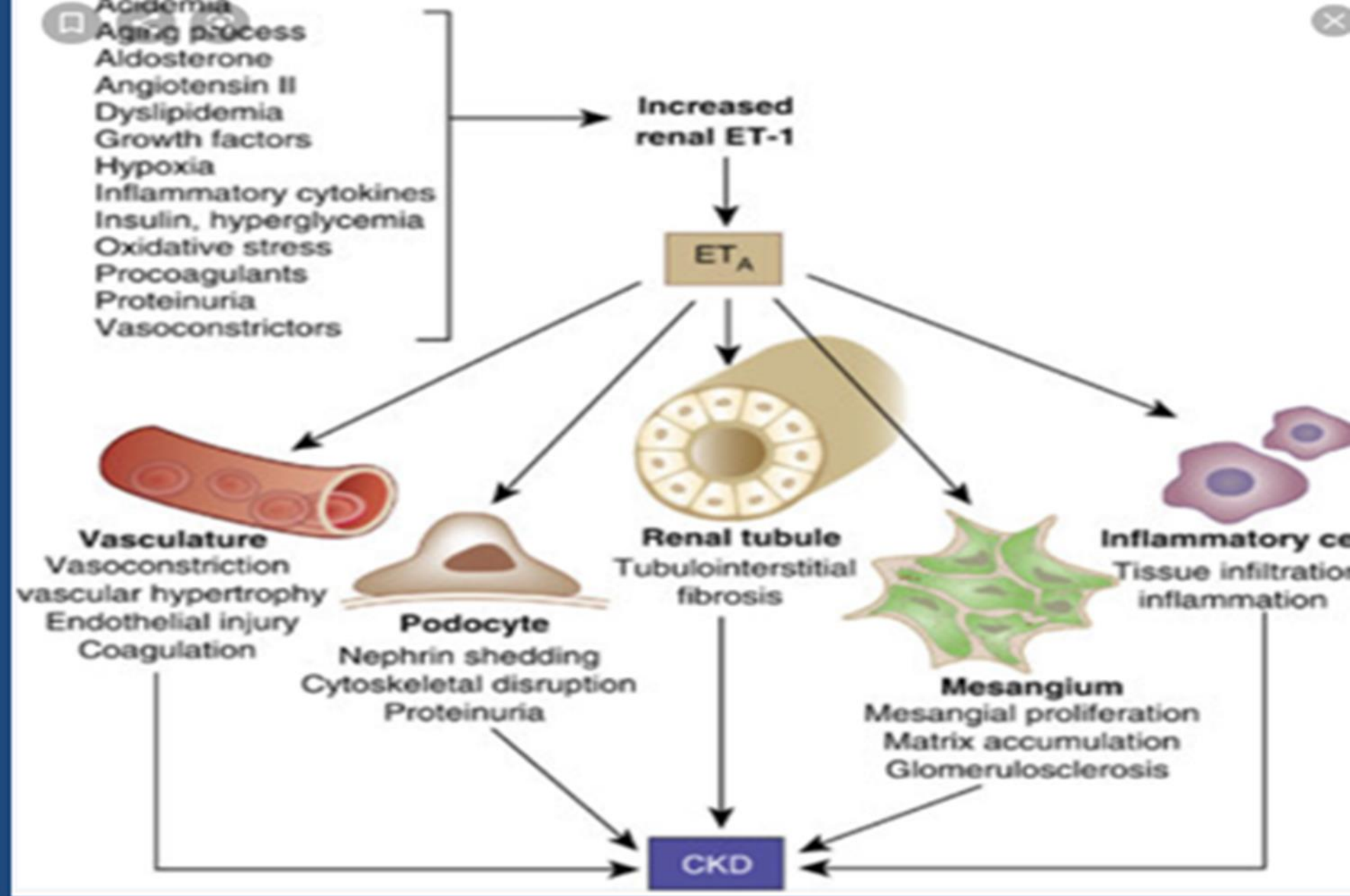
Production of endothelin in podocyte

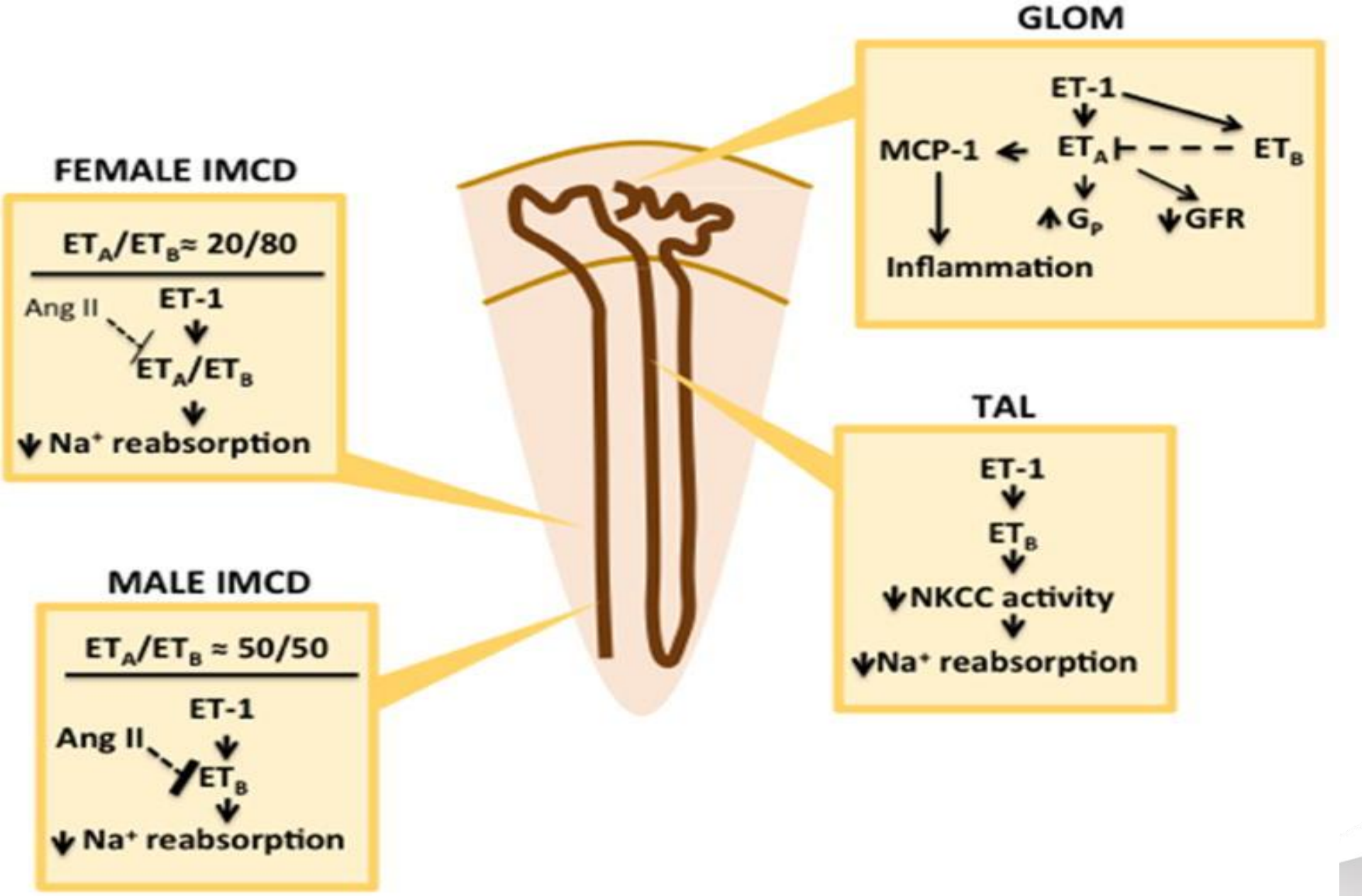
↓

Reorganization of Actin cytoskeleton

↓

Glomerular injury


Acidemia
Aging process
Aldosterone
Angiotensin II
Dyslipidemia
Growth factors
Hypoxia
Inflammatory cytokines
Insulin, hyperglycemia
Oxidative stress
Procoagulants
Proteinuria
Vasoconstrictors
Increased renal ET-1
ETA
Vasculature
Vasoconstriction
vascular hypertrophy
Endothelial injury
Coagulation
Podocyte
Nephrin shedding
Cytoskeletal disruption
Proteinuria
Renal tubule
Tubulointerstitial fibrosis
Mesangium
Mesangial proliferation
Matrix accumulation
Glomerulosclerosis
Inflammatory ce
Tissue infiltratio
inflammation
CKD


GLOM
ET-1
MCP-1
ET_A
ET_B
G_P
GFR
Inflammation
FEMALE IMCD
$ET_A/ET_B \approx 20/80$
Ang II
ET-1
ET_A/ET_B
Na^+ reabsorption
TAL
ET-1
ET_B
NKCC activity
Na^+ reabsorption
MALE IMCD
$ET_A/ET_B \approx 50/50$
ET-1
Ang II
ET_B
Na^+ reabsorption

AUTOIMMUNE DISEASE AND TRANSPLANTATION

- Lymphocyte and Leukocyte
- Stimulates formation of cytokines:
  - -Interleukins
  - -Tumor necrosis factor (TNF)
- Play imortant role in connective tissue disorder
  - Lupus erythematosus
  - Systemic sclerosis
  - Sjoegren's Syndrom
  - Scleroderma
- Acute and Chronic Rejection after solid organ transplantation

↓

- Graft atherosclerosis, fibrosis, glomerulosclerosis

Pharmacological role in Renal Disease

RENAL DISEASE..

- Studies have investigated the antiproteinuric effect of endothelin receptor antagonists in normotensive or severely hypertensive animal Models
- In these studies, treatment not only reversed proteinuria but also lead to a healing of the previously injured glomeruli and podocytes
- Renal disease is a particularly relevant area for the clinical application of endothelin receptor blockers with the potential to reverse established disease

Pharmacological role in Renal Disease

RENAL DISEASE

- A large number of experimental prevention studies have investigated the effects of chronic endothelin blockade on the development of glomerulosclerosis
- Studies found pronounced nephroprotective effects
- Only relatively few studies have investigated the effects of endothelin receptor blockade in conditions in which renal disease was already established

Diabetic Nephropathy

- Endothelin system plays an important role in the pathogenesis of DKD. Endothelin receptor 1 stimulation increases renal vasoconstriction, extracellular matrix accumulation and IFTA.
- Endothelin A receptor antagonists have shown promise in the treatment of DKD, along with the use of ACE inh in animal studies.

Diabetic Nephropathy

- Human trials are ongoing; however one clinical trial studying avosentan was terminated early due to increased CVD and CHF.
- Another endothelin antagonist, atrasentan was shown to reduce proteinuria in a short study. Longer and larger trials are in progress.

REVIEW ARTICLE

Endothelin receptor antagonism during preeclampsia: a matter of timing?

Emilie Hitzerd, Rugina I. Neuman, Katrina M. Mirabito Colafella, Irwin K.M. Reiss, Anton H. van den Meiracker, A.H. Jan Danser, Willy Visser, Jorie Versmissen, Langeza Saleh

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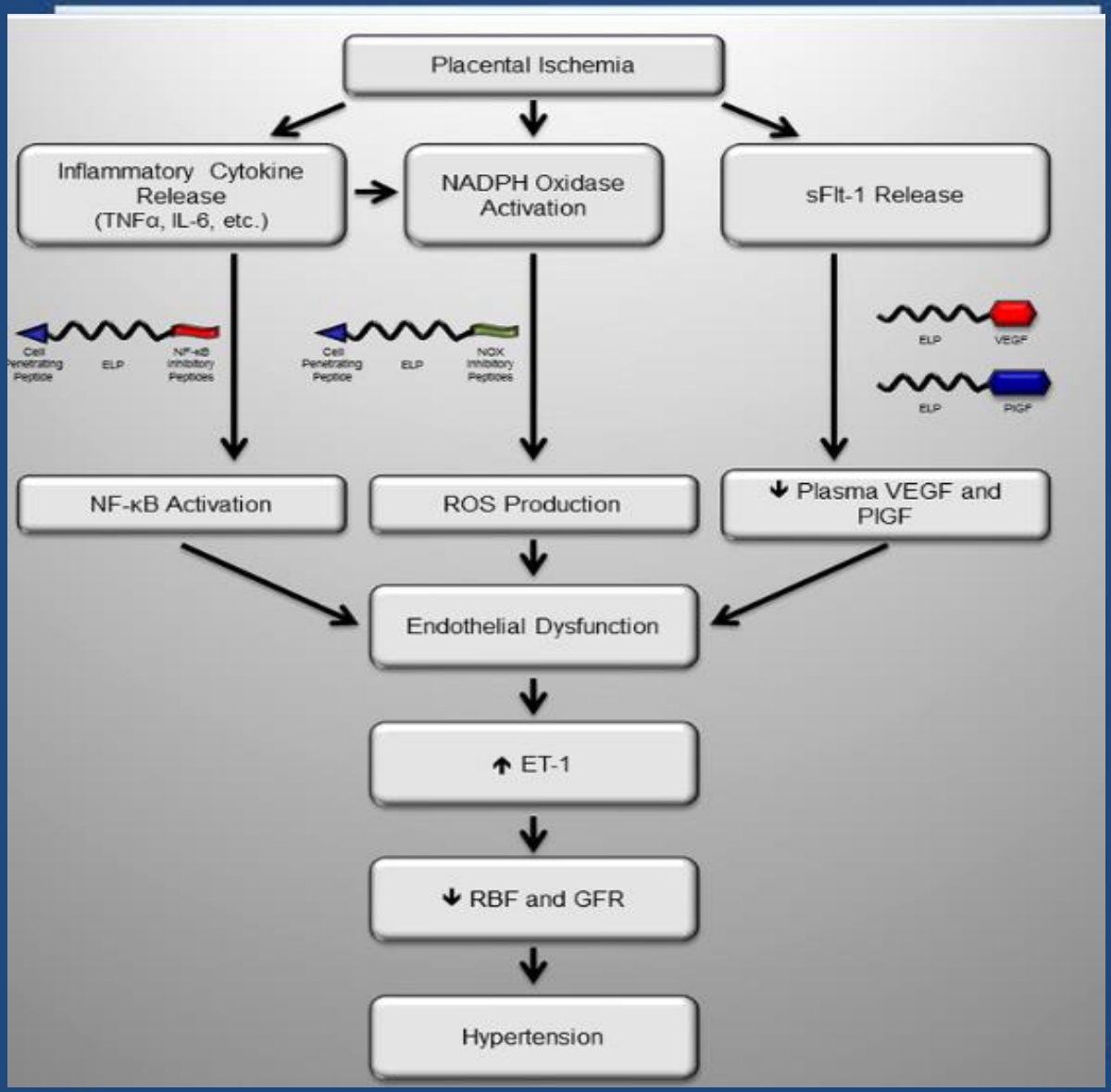
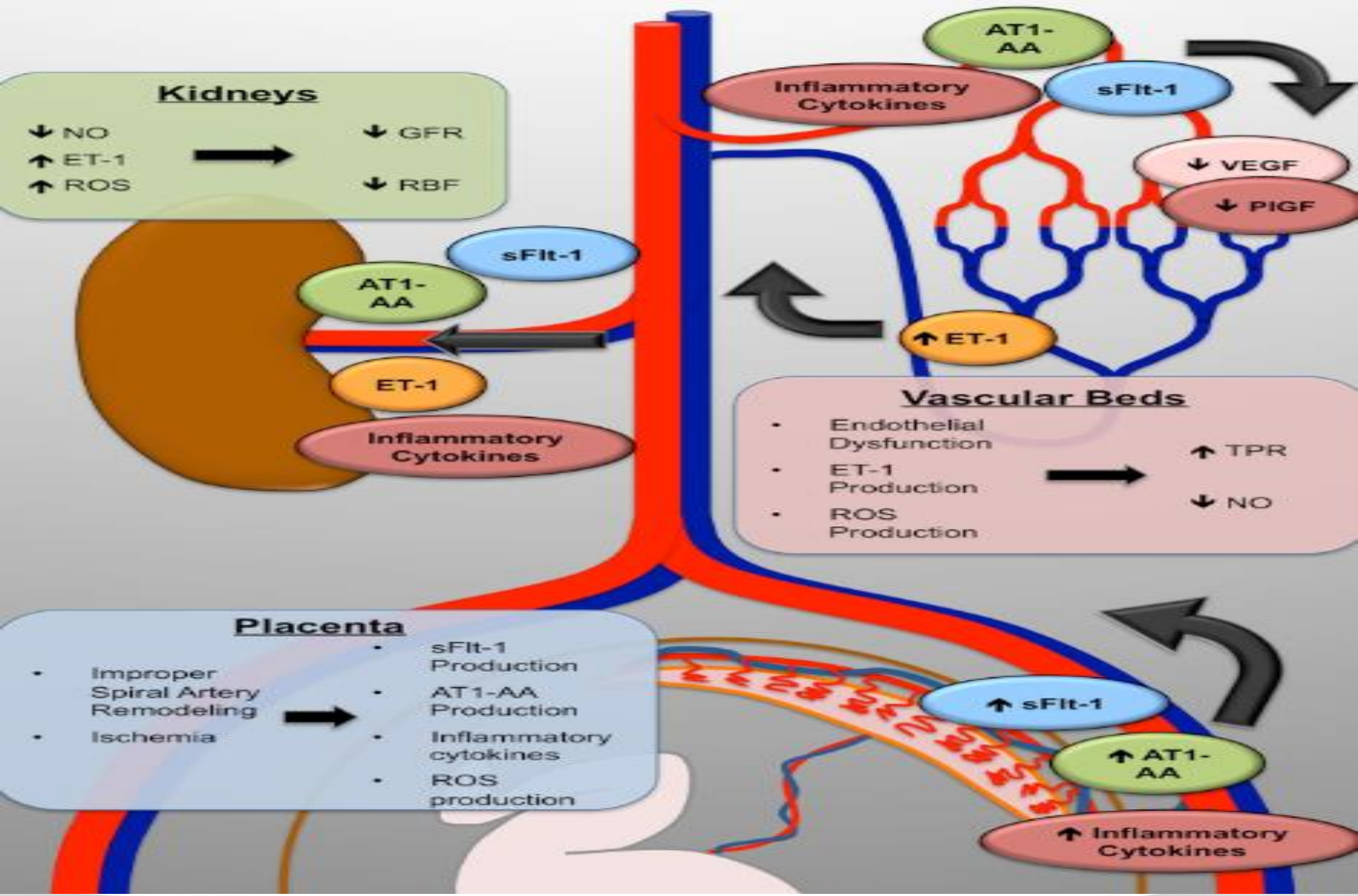
Abstract

Preeclampsia (PE) is a pregnancy complication, featuring elevated blood pressure and proteinuria, with no appropriate treatment. Activation of the endothelin system has emerged as an important pathway in PE pathophysiology based on experimental PE models where endothelin receptor antagonists (ERAs) prevented or attenuated hypertension and proteinuria. Hence, ERAs have been suggested as potential therapy for PE. However, developmental toxicity studies in animals have shown severe teratogenic effects of ERAs, particularly craniofacial malformations. Nonetheless, sporadic cases of pregnancy in women using ERAs to treat pulmonary hypertension have been described. In this review we give an overview of cases describing ERA use in pregnancy and critically address their possible teratogenic effects. A systematic search in literature yielded 18 articles describing 39 cases with ERA exposure during human pregnancy. In most cases there was only exposure in the first trimester, but exposure later or throughout pregnancy was reported in five cases. Elective termination of pregnancy was performed in 12 pregnancies (31%), two ended in a spontaneous miscarriage (5%) and no fetal congenital abnormalities have been described in the remaining cases. These preliminary findings support the idea that ERA treatment for severe, early onset PE might be an option if applied later in pregnancy, when organogenesis is completed to avoid teratogenic risks. However, third trimester toxicology studies are warranted to evaluate drug safety. Subsequently, it remains to be established whether ERA treatment is effective for alleviating maternal symptoms, as demonstrated in preclinical PE models, allowing pregnancy prolongation without leading to adverse neonatal outcomes.


Placental Ischemia
Inflammatory Cytokine Release (TNFα, IL-6, etc.)
NADPH Oxidase Activation
sFlt-1 Release
Cell Penetrating Peptide
ELP
NF-κB inhibitory Peptides
Cell Penetrating Peptide
ELP
NOX inhibitory Peptides
ELP
VEGF
ELP
PlGF
NF-κB Activation
ROS Production
↓ Plasma VEGF and PlGF
Endothelial Dysfunction
↑ ET-1
↓ RBF and GFR
Hypertension


Kidneys
NO
ET-1
ROS
GFR
RBF
sFlt-1
AT1-AA
ET-1
Inflammatory Cytokines
AT1-AA
Inflammatory Cytokines
sFlt-1
VEGF
PIGF
ET-1
Vascular Beds
Endothelial Dysfunction
ET-1 Production
ROS Production
TPR
NO
Placenta
Improper Spiral Artery Remodeling
Ischemia
sFlt-1 Production
AT1-AA Production
Inflammatory cytokines
ROS production
sFlt-1
AT1-AA
Inflammatory Cytokines

Endothelin-1

- Increased ET-1 in amniotic fluid & plasma of infant and mother in preeclampsia
- Asso with abnormal placentation

- J Vet Intern Med. 2005 Jul-Aug : 19 : 594-8

Journal of Human Hypertension (2011), 1–6

www.nature.com/jhh

ORIGINAL ARTICLE

The relationship between circulating endothelin-1, soluble fms-like tyrosine kinase-1 and soluble endoglin in preeclampsia

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Placental overproduction of anti-angiogenic soluble fms-like tyrosine kinase-1 (sFlt-1) and soluble endoglin (sEng) has a key role in the development of preeclampsia (PE). Circulating endothelin-1 (ET-1) levels are also elevated in PE. In this study, we investigated the correlation between ET-1 and sFlt-1, placental growth factor (PlGF), sEng levels during uncomplicated normotensive pregnancy and PE. A total of 218 pregnant primigravid women were enrolled: 110 with PE and 108 uncomplicated normotensive pregnancies. PE was defined as new onset of elevated blood pressure (BP) >140/90 mm Hg and ⩾2+ proteinuria on two occasions after 20 weeks of gestation in previously normotensive pregnant women. Circulating ET-1, sFlt-1, sEng and PlGF levels were estimated using enzyme immunoassays, and correlation between variables was ascertained. Women with PE showed higher levels of sFlt-1 (41.5 ± 15.7 vs 6.15 ± 3.4 ng ml^{-1}, $P<0.001$), sEng (84.9 ± 38.8 vs 13.2 ± 6.3 ng ml^{-1}, $P<0.001$), ET-1 (1.52 ± 0.55 vs 0.88 ± 0.35 pg ml^{-1}, $P<0.001$) and sFlt-1:PlGF ratio (591.1 ± 468.4 vs 18.3 ± 2.1, $P<0.001$); and lower levels of PlGF (96.3 ± 47.2 vs 497.6 ± 328.2pg ml^{-1}, $P<0.001$). BP levels showed an independent relationship with sFlt-1:PlGF ratio in normotensive pregnant women and with sFlt-1:PlGF ratio and ET-1 in PE. sFlt-1 and sFlt-1:PlGF ratio correlated with proteinuria. ET-1 correlated significantly with sFlt-1, sEng and sFlt-1:PlGF ratio in PE. Our results show an association between elevation of sFlt-1 and sEng and ET-1 in the maternal circulation in PE, and strengthen the possibility that ET-1 may be a mediator in genesis of PE syndrome secondary to anti-angiogenic factors released by the placenta.
Journal of Human Hypertension advance online publication, 31 March 2011; doi:10.1038/jhh.2011.29

Keywords: pregnancy; endothelin-1; soluble fms-like tyrosine kinase-1; soluble endoglin; placental growth factor; preeclampsia

Introduction

Preeclampsia (PE), a multifactorial hypertensive syndrome of late pregnancy of unknown etiology, is an important cause of maternal and fetal morbidity and mortality.[1,2] The key pathophysiological processes are believed to be initiated by reduced placental perfusion secondary to inadequate trophoblast invasion.[3,4] Placental response to ischemia is manifested by overproduction of anti-angiogenic peptides, such as soluble fms-like tyrosine kinase-1 (sFlt-1) and soluble endoglin (sEng),[5] resulting in a clinical syndrome characterized by widespread systemic endothelial dysfunction.

Both sFlt-1 (a splice variant of fms-like tyrosine kinase-1) and sEng (a truncated form of endoglin) are thought to act by binding with their ligands, vascular endothelial growth factor (VEGF) and placental growth factor (PlGF); and transforming growth factor-β, respectively, in circulation, thereby preventing the binding of these pro-angiogenic molecules to their native endothelial cell-surface receptors. Experimental studies confirmed the development of hypertension, proteinuria and histological lesions of PE in various organs in pregnant rats on infusion of recombinant adenovirus encoding sFlt-1 and sEng1.[6,7]

Elevations in circulating sFlt-1 and sEng and reduction in PlGF levels antedate the appearance of PE.[8–11] This suggests that perturbation of other pathways may be necessary for the development of clinical manifestations. Endothelin-1 (ET-1) is a

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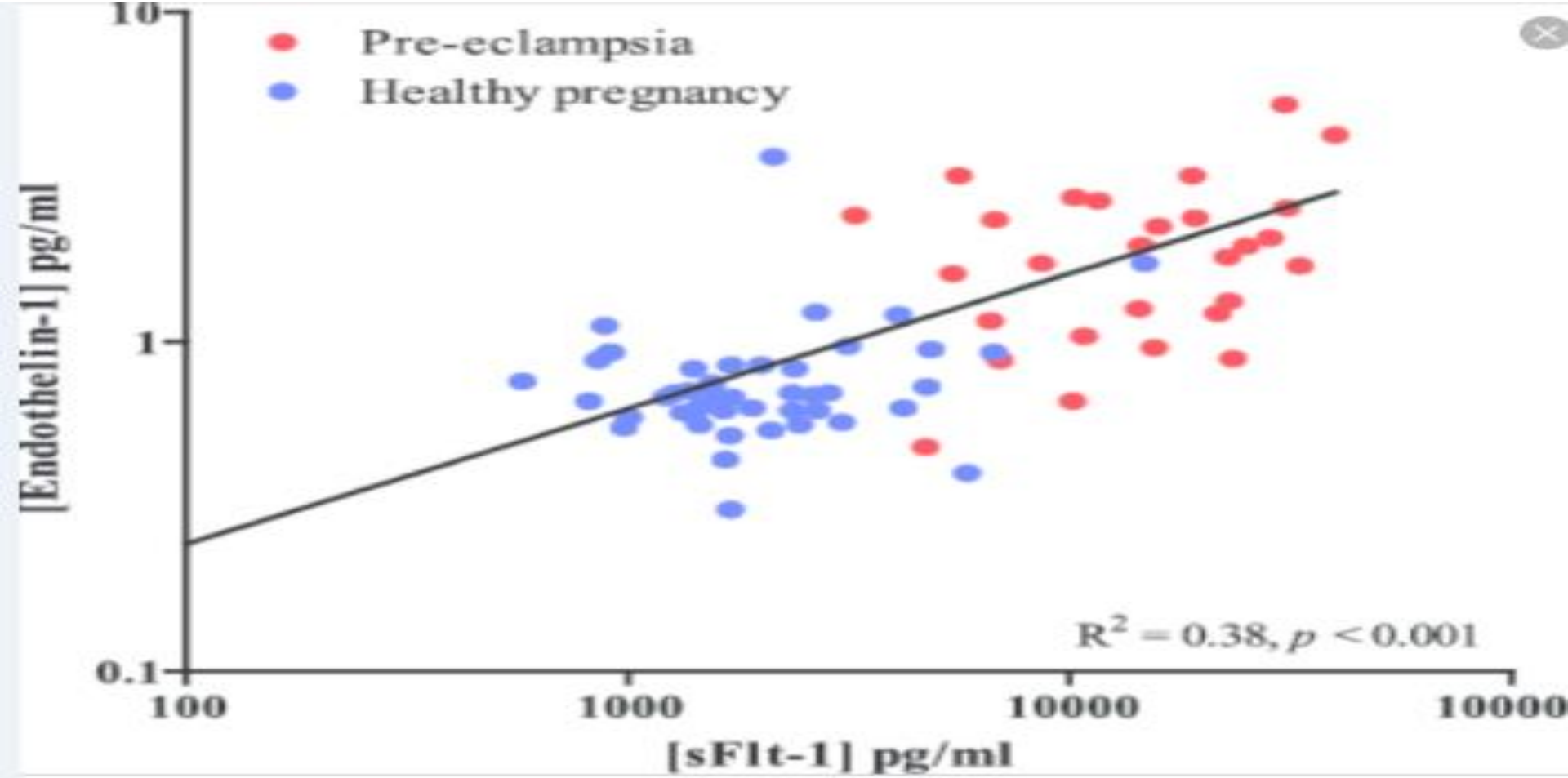
Endothelin and Preeclampsia



ENDOTHELIN RECEPTOR ANTAGONIST

Non Selective

- Bosentan
- Tezosentan

Selective ET- A antagonist

- Ambrisentan
- Atrasentan
- BQ-123
- Darusentan
- Sitaxentan
- Zibotentan

BOSENTAN

- INDICATION
- Pulmonary arterial hypertension in patients with WHO Class II to IV symptoms to improve exercise capacity and decrease clinical worsening
- DOSE: Initiate at 62.5 mg twice daily with or without food for 4 weeks, and then increase to 125 mg twice daily

BOSENTAN

- ADVERSE DRUG REACTION
  - Elevations of liver aminotransferases (ALT, AST) and liver failure
- PRECAUTIONS
  - Pre-existing hepatic impairment: Avoid use in moderate and severe impairment. Use with caution in mild impairment
  - Fluid retention: May require intervention
  - Decreases in hemoglobin and hematocrit: Monitor hemoglobin levels after 1 and 3 months of treatment, then every 3 months thereafter

Endothelin Receptor Antagonists (ERAs)

- **Bosentan**
- **Sitaxentan**, a selective endothelin (ET)-A receptor antagonist, has negligible inhibition of the beneficial effects of ETB stimulation, such as nitric oxide production and clearance of ET from circulation.
- In clinical trials, the efficacy of sitaxentan has been much the same as bosentan with reduced hepatotoxicity.Dosing is once daily

- **Ambrisentan** :

A-selective endothelin receptor antagonist

once-daily dosing.

improvements in 6-minute walk distance in patients

low risk of aminotransferase abnormalities.

The most frequent side effect of ambrisentan isfluid retention

CONCLUSION

- Endothelin is not merely a vasoconstrictor, but a multifunctional peptide
- Initial clinical indications such as heart failure have been shown not to benefit from endothelin receptor blockade on top of standard treatment and are unlikely to ever become an indication for this new form of treatment.
- Pulmonary arterial hypertension, has become the first clinical indications

CONCLUSION

- Basic science studies suggest that diseaseas such as
  - proteinuric renal disease
  - Cancer
  - connective tissue diseases
  - chronic allograft rejections

  will be indications for endothelin antagonist therapy in the near future.
- Well-designed clinical studies are warranted to test and verify the therapeutic potential of this new class of drugs for cardiovascular medicine, nephrology, oncology, and related medical fields.