

Ang II, Ang-(1-7) and Reactive Oxygen Species: Implications in Cardiovascular Disease.

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IRSO

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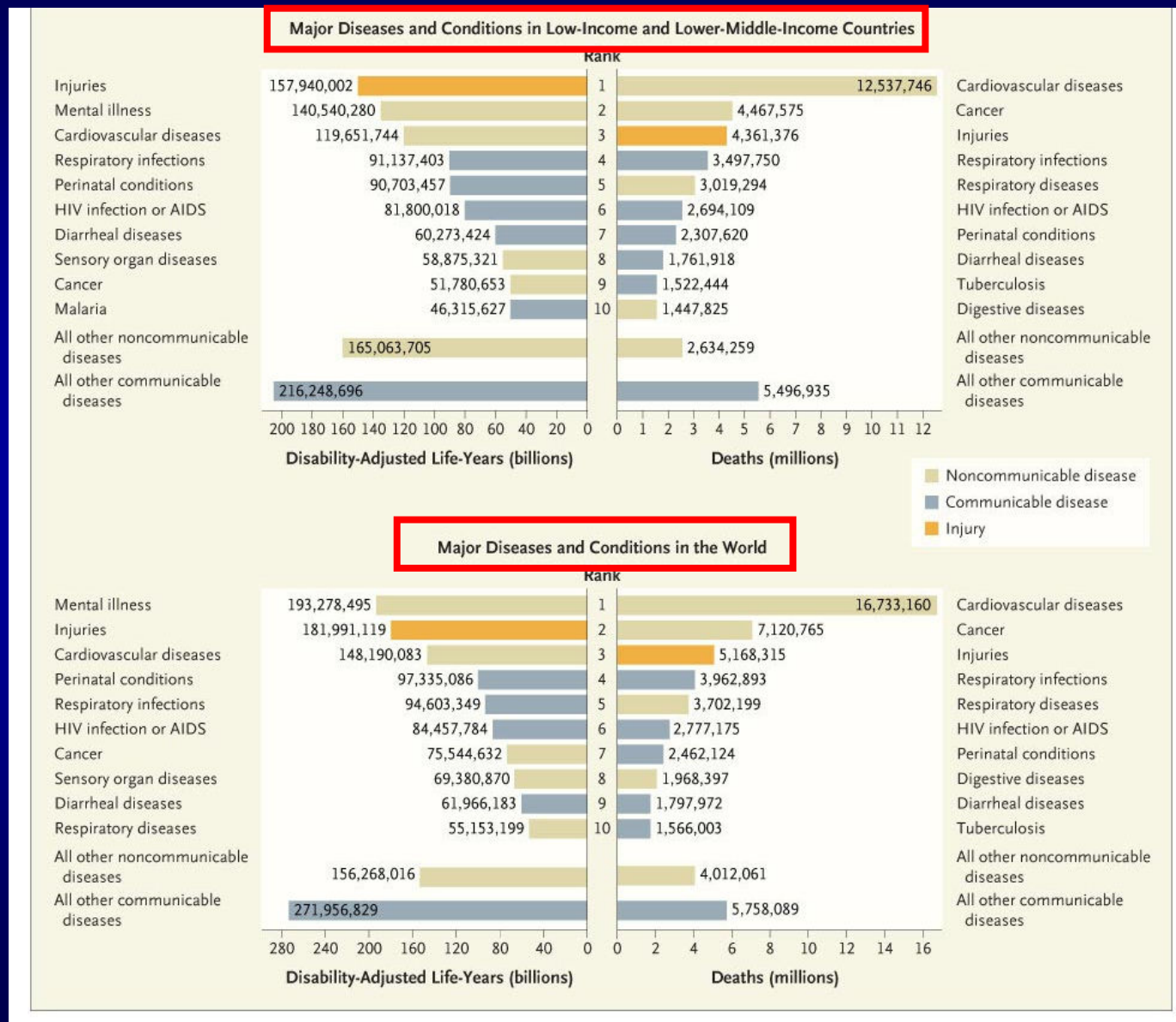


uOttawa

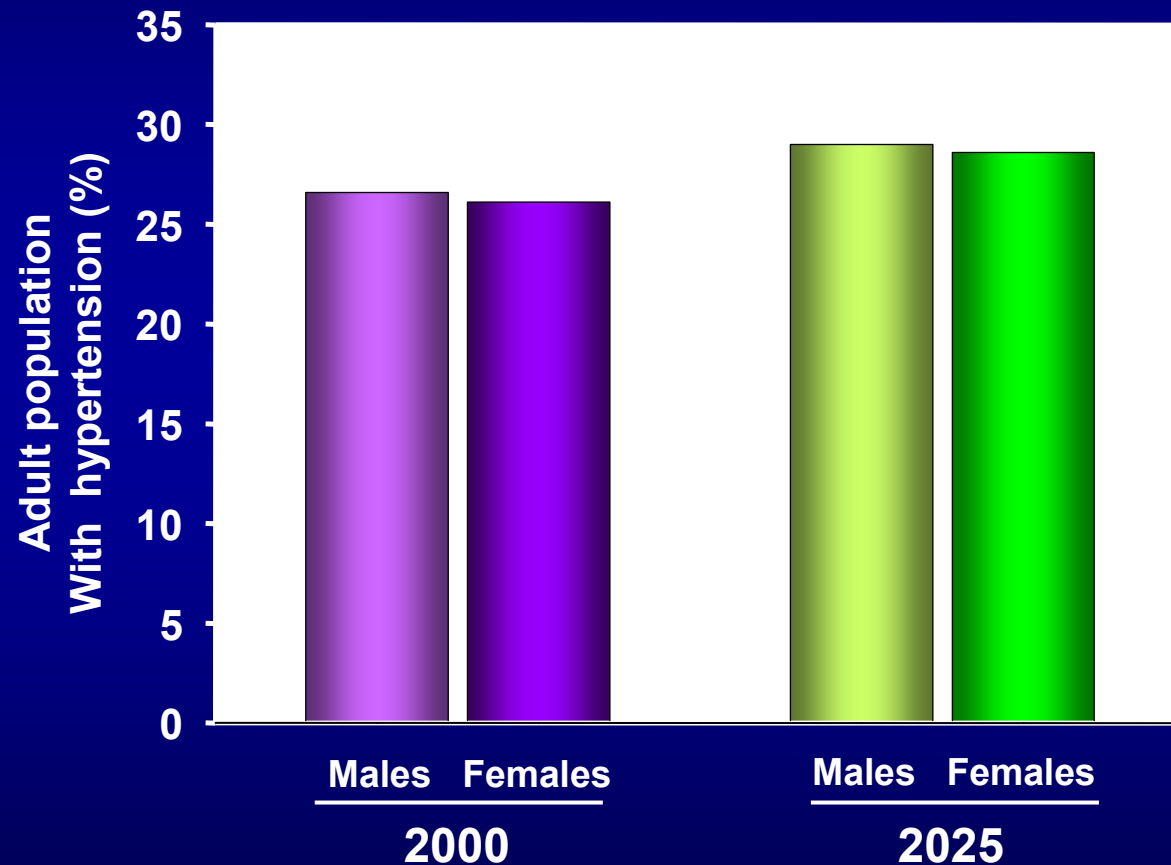
L'Université canadienne
Canada's university

Korean Society of Circulation, October 2007

Years of Healthy Life Lost (Disability-Adjusted Life-Years) and Deaths According to Disease or Condition



Global Burden of Hypertension: Analysis of Worldwide Data



Total number of adults
with hypertension

972 million

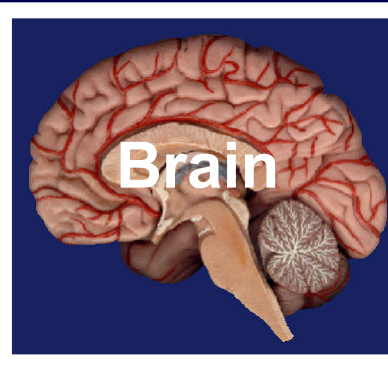
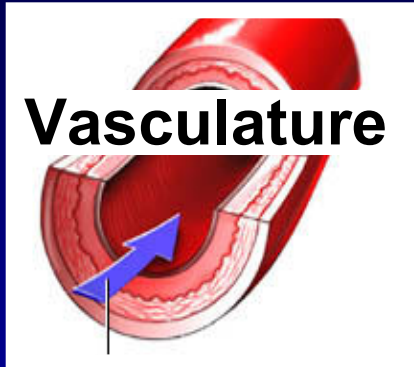
1.56 billion (60%↑)

Kearney et al. Lancet 2005;365:217

Multiple Systems Contribute to and are Targets of Hypertension

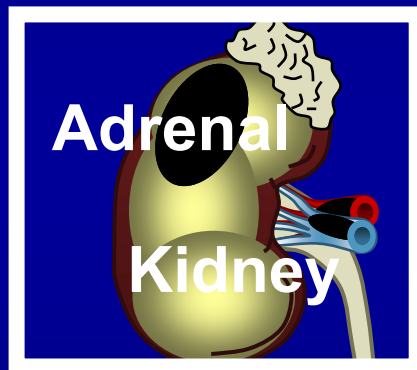
- Vasoconstriction
- Vascular Growth
- Inflammation
- Platelet aggregation

Vasculature



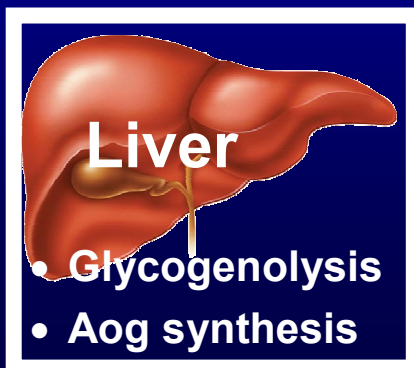
Brain

- Sympathetic activation
- Thirst



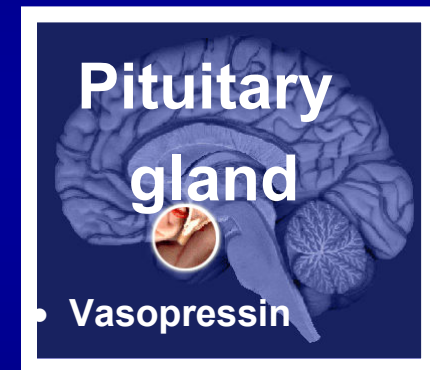
Adrenal Kidney

- Water retention
- Aldosterone
- Na⁺ reabsorption
- Efferent arteriolar vasoconstriction
- Catecholamine release



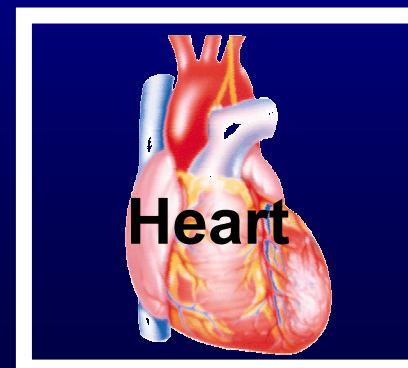
Liver

- Glycogenolysis
- Aog synthesis



Pituitary gland

- Vasopressin



Heart

- Inotropic effects
- Chronotropic effects
- Hypertrophy

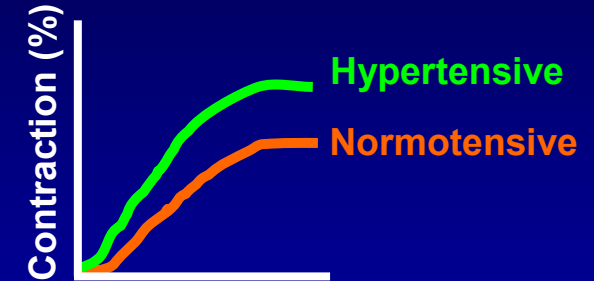
↑ Blood Pressure

Vascular Phenotype in Hypertension

RAS

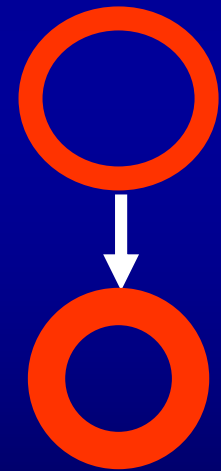
Functional

- ↑ contraction
- ↓ dilation
- endothelial dysfunction



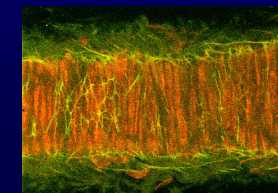
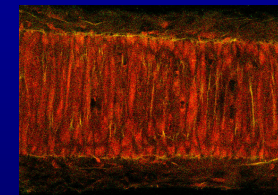
Structural

- vascular remodeling
- inflammation
- fibrosis

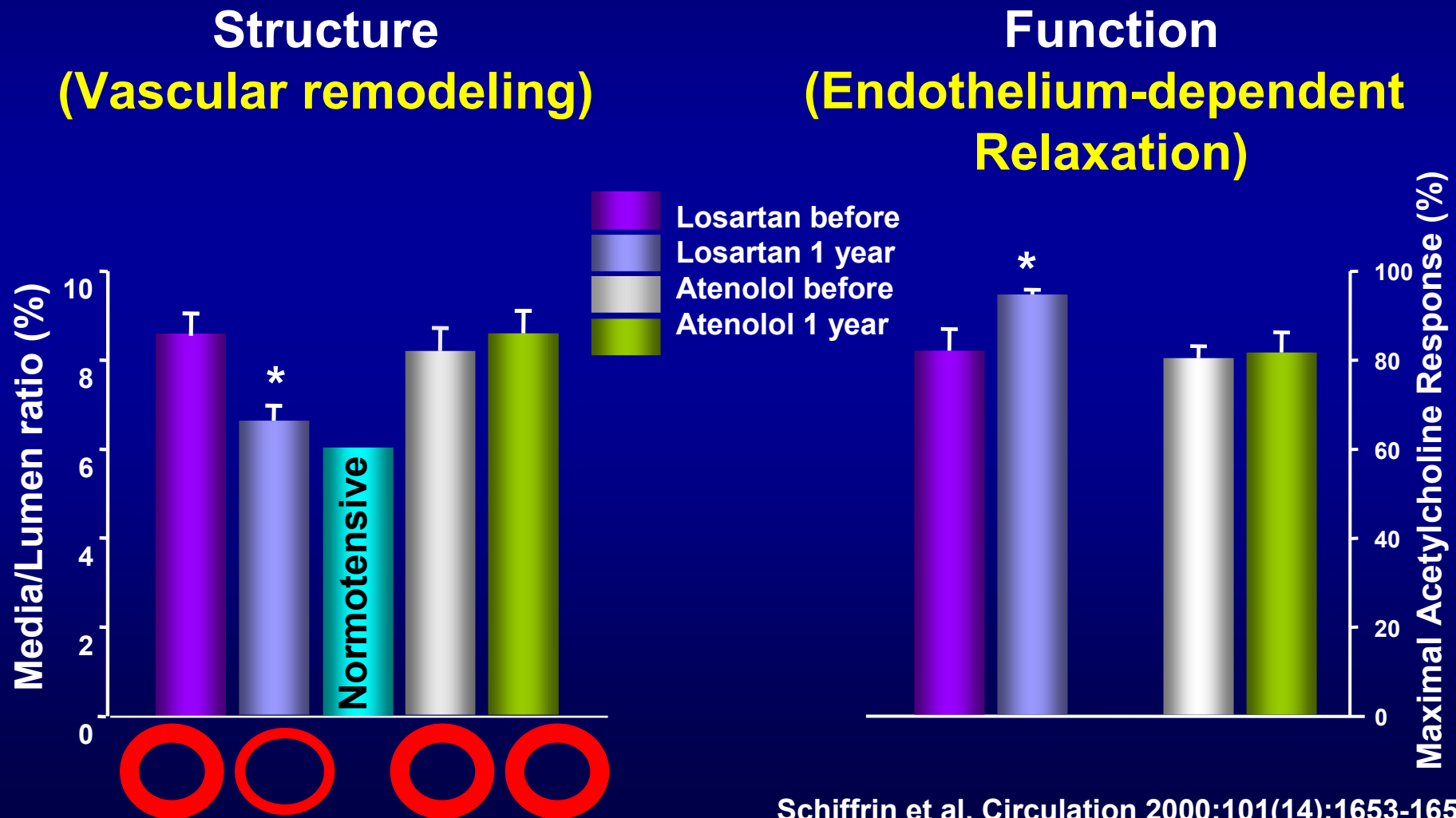


Mechanical

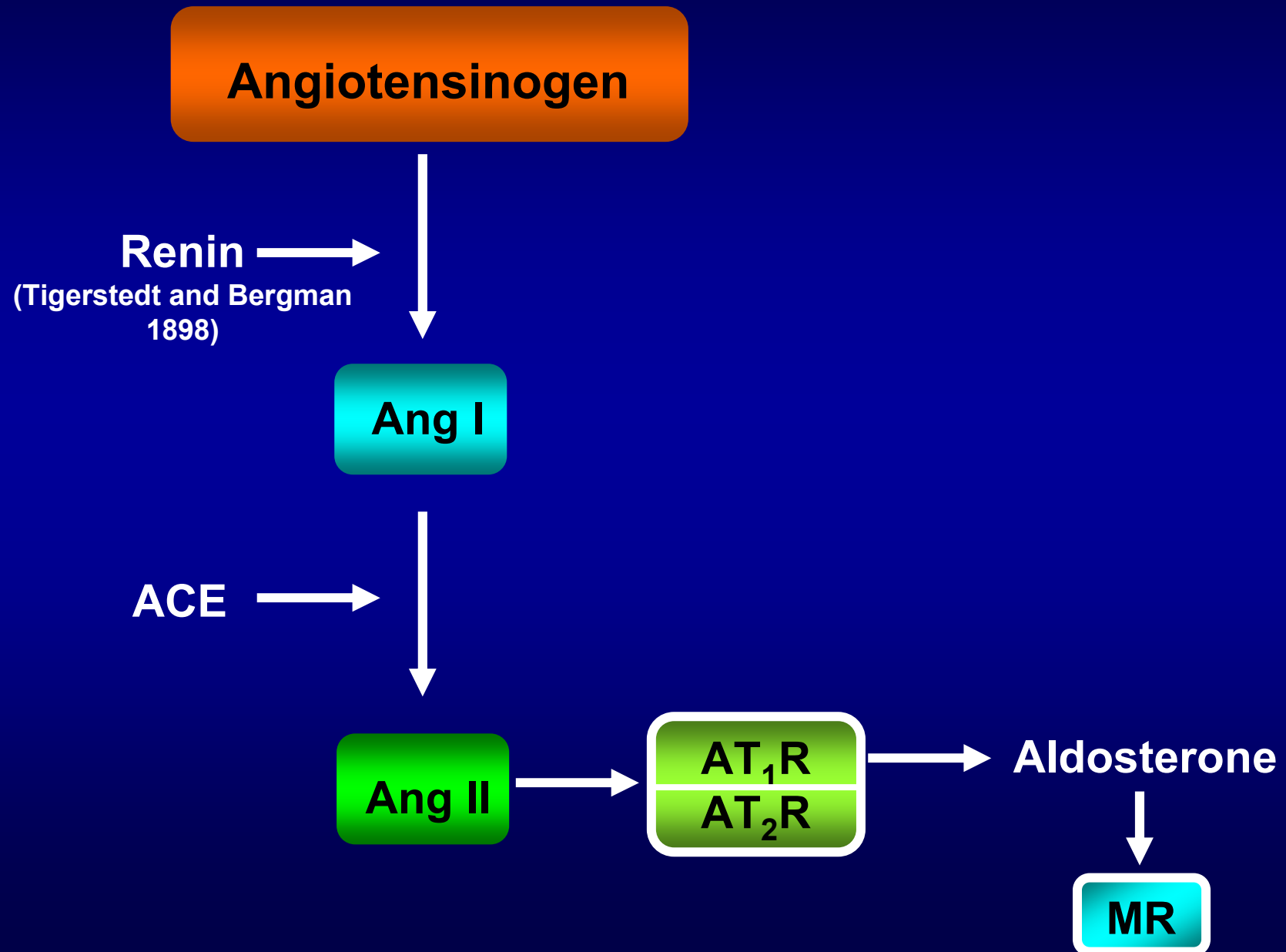
- ↓ distensibility
- ↑ stiffness
- ↓ elasticity



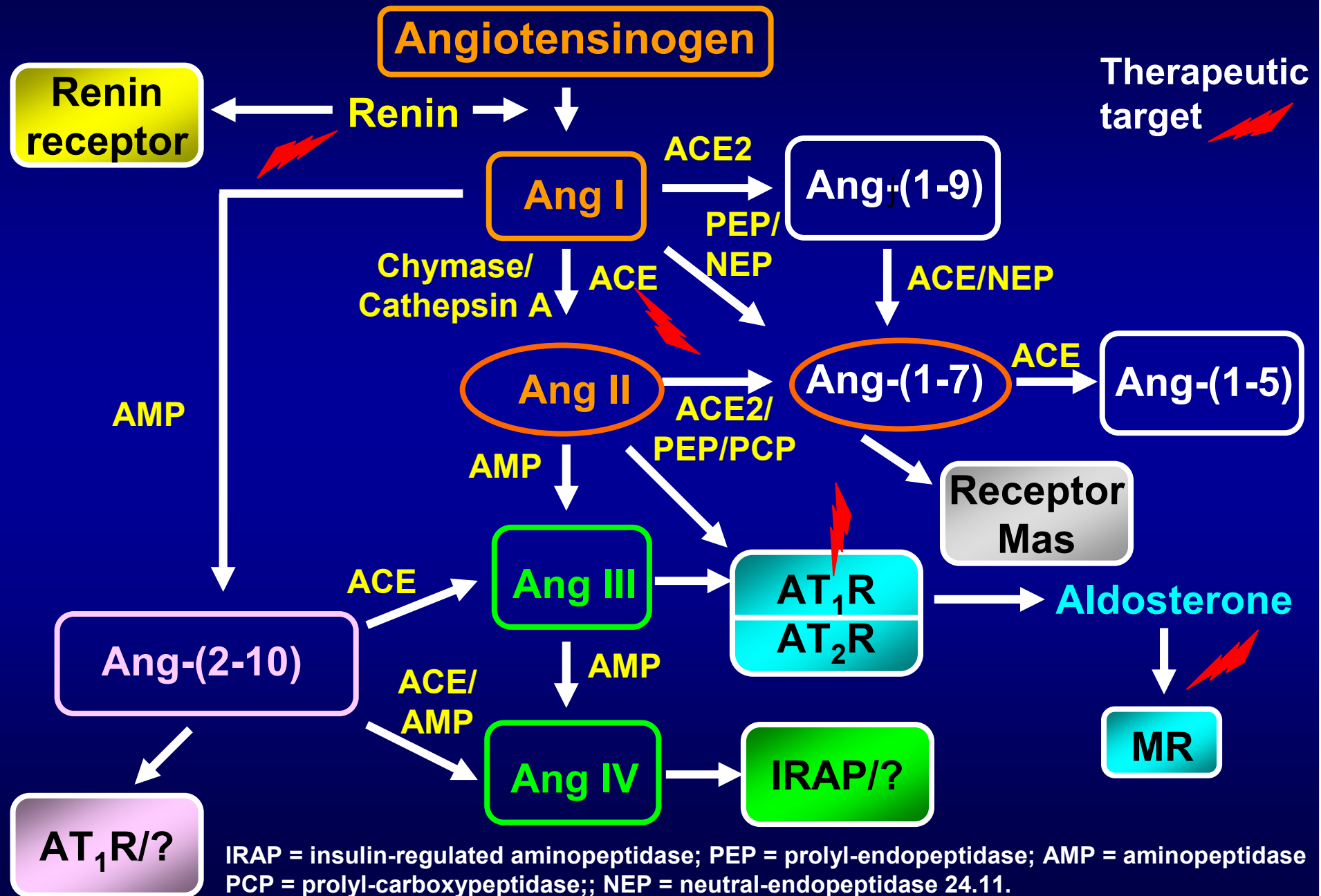
AT₁R Blockade Decreases BP, Improves Vascular Function and Regresses Remodeling in Hypertension – BP-independent Actions.



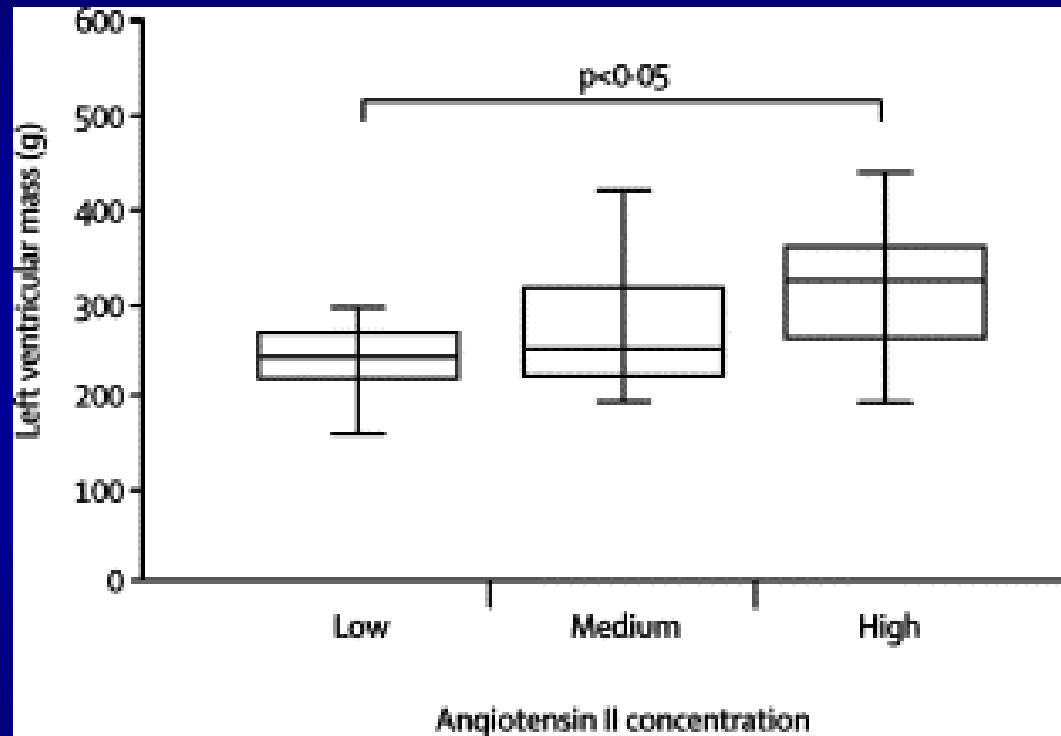
The RAS – a Simple Paradigm



The RAS – a Complex Network



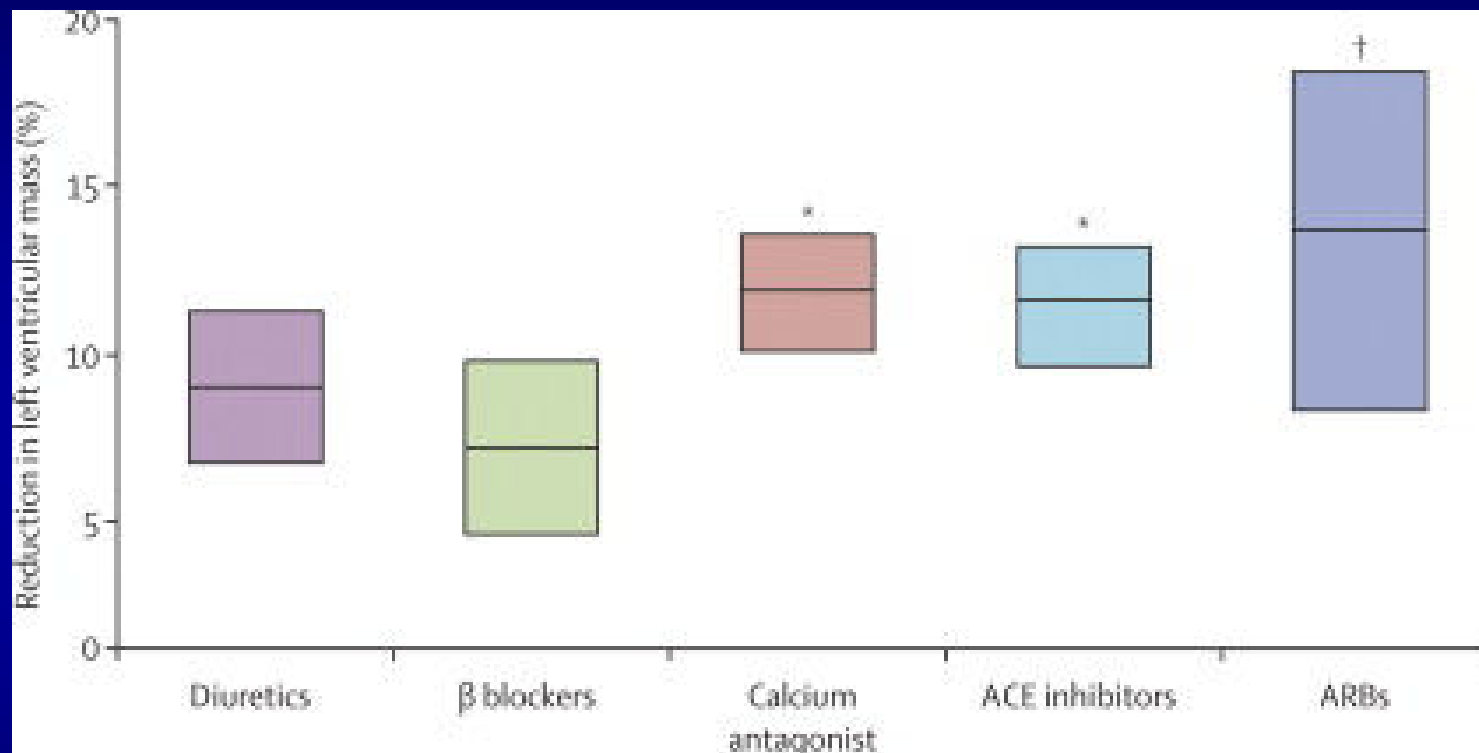
High Ang II Concentrations are Associated with LVH in Hypertensive Patients



Box plot of left ventricular mass in never treated hypertensive patients, according to Ang II concentrations.

Schmieder Circulation 1996; 94: 1304–09.

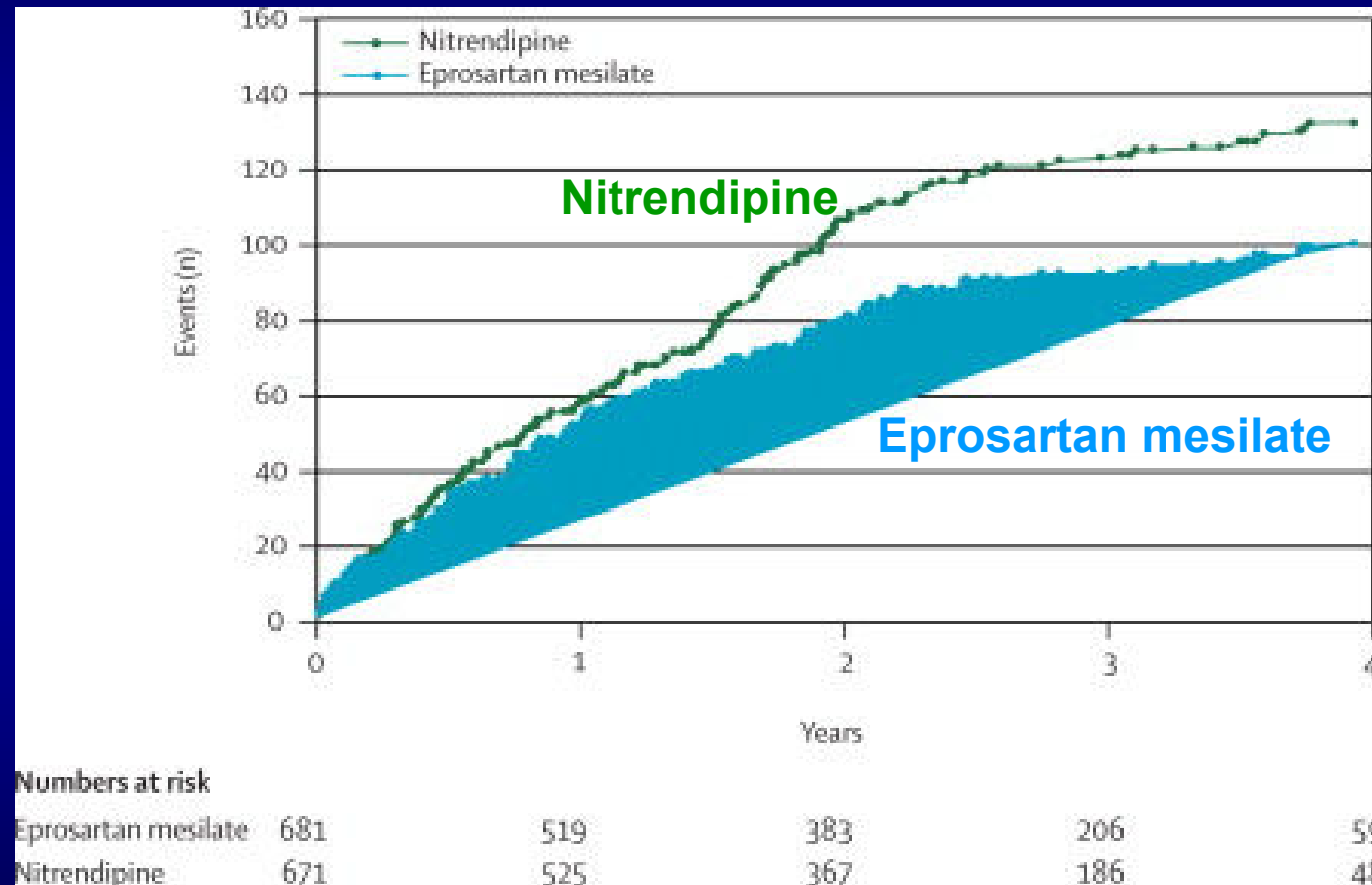
A Meta-analysis of the Effects of Treatment on Left Ventricular Mass in Essential Hypertension



Reduction of left ventricular mass stratified according to various antihypertensive regimens. * $p < 0.05$, † $p < 0.01$ versus β blocker.

The RAAS and Stroke

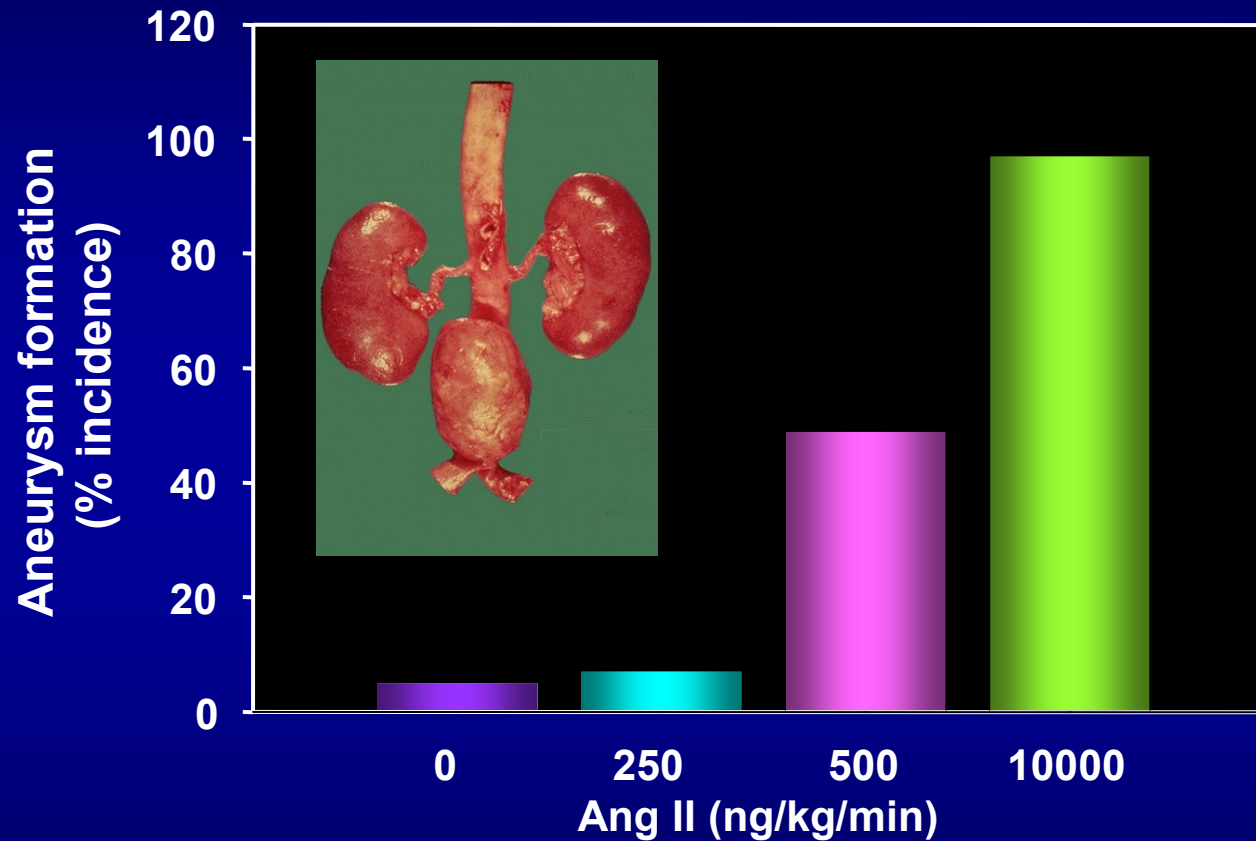
- The most crucial factor in stroke prevention is best possible BP control.
- Meta-analyses suggest that ARBs are effective in stroke prevention.



Cumulative incidence of cerebrovascular events in patients in the Morbidity and Mortality after Stroke (MOSES) study

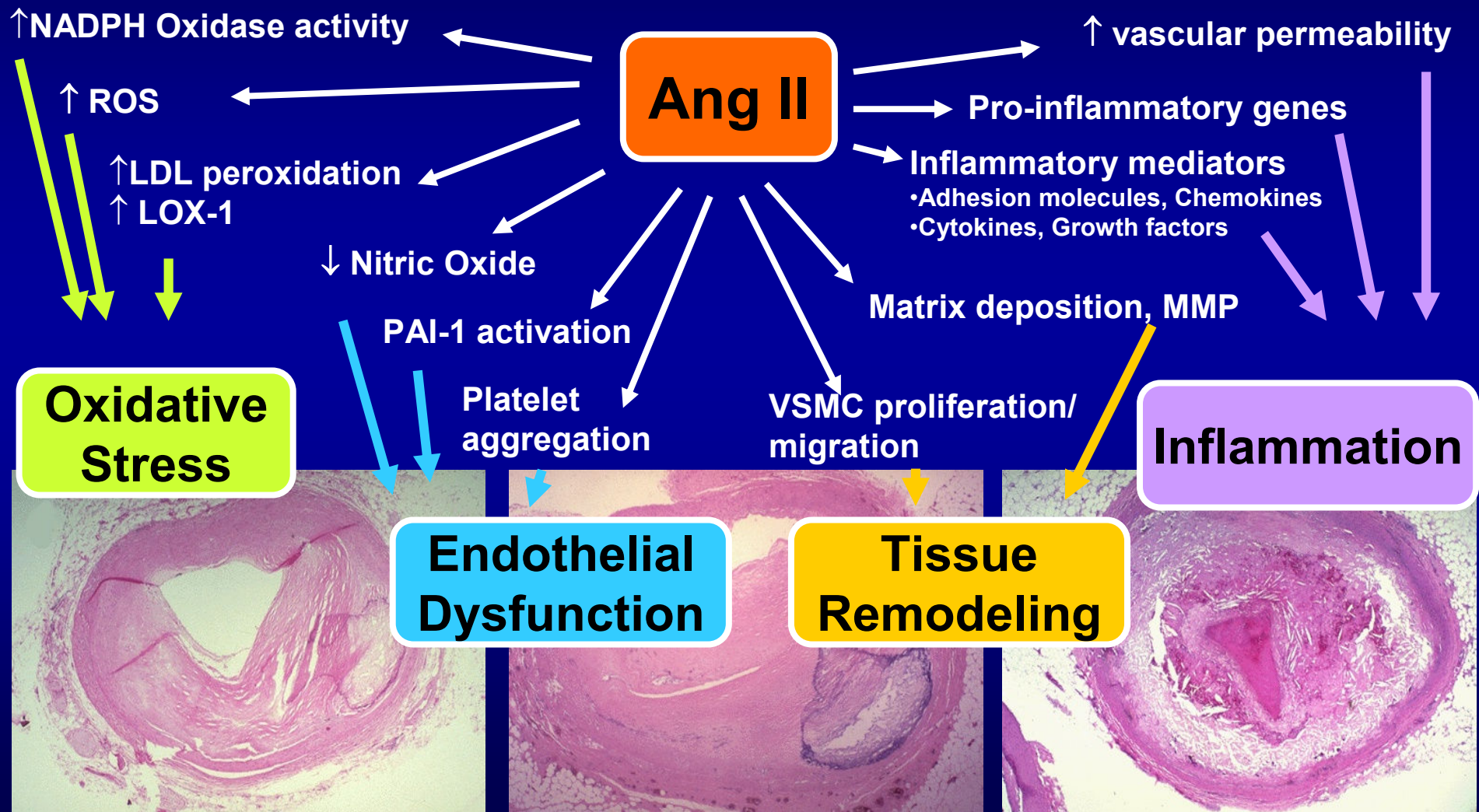
Schrader et al. Stroke 2005;36:1218

RAAS and Aortic Aneurysm Formation



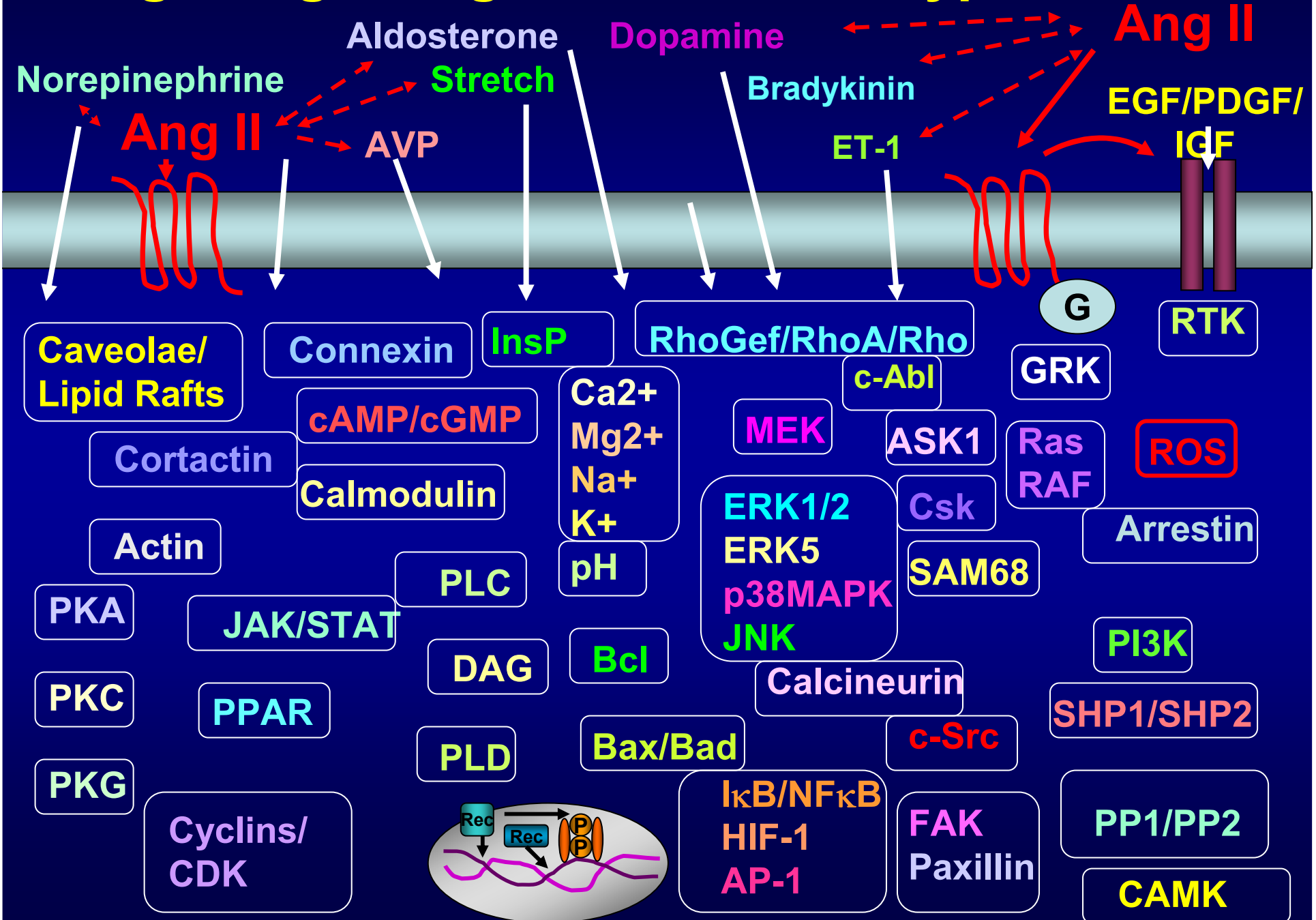
Ang II was infused in apoE^{-/-} mice fed a high fat diet

The RAAS and Atherosclerosis



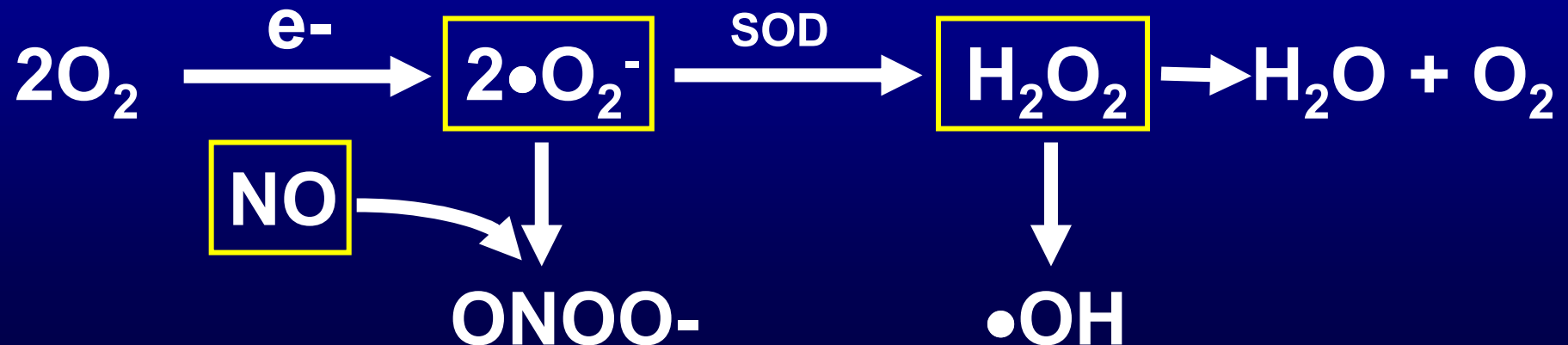
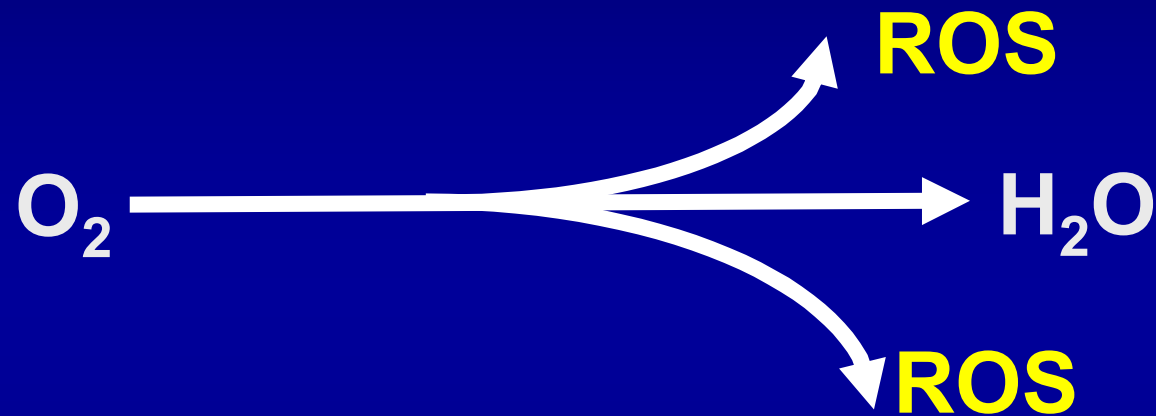
What are the Underlying Molecular and Cellular Processes that Contribute to Vascular Injury in Cardiovascular Disease?

Ang II-Signaling Molecules in Hypertension



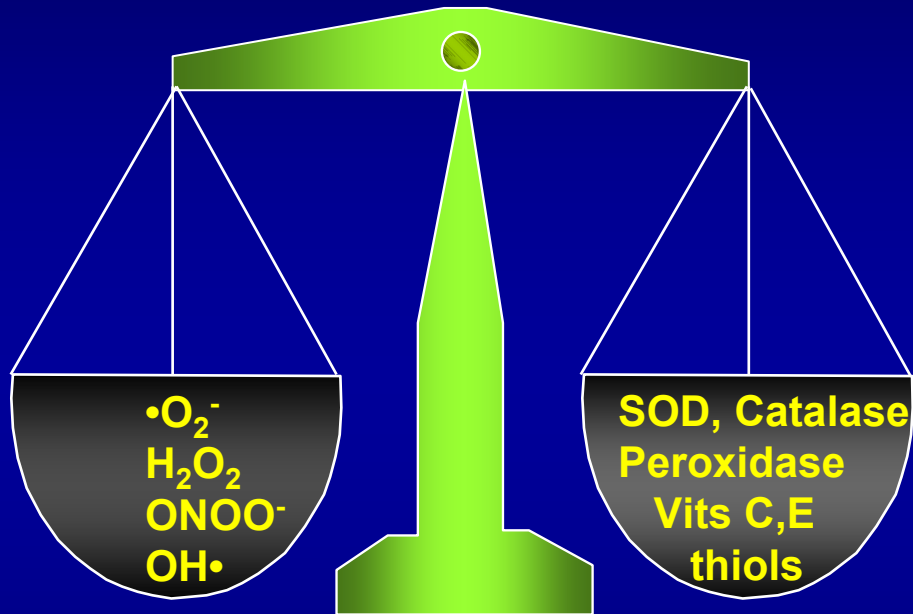
What are Reactive Oxygen Species?

ROS are intermediates in redox processes leading from oxygen to water.



Oxidative Stress

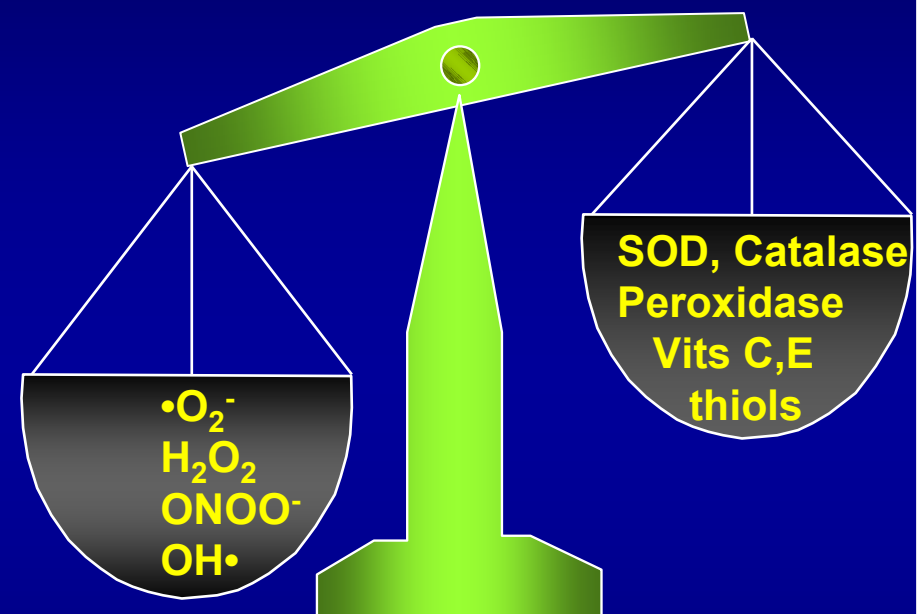
Physiological



prooxidants = antioxidants

Aging, Healing, Repair

Pathological

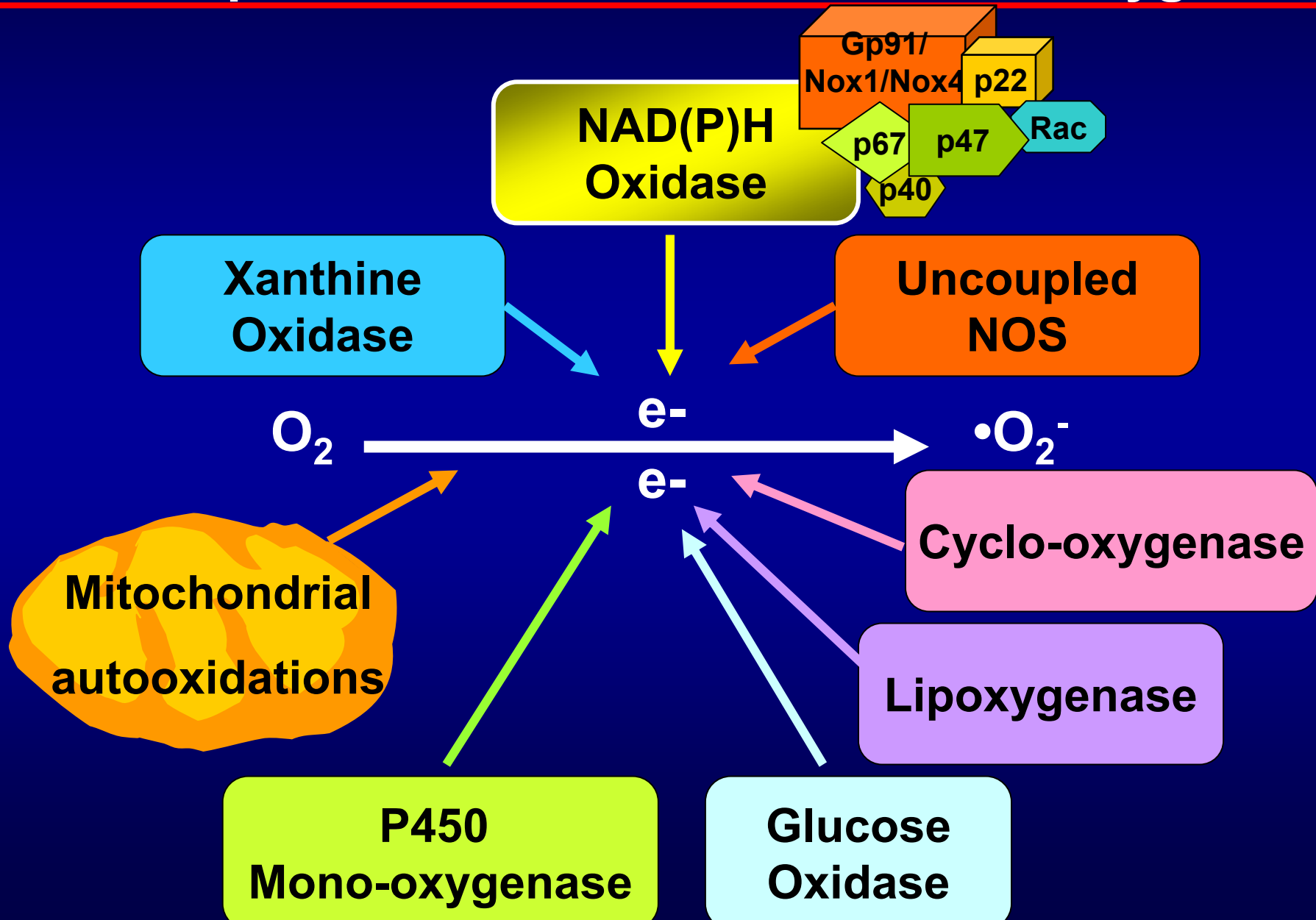


prooxidants > antioxidants

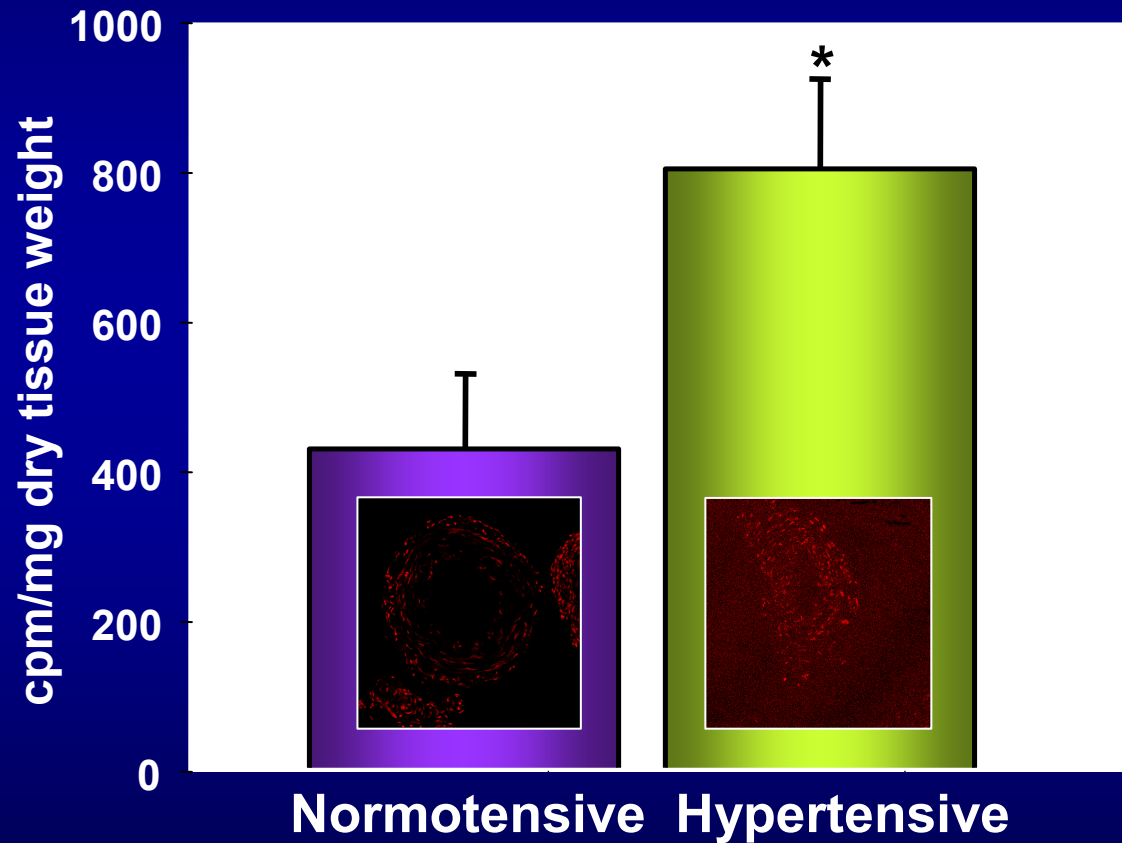
↓
oxidative stress

CGD, Cancer, Diabetes, CVD, AML
CKD, Progeria, Hypertension

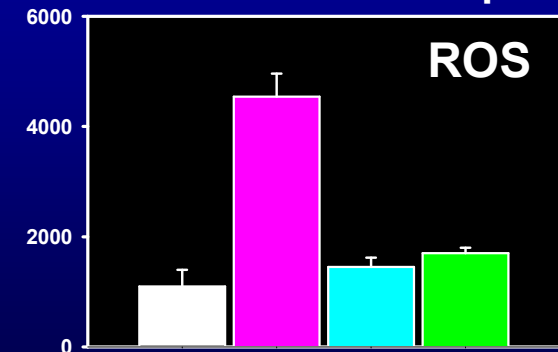
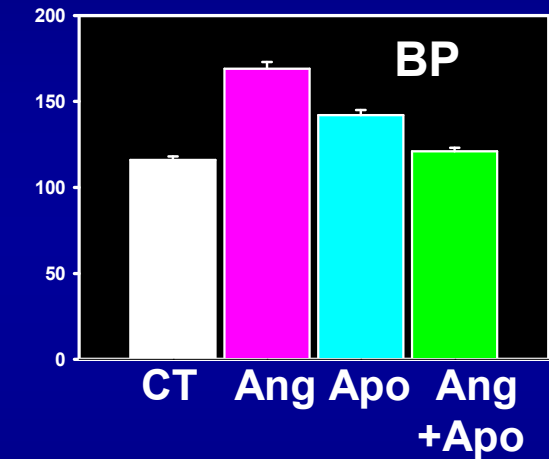
Many Cellular Enzymes Catalyze the Generation of Superoxide Anion from Molecular Oxygen



Increased ROS (oxidative stress) in Resistance Arteries from Hypertensive Patients

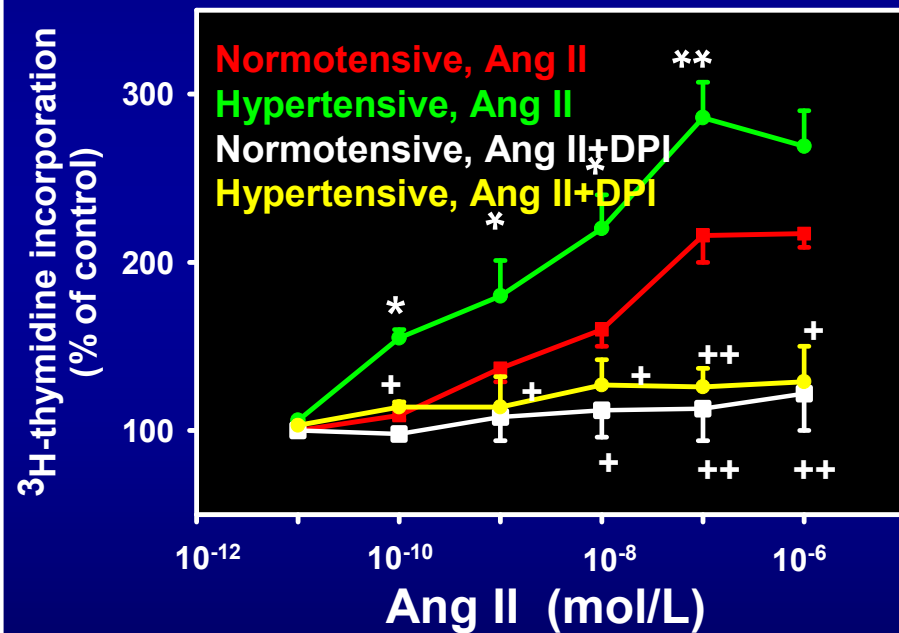


NADPH oxidase inhibition Decreases BP and Oxidative Stress

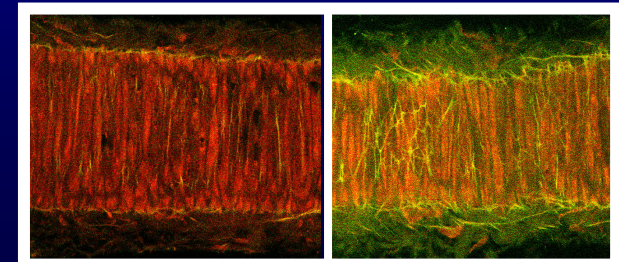
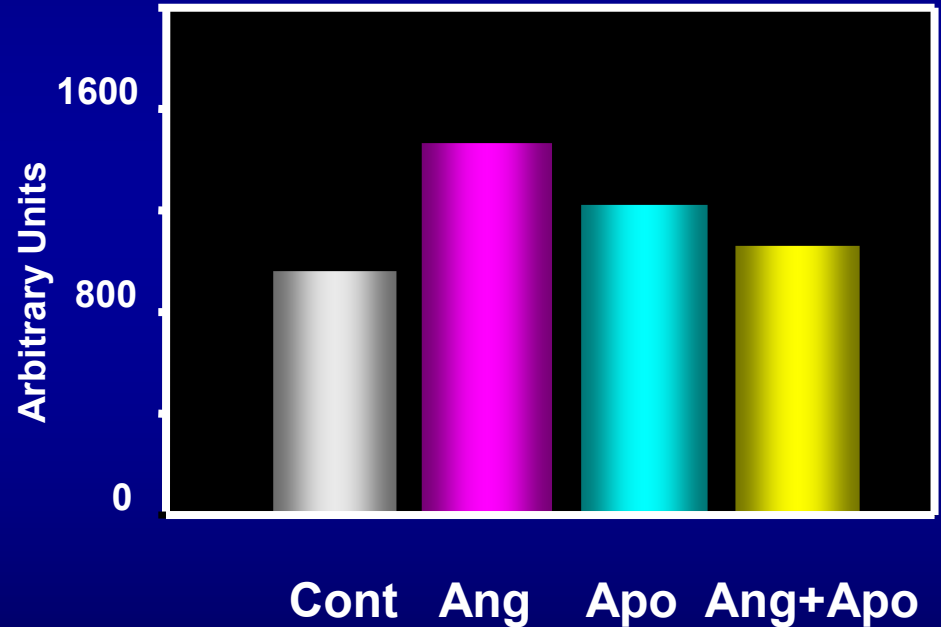
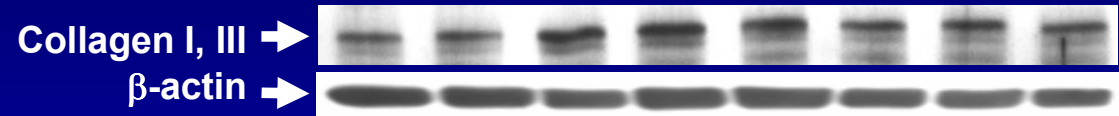


Ang II Stimulates Vascular Growth and Fibrosis via NADPH Oxidase-driven Generation of ROS

Growth

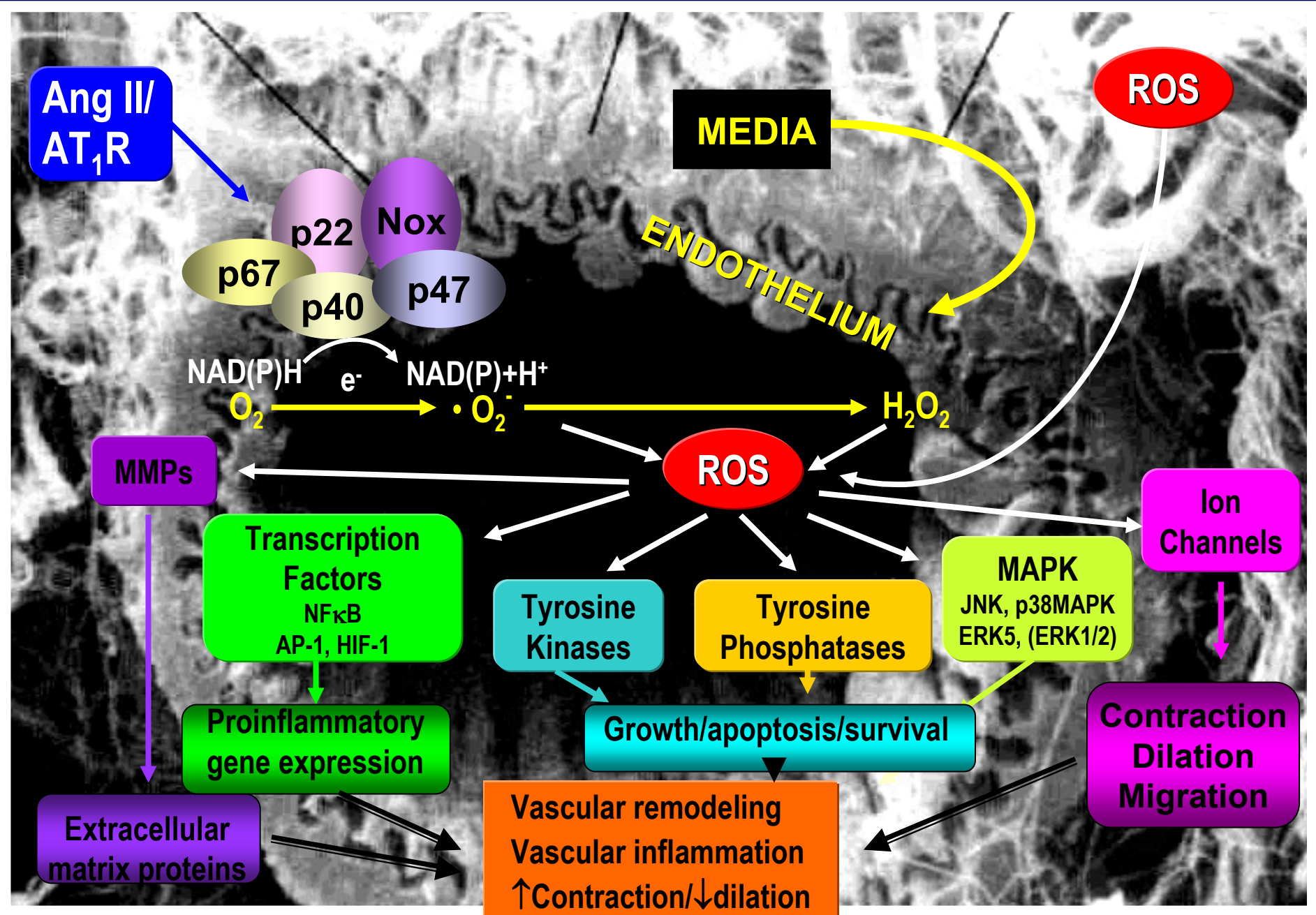


Fibrosis

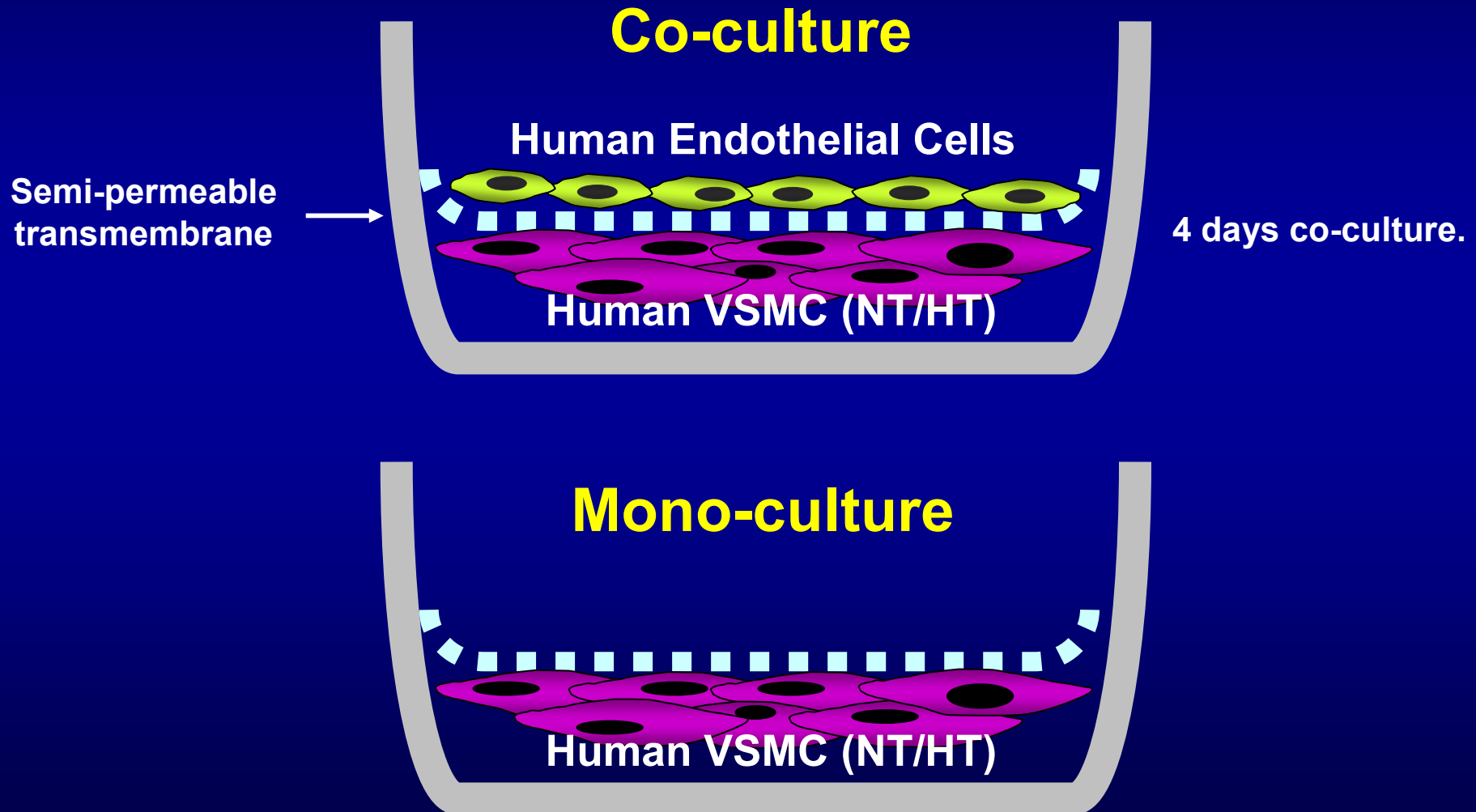


Touyz et al. J Hypertens. 2001;19(7):1245.

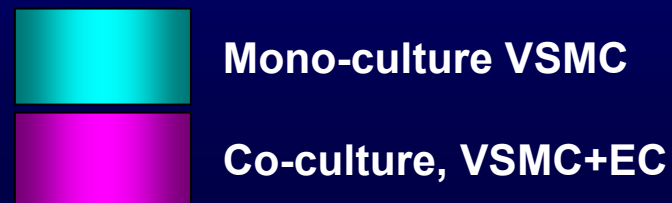
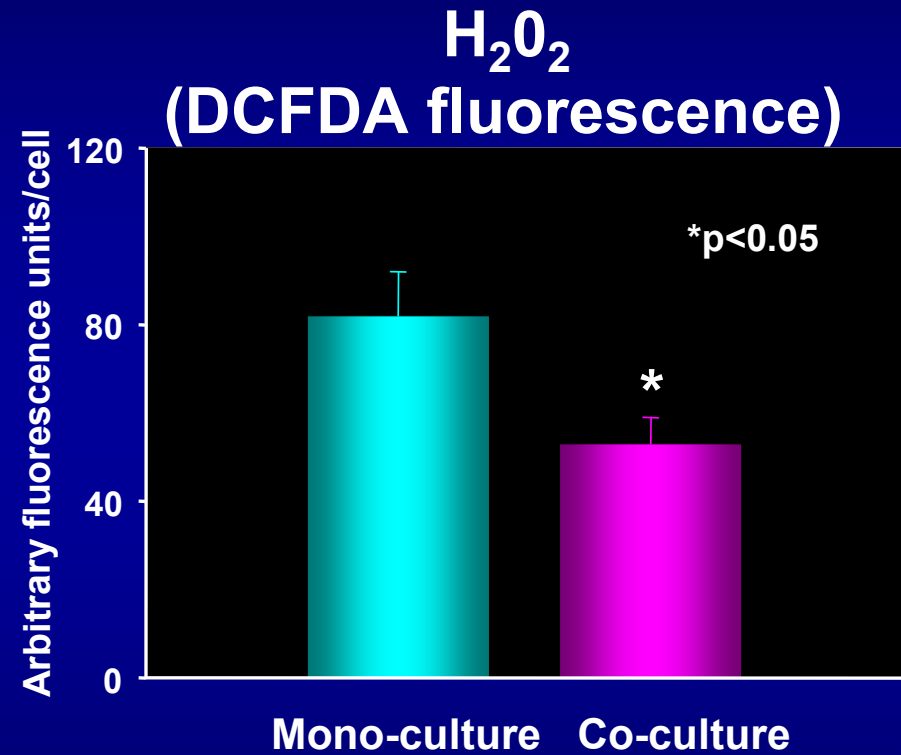
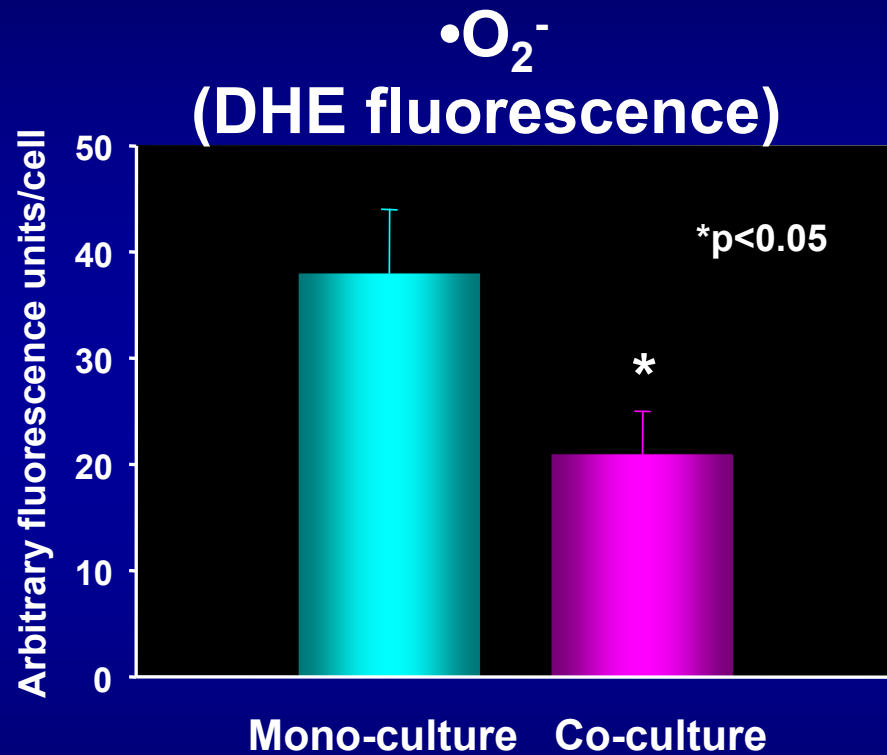
ROS Signaling and Functional Responses



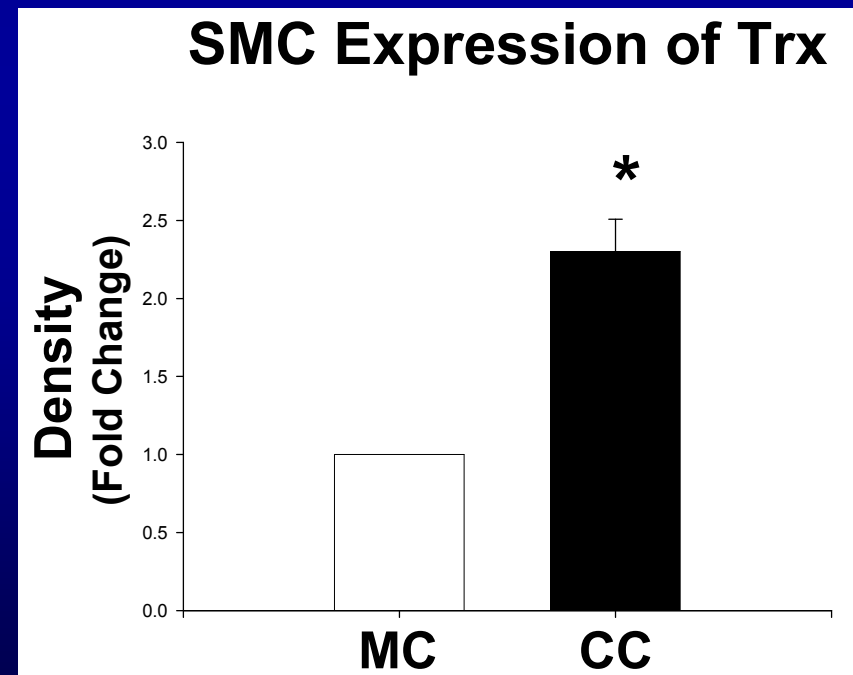
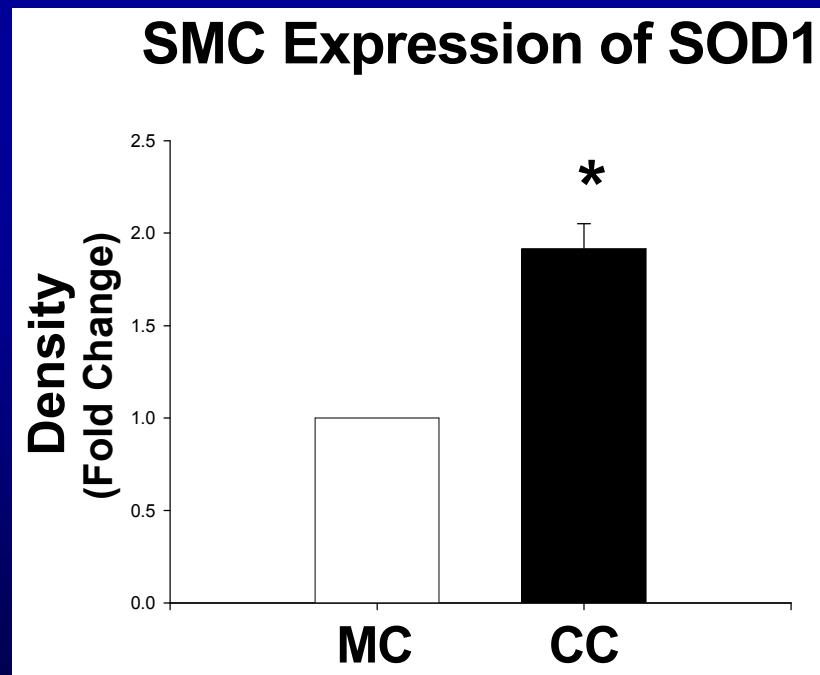
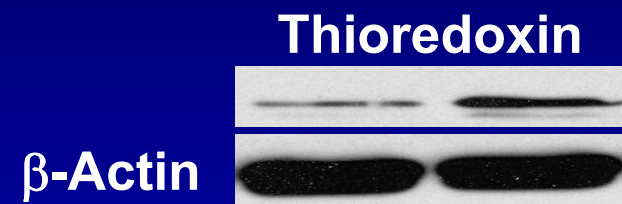
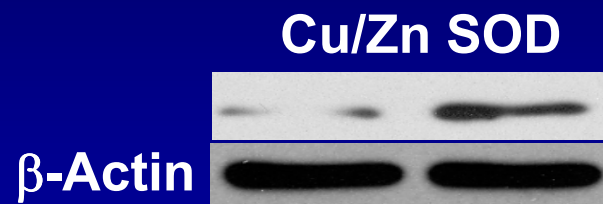
Interactions Between Endothelial and Vascular Smooth Muscle Cells



Endothelial Cells Negatively Modulate VSMC Levels of $\bullet\text{O}_2^-$ and H_2O_2

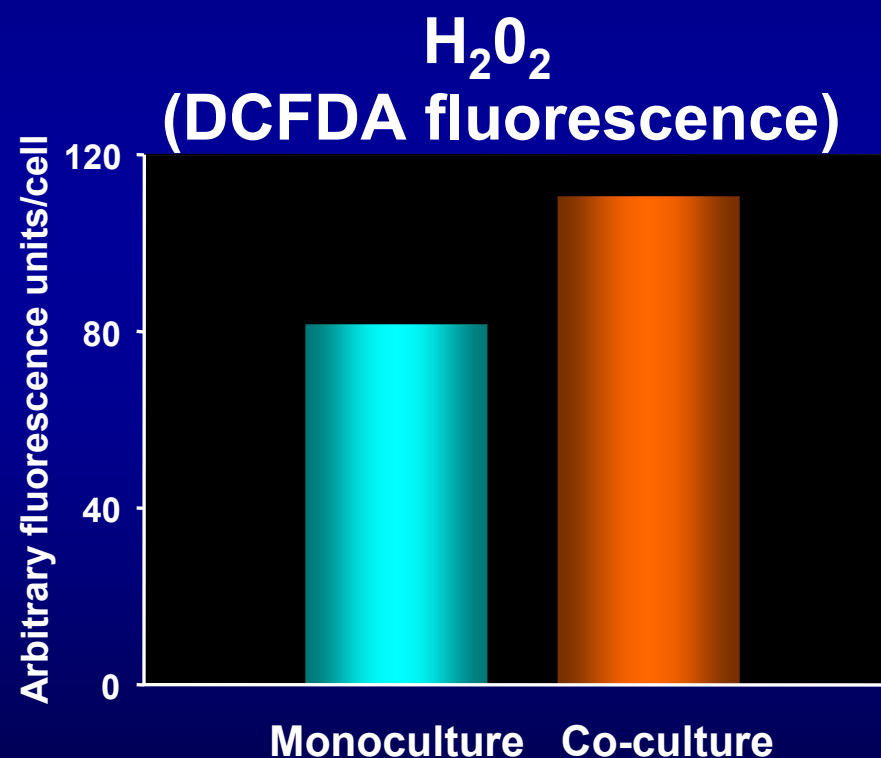
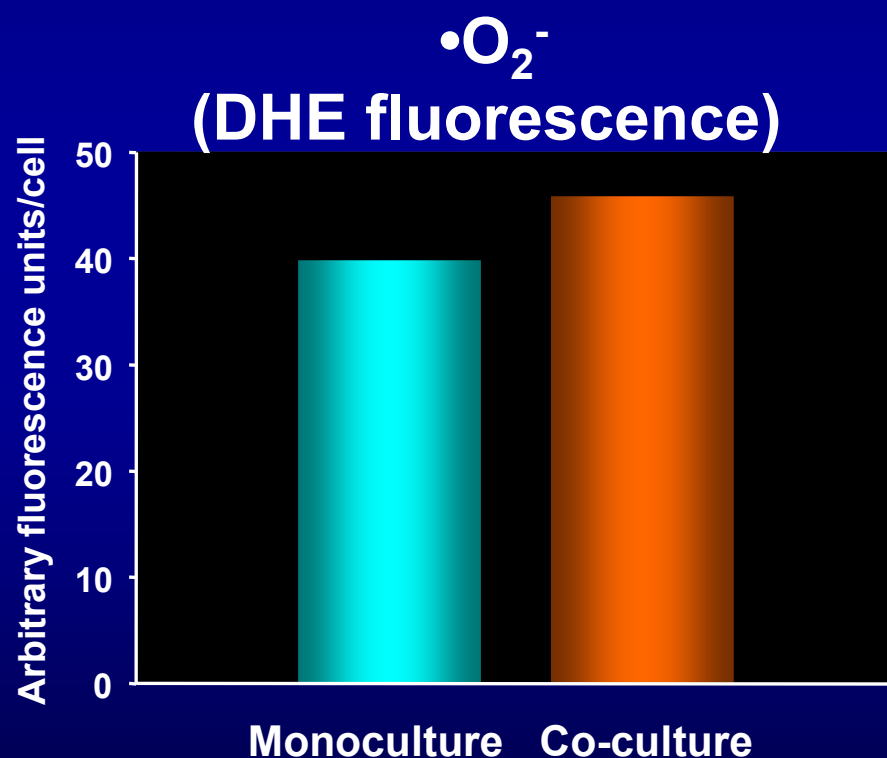


ECs Upregulate Expression of Antioxidants in Human VSMCs

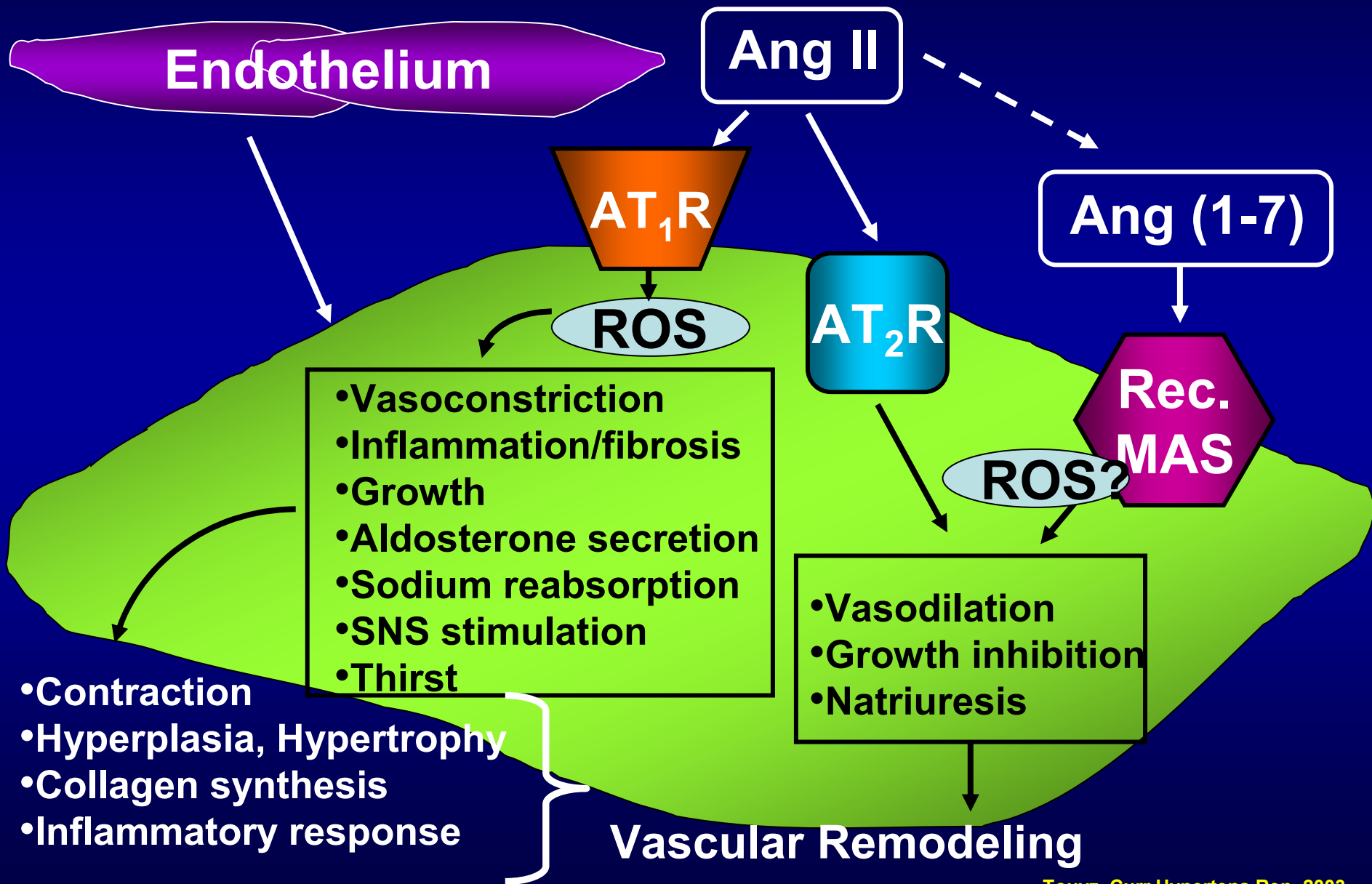


MC, monoculture; CC, co-culture

Endothelial Cells do not Modulate VSMCs from HT Patients



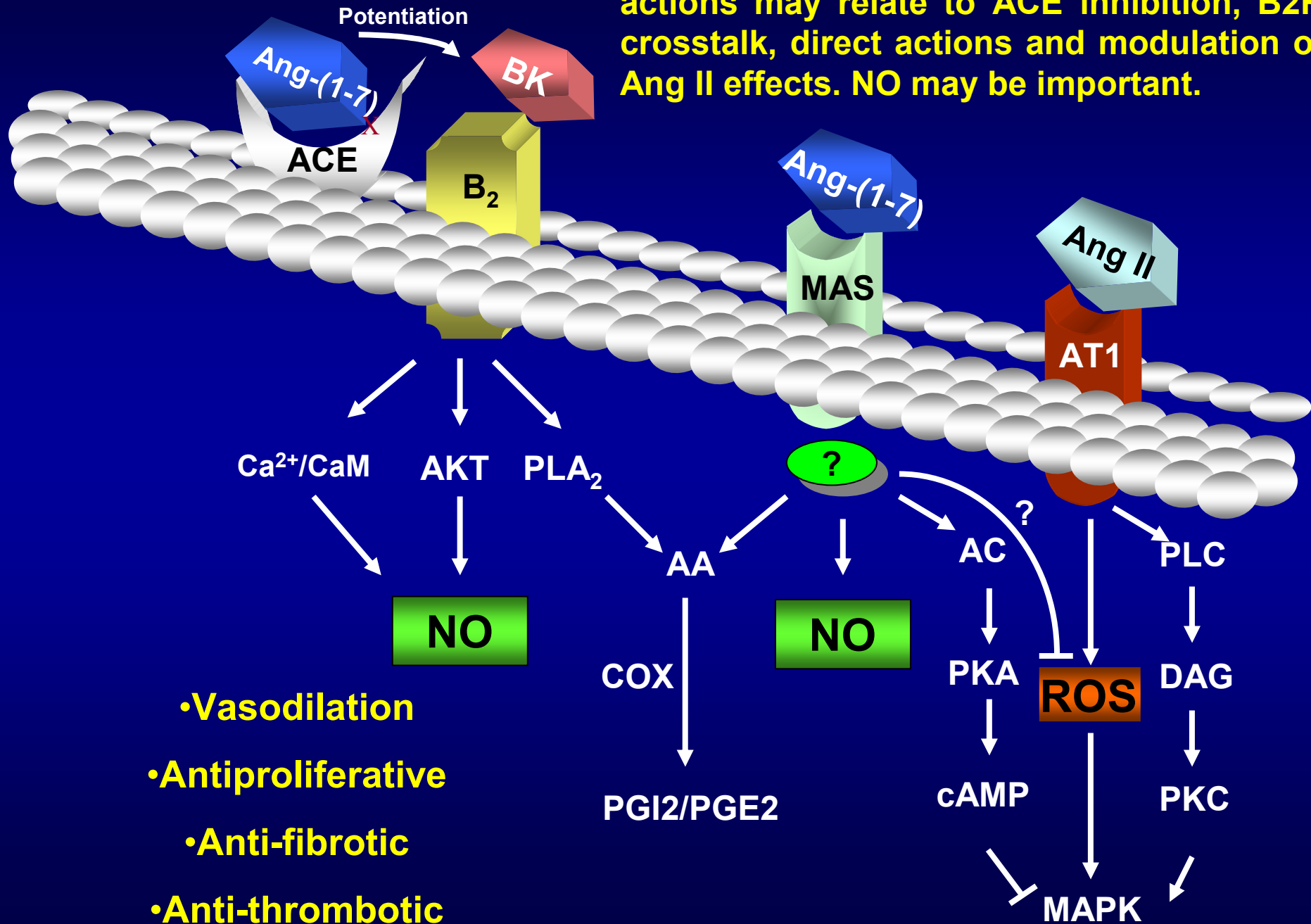
Receptor-mediated Effects of Ang II and Ang (1-7)



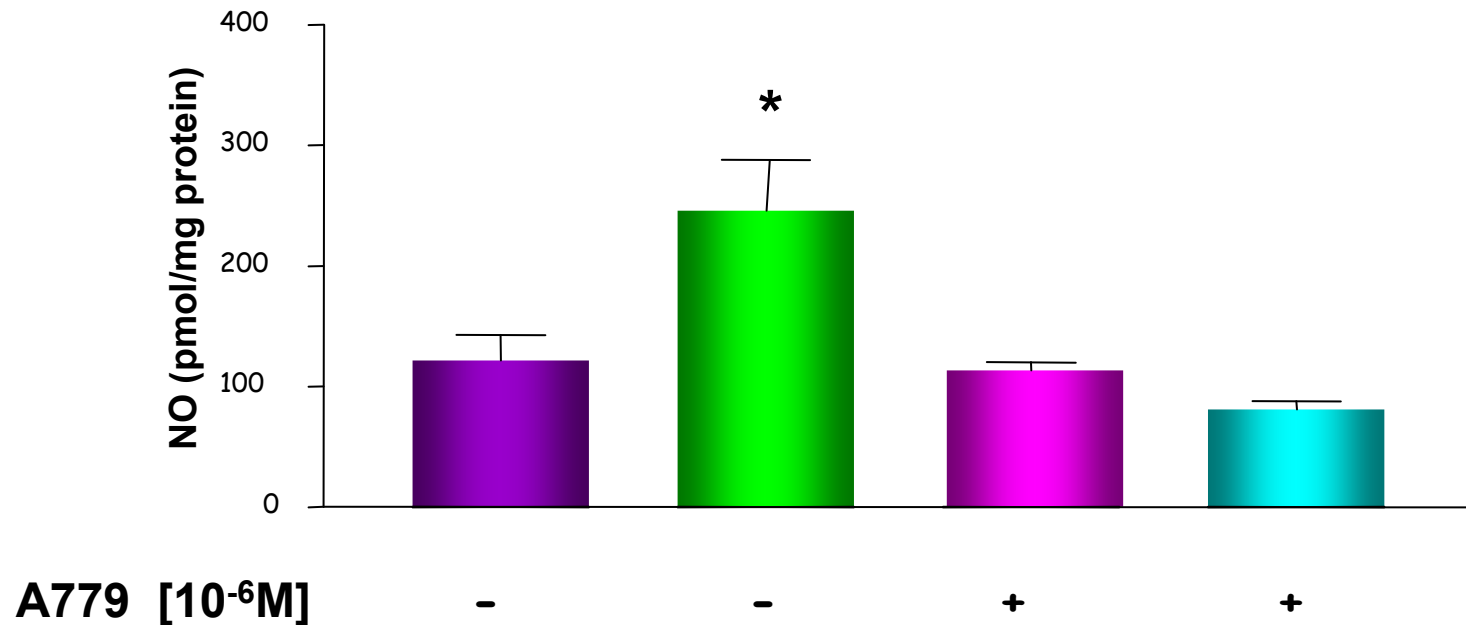
What is Ang-(1-7)?

- Ang-(1-7) is a 7 amino acid peptide
- Ang-(1-7) is formed by different enzymes: ACE2, NEP, Oligopeptidases.
- Ang-(1-7) does not bind to AT1R or AT2R.
- Mas oncogene receptor binds Ang-(1-7)
- **Cardiac effects of Ang-(1-7)**
 - protective against ischemia
 - corrects arrhythmias
 - prevents remodeling
- **Vascular effects of Ang-(1-7)**
 - induces vasodilation
 - antigrowth
 - erectile dysfunction
- **Renal effects** – natriuretic and diuretic actions

Mechanisms involved in Ang (1-7) vascular actions may relate to ACE inhibition, B2R crosstalk, direct actions and modulation of Ang II effects. NO may be important.

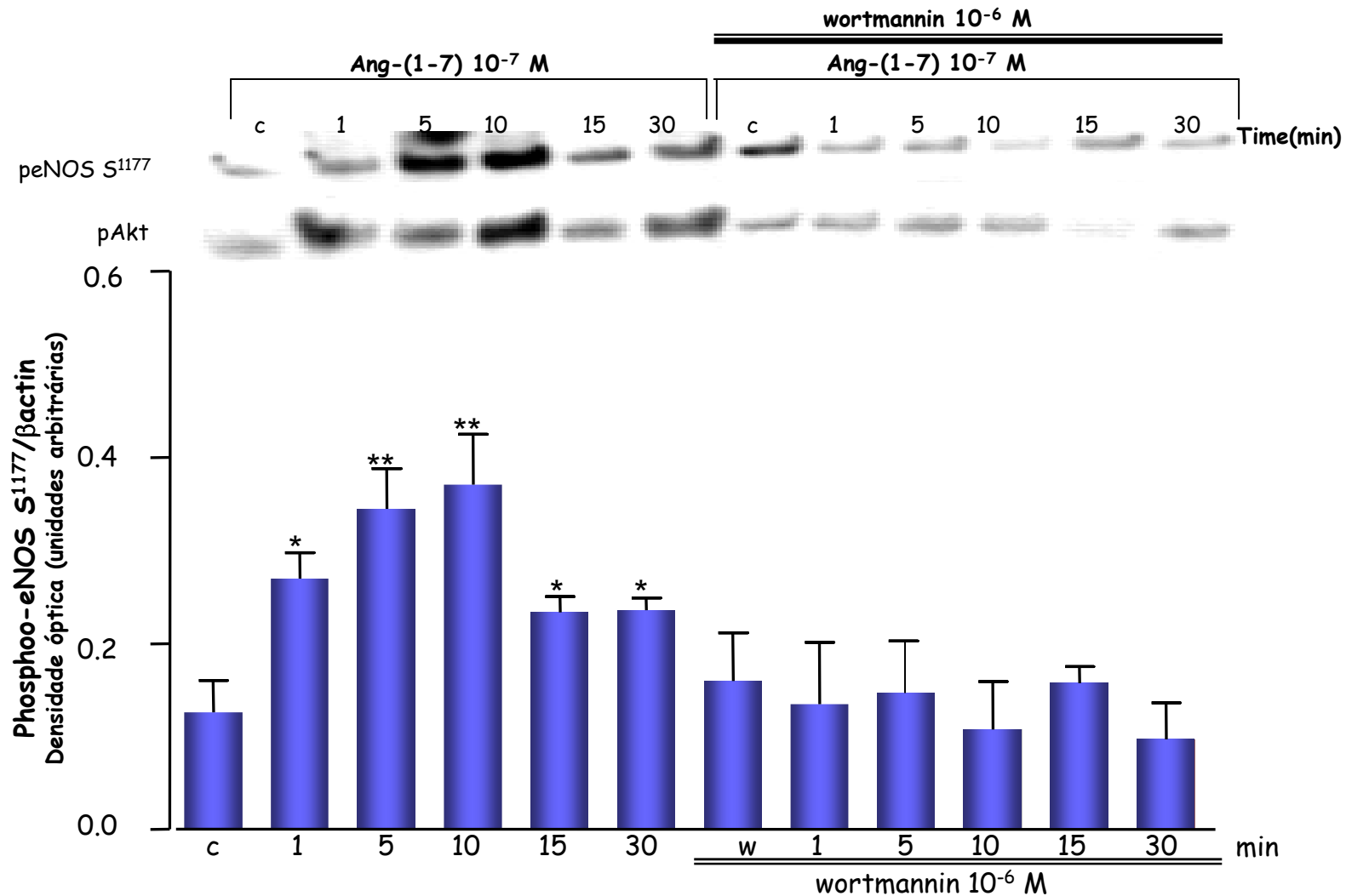


Ang (1-7) Stimulates NO Production Through Receptor Mas



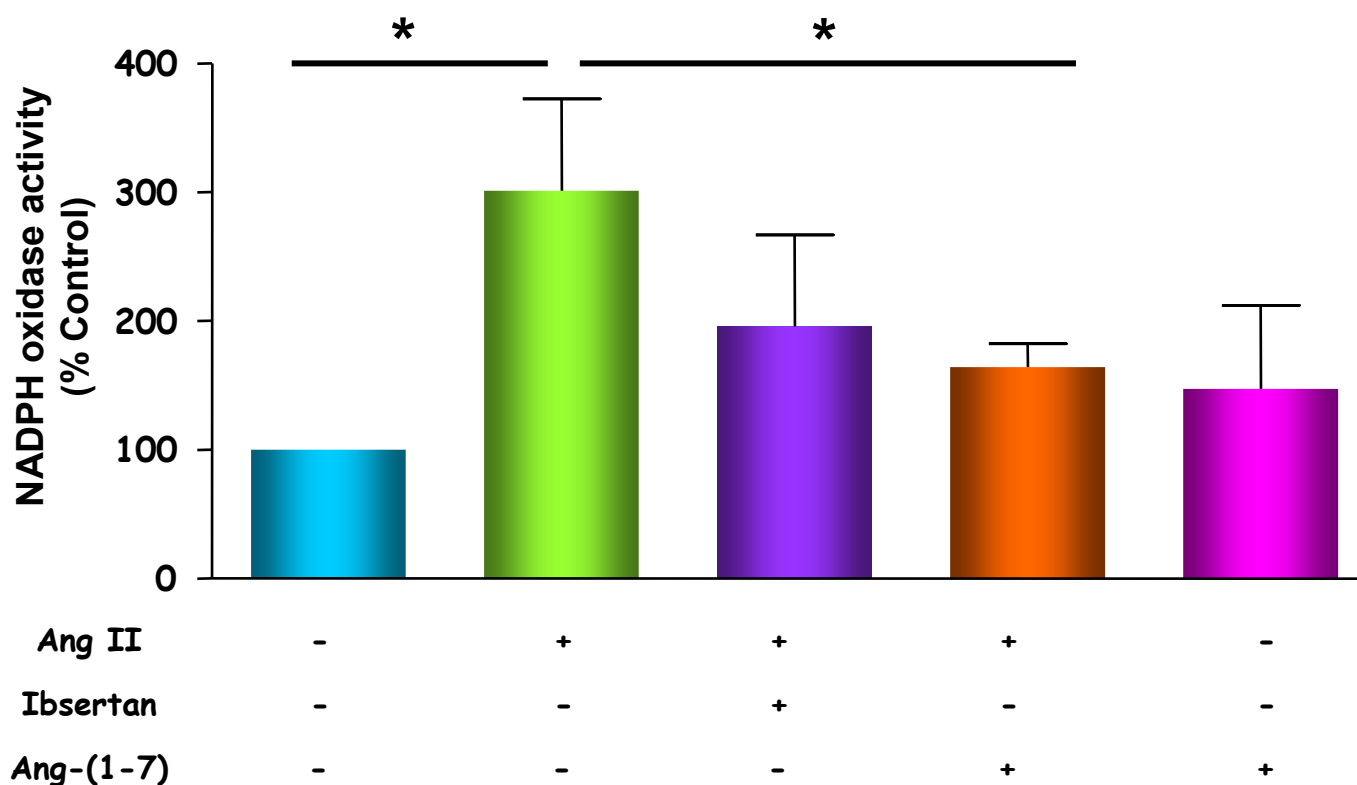
Effect of Ang-(1-7) (10^{-7} M, 30 min) on nitric oxide release in CHO-Mas cells. In some experiments the cells were treated with Ang-(1-7) antagonist ,A-779 (10^{-6} M, 10 min de pre-incubation).

Ang-(1-7)-stimulated eNOS Phosphorylation in Human Endothelial Cells Involves Protein Kinase B/Akt



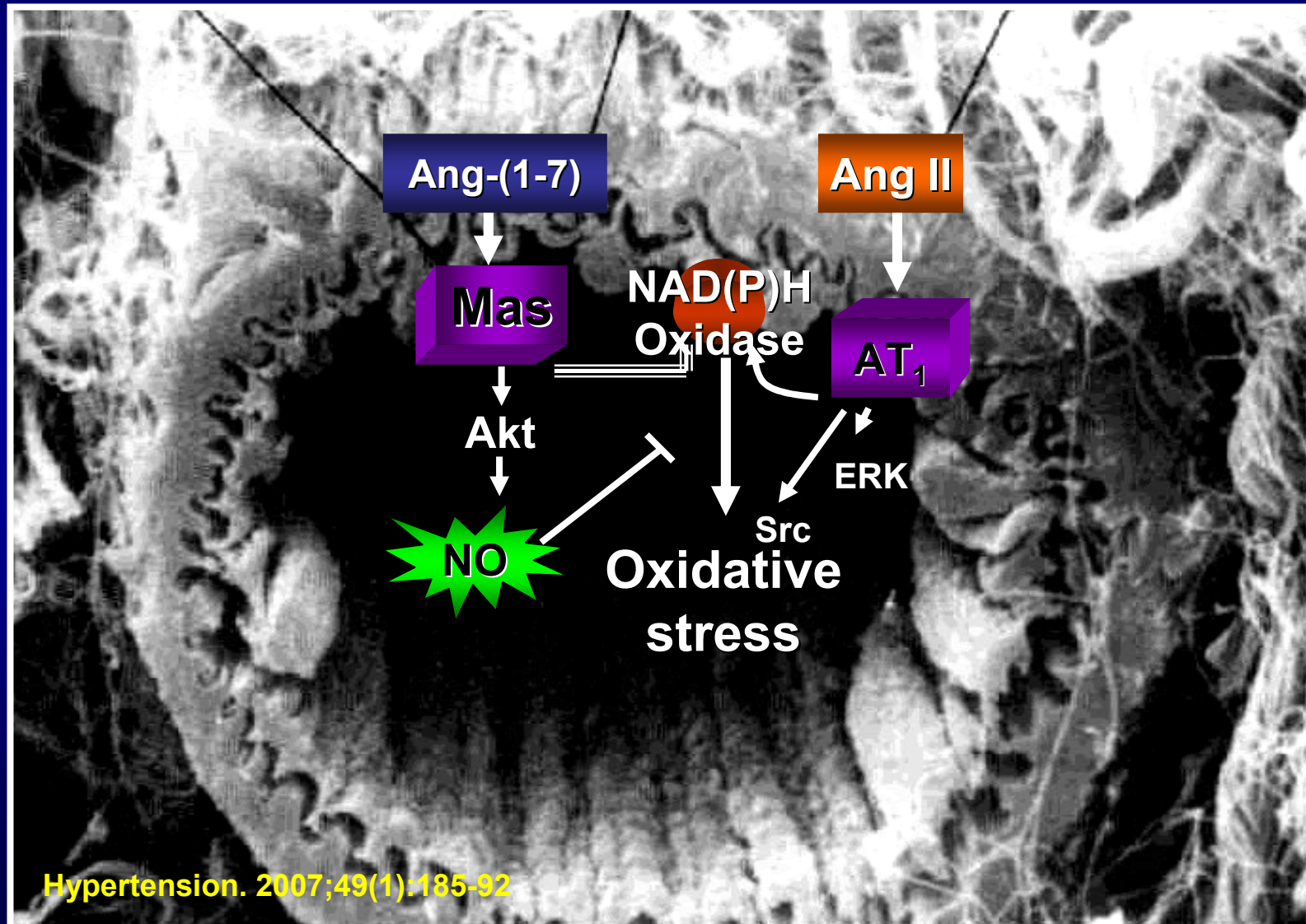
Akt participation in Ang-(1-7)-stimulated eNOS (S1177) phosphorylation in human aortic endothelial cells. The PI3K antagonist, wortmannin, completely blocked the Ang-(1-7) effects.

Ang-(1-7) Modulates Ang II-stimulated NAD(P)H oxidase Activity in Human Endothelial Cells.



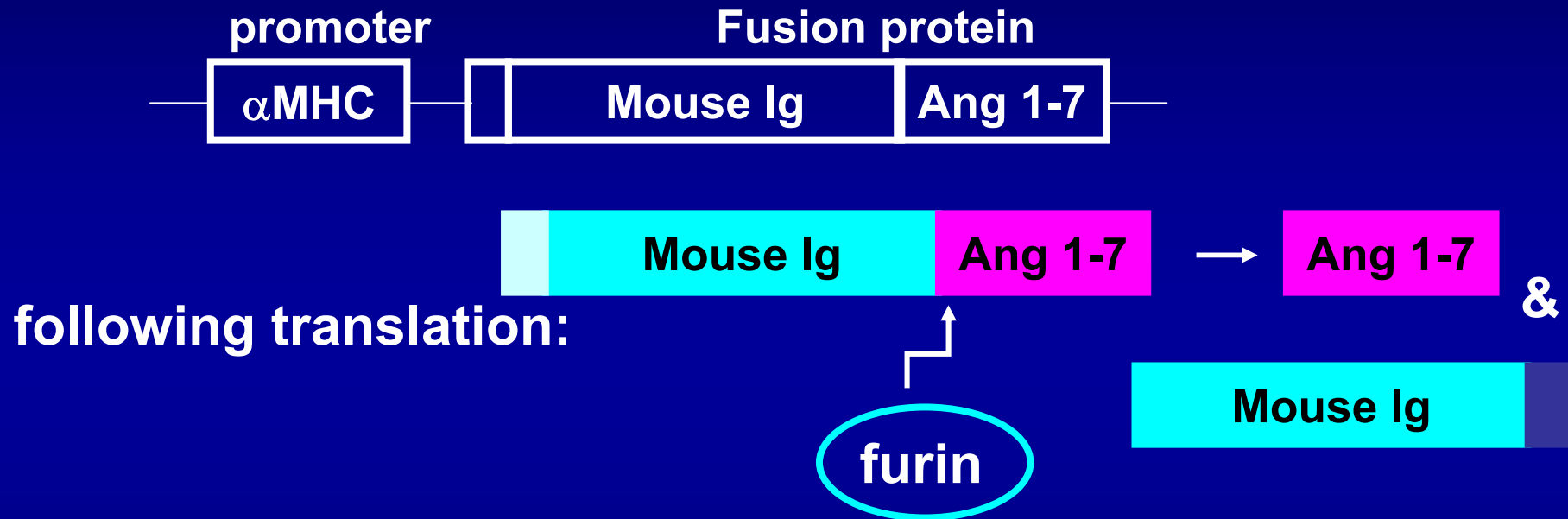
Modulatory effect of Ang-(1-7) (10^{-7} M, 15 min de pre-incubation) on Ang II-stimulated (10^{-7} M, 10 min) NAD(P)H oxidase in HAECs. In some experiments, cells were pre-treated with Ibseratan (10^{-5} M, 30 min).

Ang-(1-7) Negatively Modulates Ang II in Human Endothelium



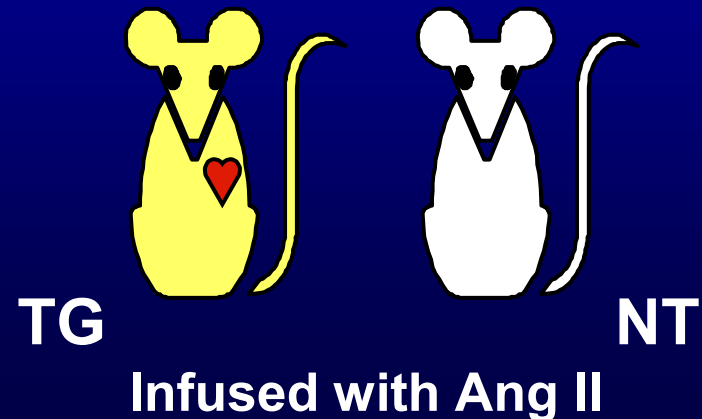
Functional Significance of Ang-1-7:

Ang 1-7 Overexpression in the heart

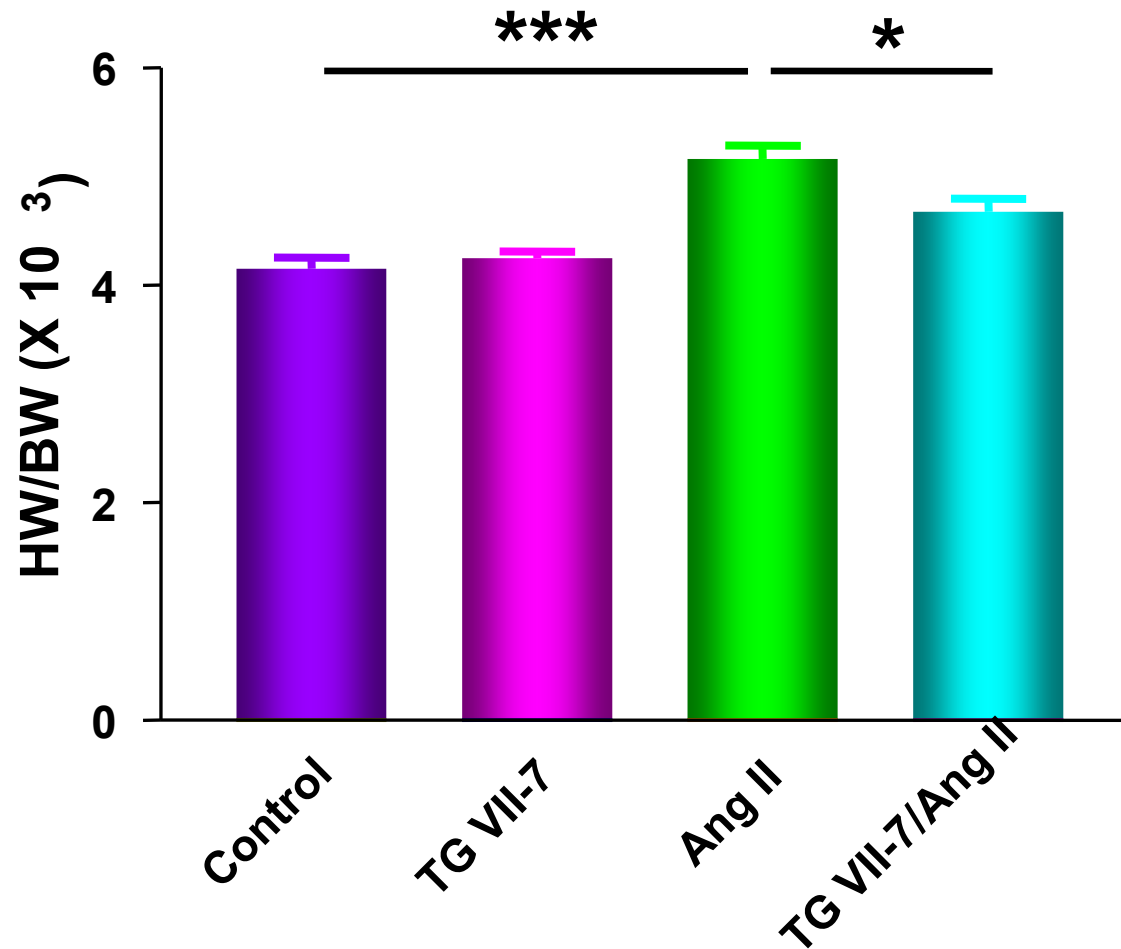


3 independent founder lines:

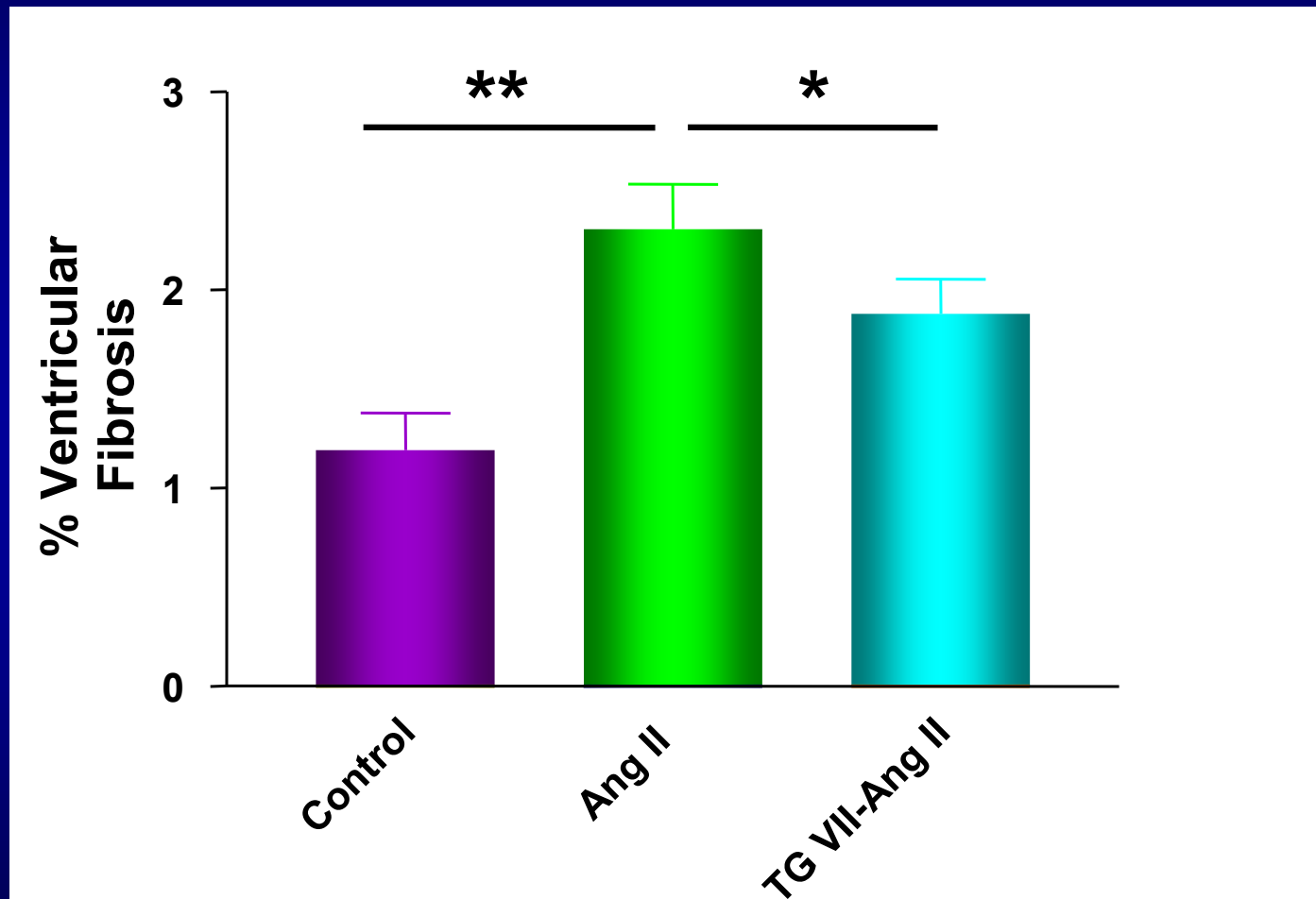
VII-7, VII-7b, VII-7c



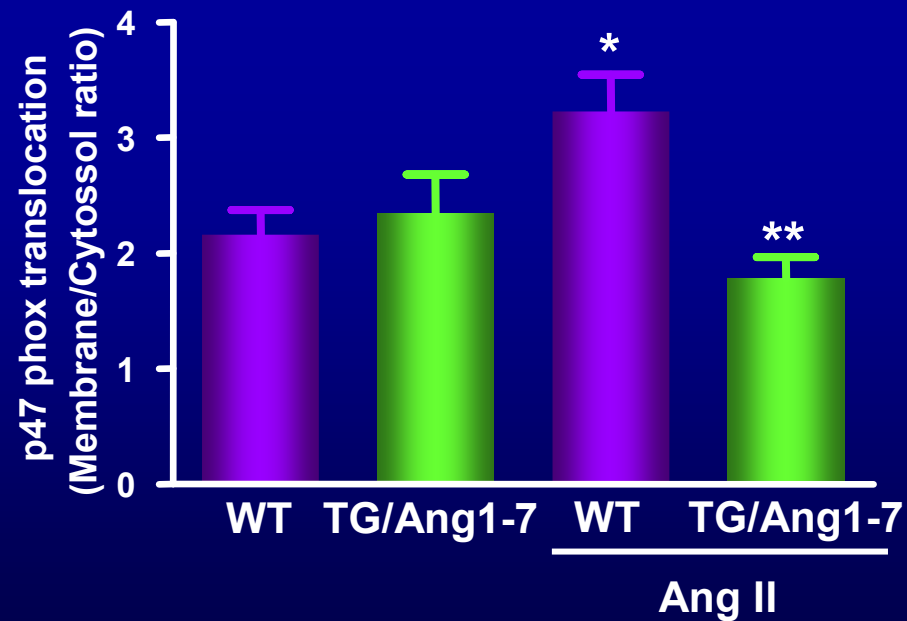
Ang-(1-7) Reduces Cardiac Hypertrophy in Ang II-infused mice.



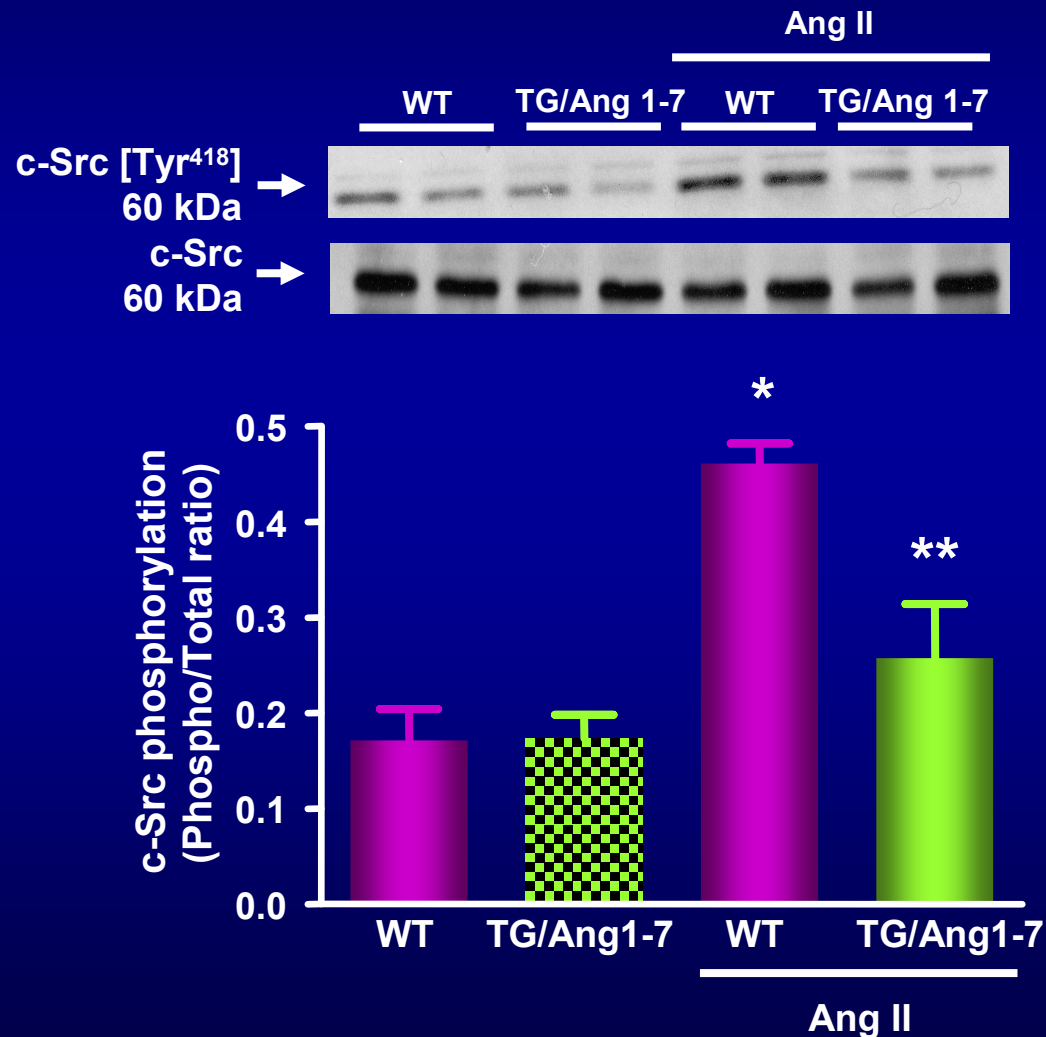
Ang 1-7 also Reduces Interstitial Fibrosis



Ang II-mediated p47phox translocation is blunted in TG/Ang 1-7 mice



Phosphorylation of c-Src induced by Ang II is inhibited in the heart of TG/Ang 1-7 mice



Conclusions

- The RAAS includes metabolically active endogenous peptides, such as Ang-(1-7), other than Ang II.
- Ang II has pleiotropic effects, with multiple targets.
- The RAAS plays a pathophysiological role in hypertension, atherosclerosis, LVH, diabetes, CKD and stroke.
- Blockade of the RAAS has cardioprotective effects through BP-dependent and -independent actions.
- Ang II signals through multiple signaling pathways.
- ROS play an important role in Ang II signaling
- Ang-(1-7) negatively modulates Ang II effects
- Ang-(1-7) has cardio-protective effects.

Targeting the RAAS

