Endothelial dysfunction in hypertension

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ABNORMAL ENDOTHELIUM-DEPENDENT VASCULAR RELAXATION IN PATIENTS WITH ESSENTIAL HYPERTENSION

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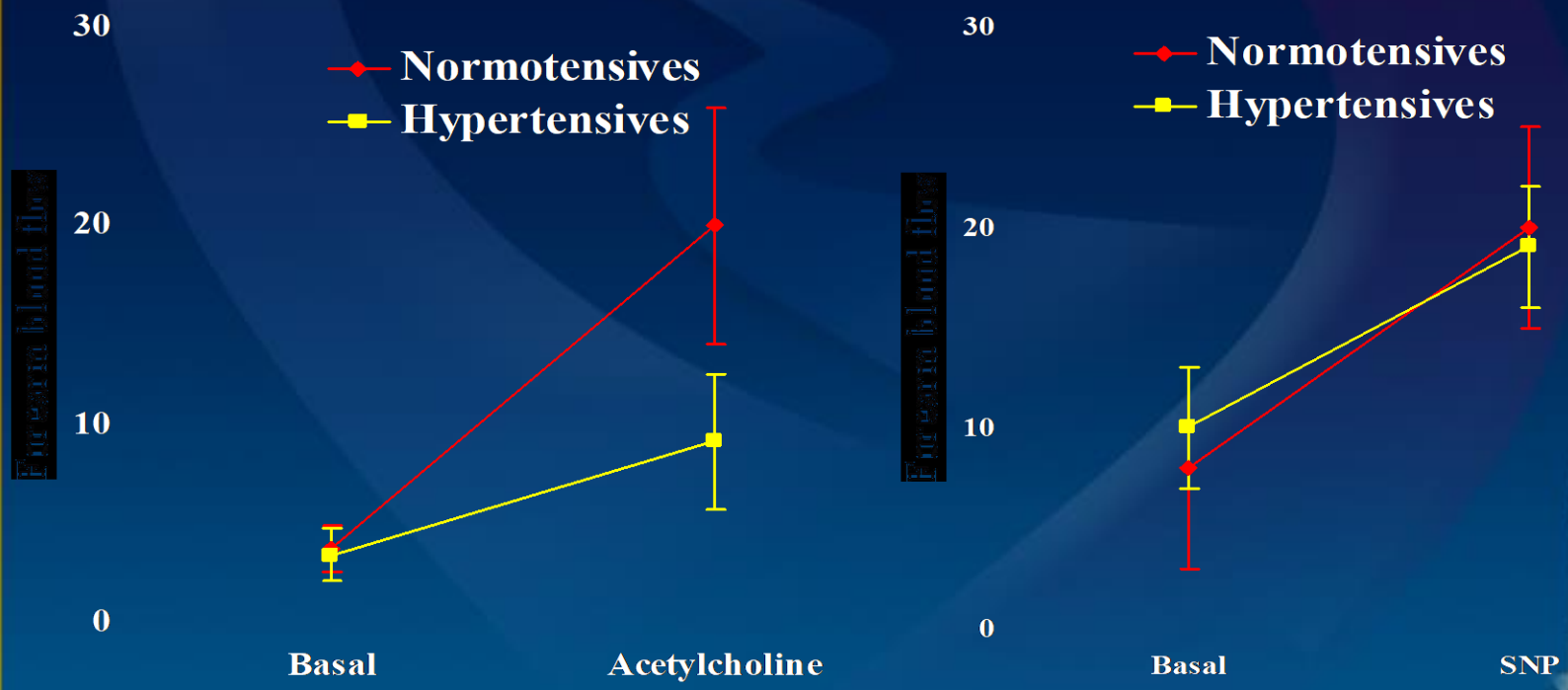
Abstract *Background.* Endothelium regulates vascular tone by influencing the contractile activity of vascular smooth muscle. This regulatory effect of the endothelium on blood vessels has been shown to be impaired in atherosclerotic arteries in humans and animals and in animal models of hypertension.

Methods. To determine whether patients with essential hypertension have an endothelium-dependent abnormality in vascular relaxation, we studied the response of the forearm vasculature to acetylcholine (an endothelium-dependent vasodilator) and sodium nitroprusside (a direct dilator of smooth muscle) in 18 hypertensive patients (mean age [±SD], 50.7±10 years; 10 men and 8 women) two weeks after the withdrawal of antihypertensive medications and in 18 normal controls (mean age, 49.9±9; 9 men and 9 women). The drugs were infused at increasing concentrations into the brachial artery, and the response in forearm blood flow was measured by strain-gauge plethysmography.

Results. The basal forearm blood flow was similar patients and controls (mean ±SD, 3.4±1.3 and 3.7±0.8 ml per minute per 100 ml of forearm tissue, respectively; P not significant). The responses of blood flow and vascular resistance to acetylcholine were significantly reduced in the hypertensive patients ($P<0.0001$); maximal forearm flow was 9.1±5 ml per minute per 100 ml in the patients and 20.0±8 ml per minute per 100 ml in the controls ($P<0.0002$). However, there were no significant differences between groups in the responses of blood flow and vascular resistance to sodium nitroprusside. Because the vasodilator effect of acetylcholine might also be due to presynaptic inhibition of the release of norepinephrine by adrenergic nerve terminals, the effect of acetylcholine was assessed during phentolamine-induced α-adrenergic blockade. Under these conditions, it was also evident that the responses to acetylcholine were significantly blunted in the hypertensive patients ($P<0.03$).

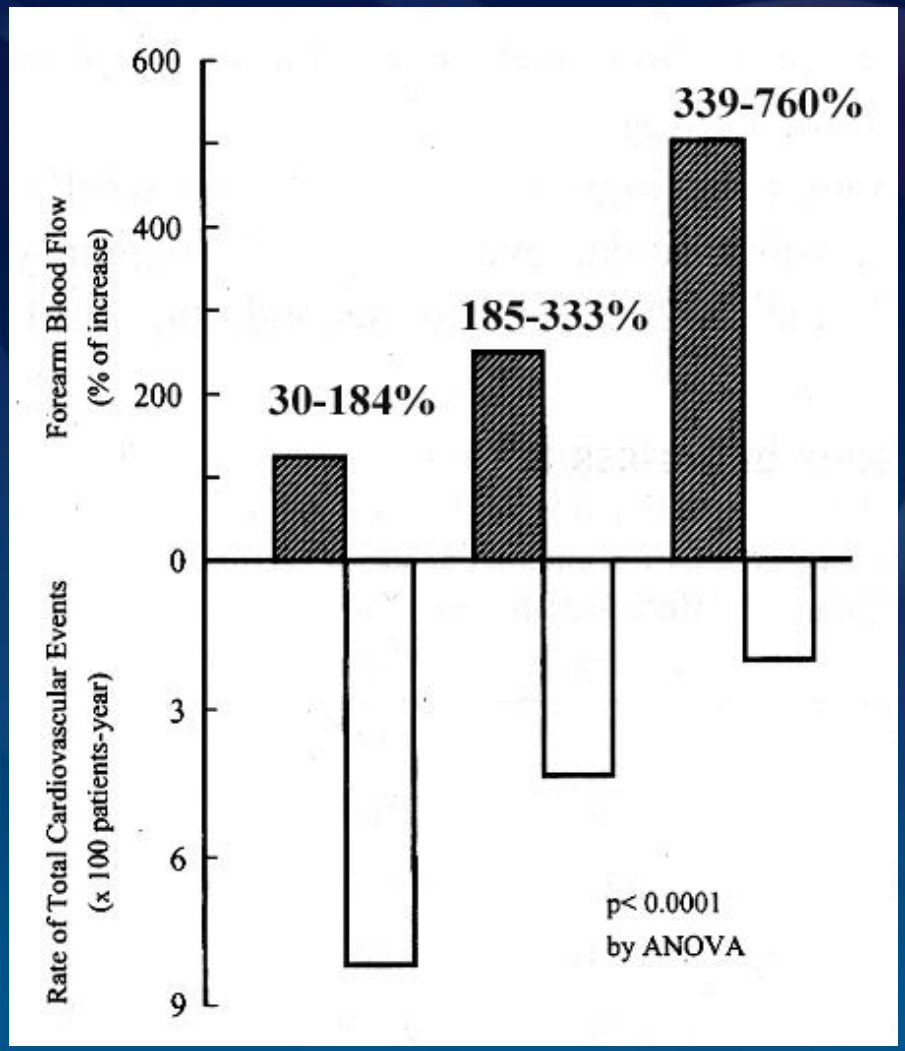
Conclusions. Endothelium-mediated vasodilation is impaired in patients with essential hypertension. This defect may play an important part in the functional abnormalities of resistance vessels that are observed in hypertensive patients. (N Engl J Med 1990; 323:22-7.)

Endothelial dysfunction hypertensive patients



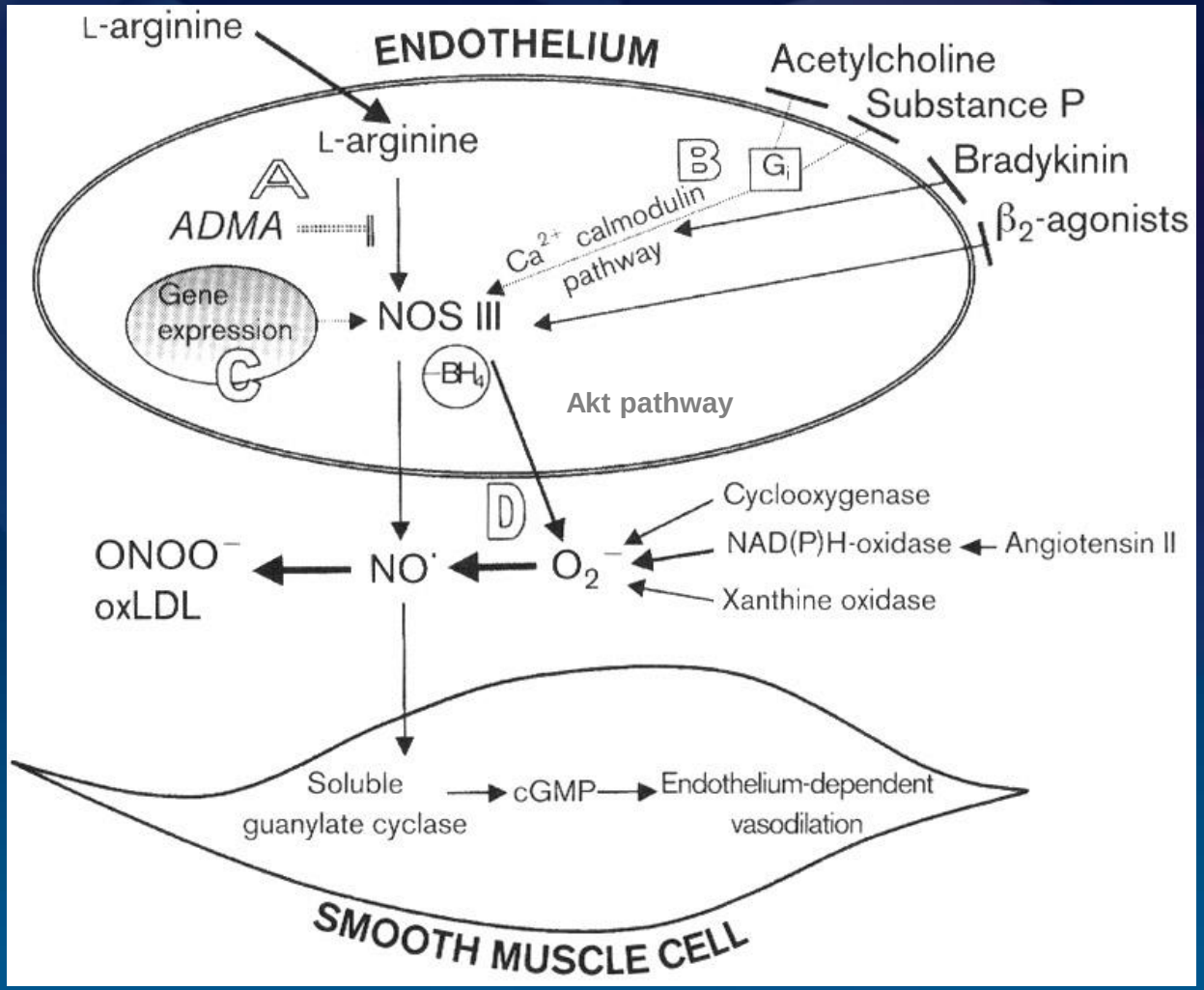
Panza JA, *N Engl J Med* 1990; 323: 1772

Prognostic significance of endothelial dysfunction in hypertensive patients

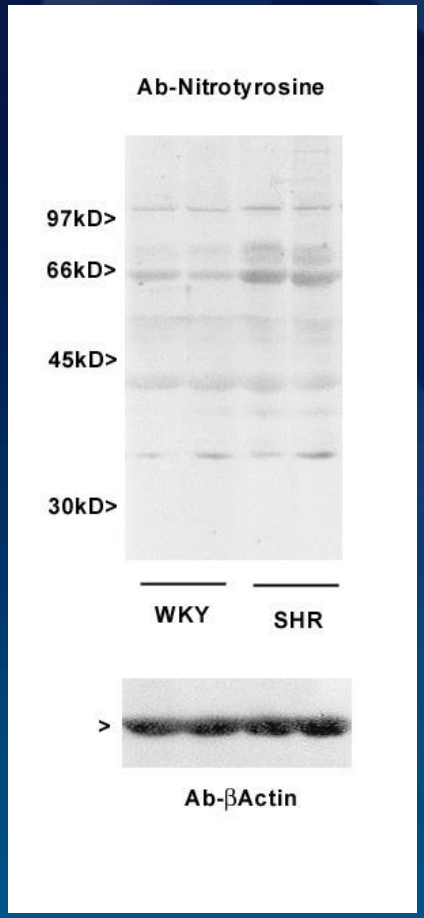


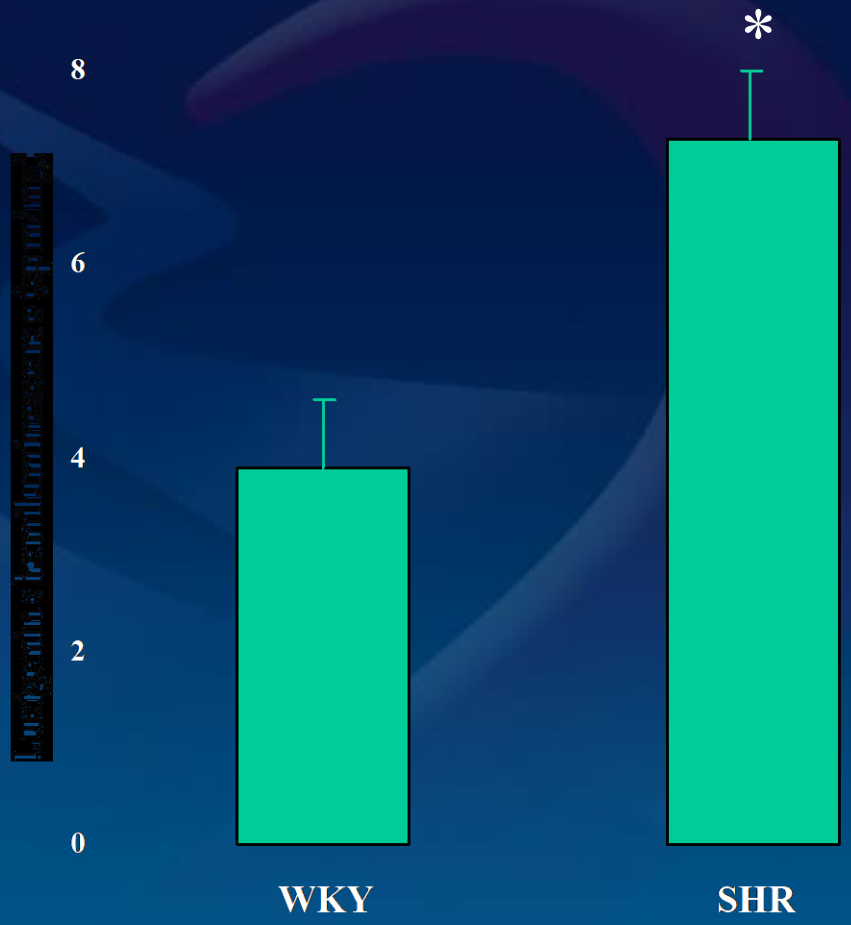
Perticone F, *Circulation* 2001; 104: 191

Mechanisms involved in endothelial NO metabolism



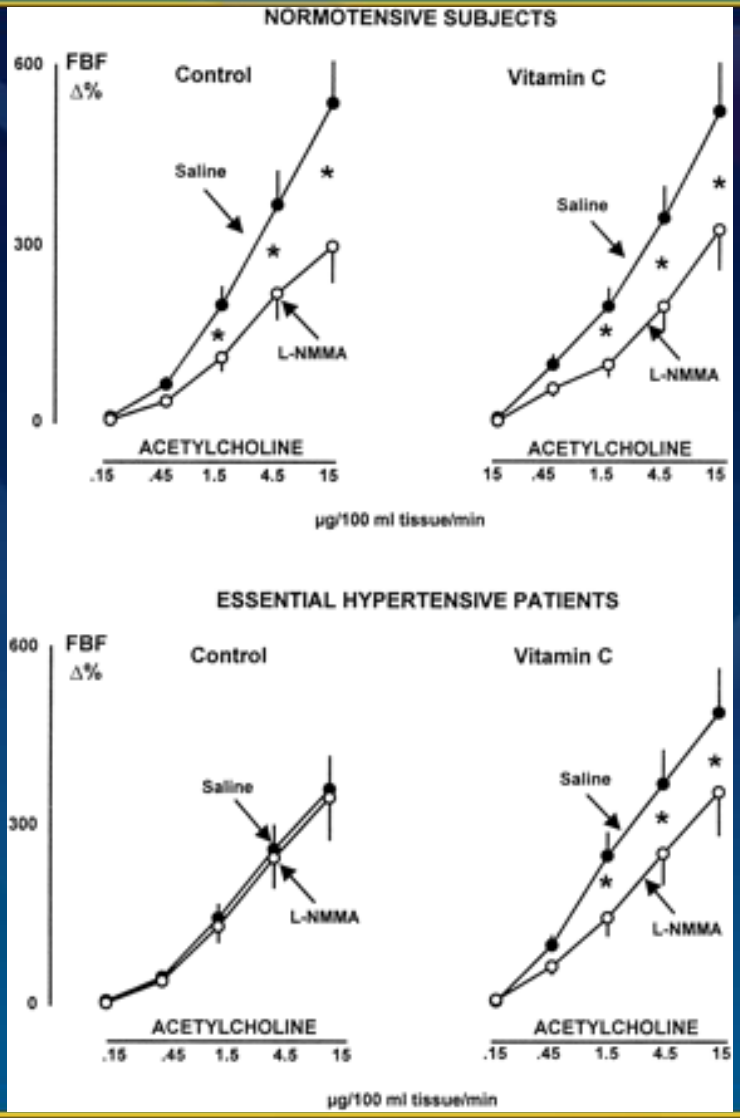
Increased oxidative stress in hypertension





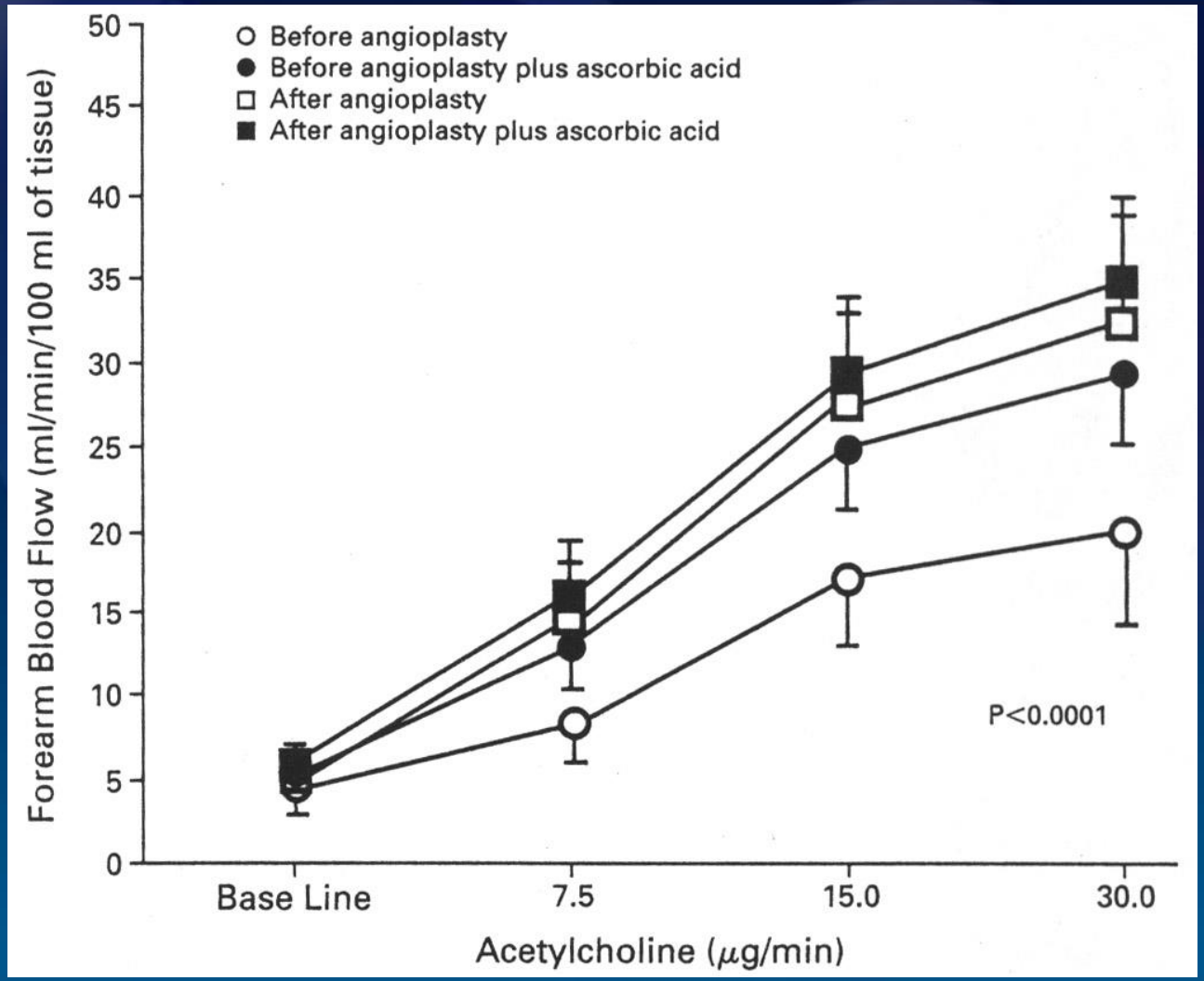
Maffei A, *J Hypertens* 2002; 20: 1135

Antioxidant rescues endothelial NO function in hypertension

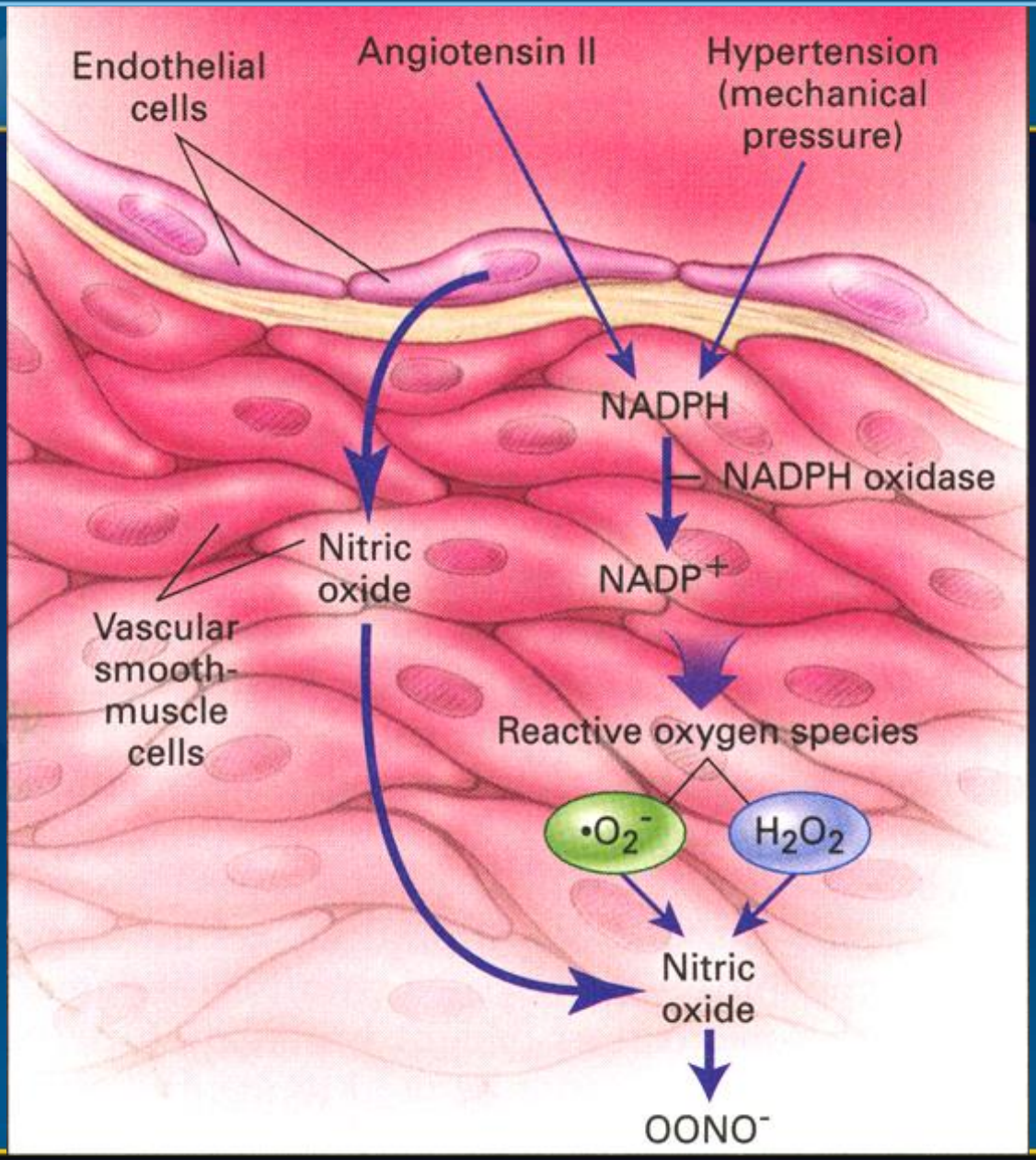


Taddei S, *Circulation* 1998; 97: 2222

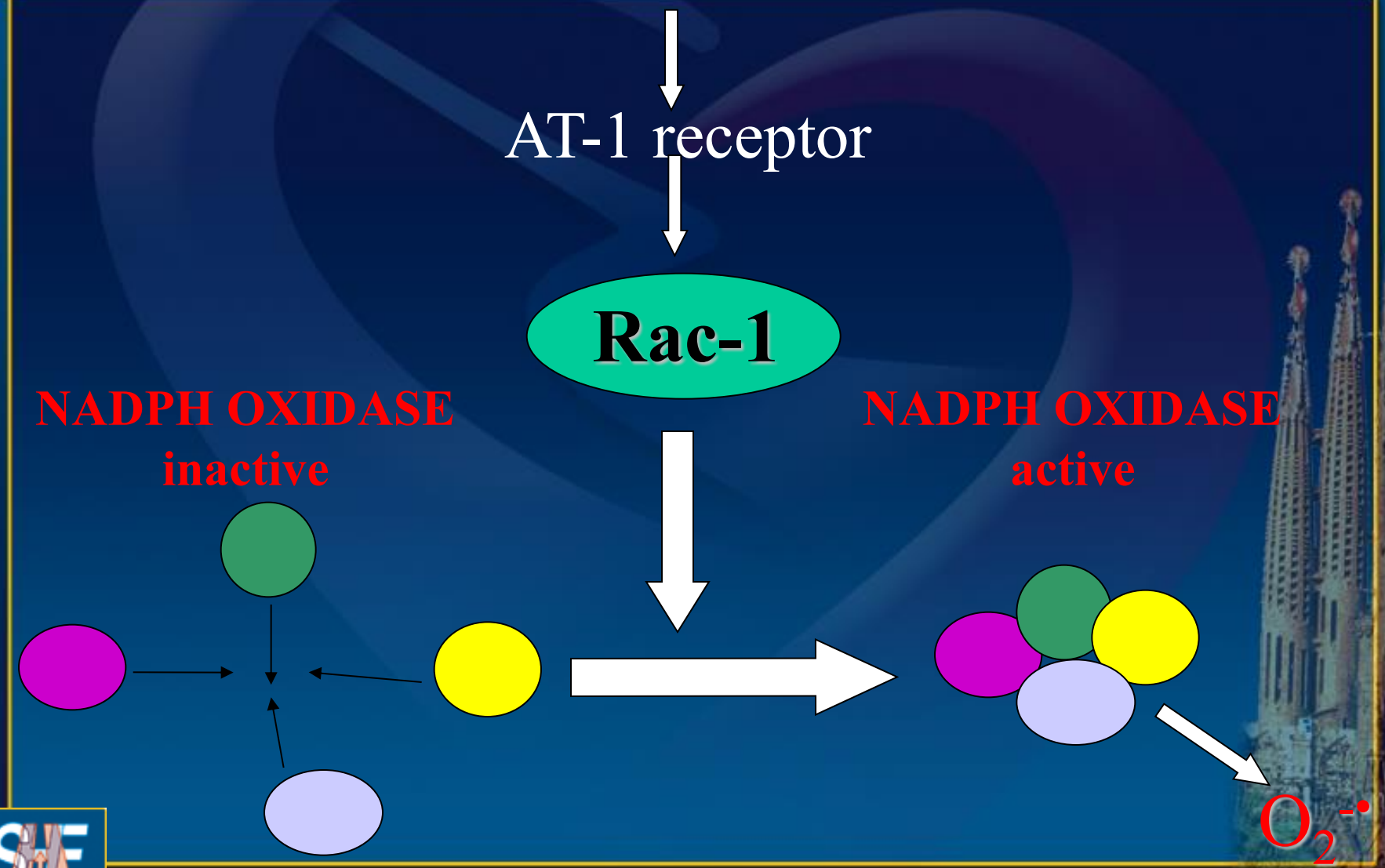
Antioxidant administration restores NO function in renovascular hypertension



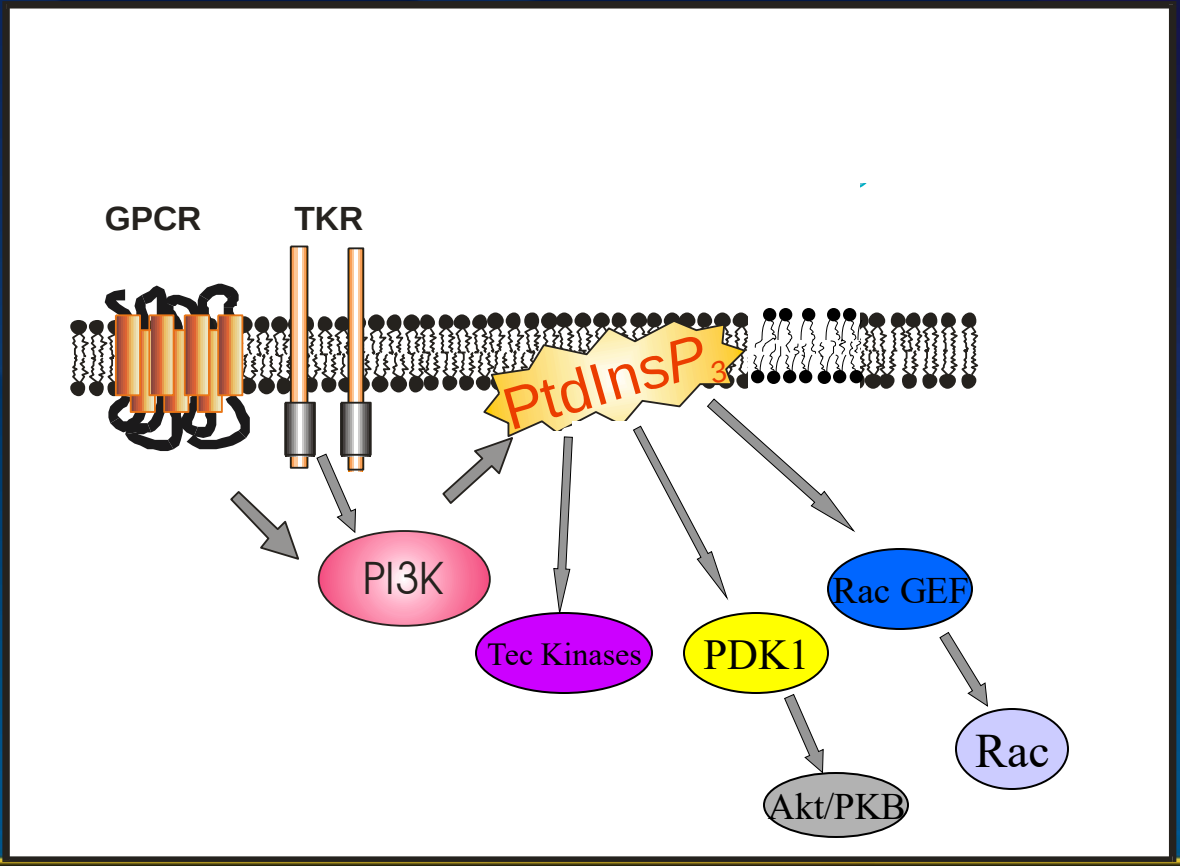
Higashi Y, *N Engl J Med* 2002; 346: 1954


Endothelial cells
Angiotensin II
Hypertension (mechanical pressure)
NADPH
NADPH oxidase
NADP+
Nitric oxide
Vascular smooth-muscle cells
Reactive oxygen species
•O2-
H2O2
Nitric oxide
OONO-

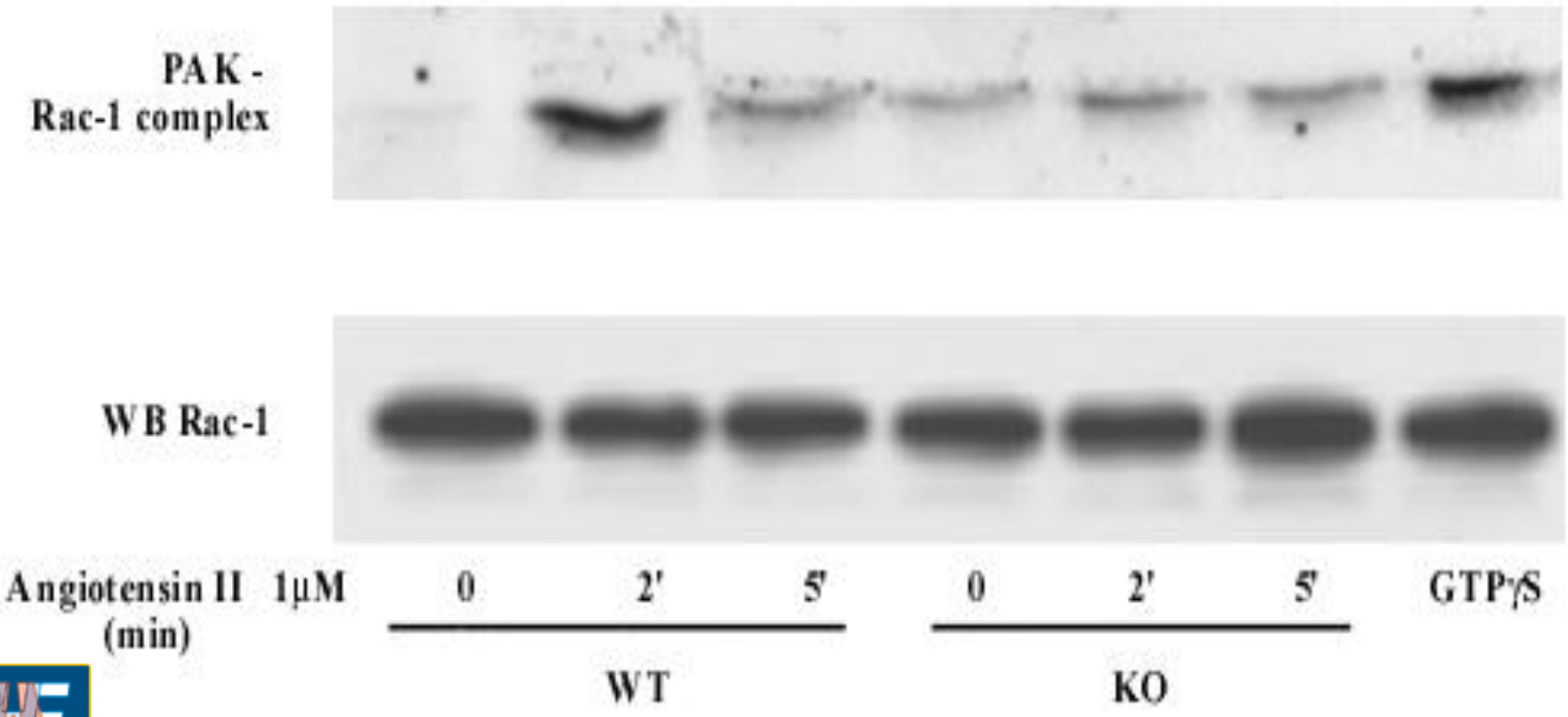
Angiotensin II



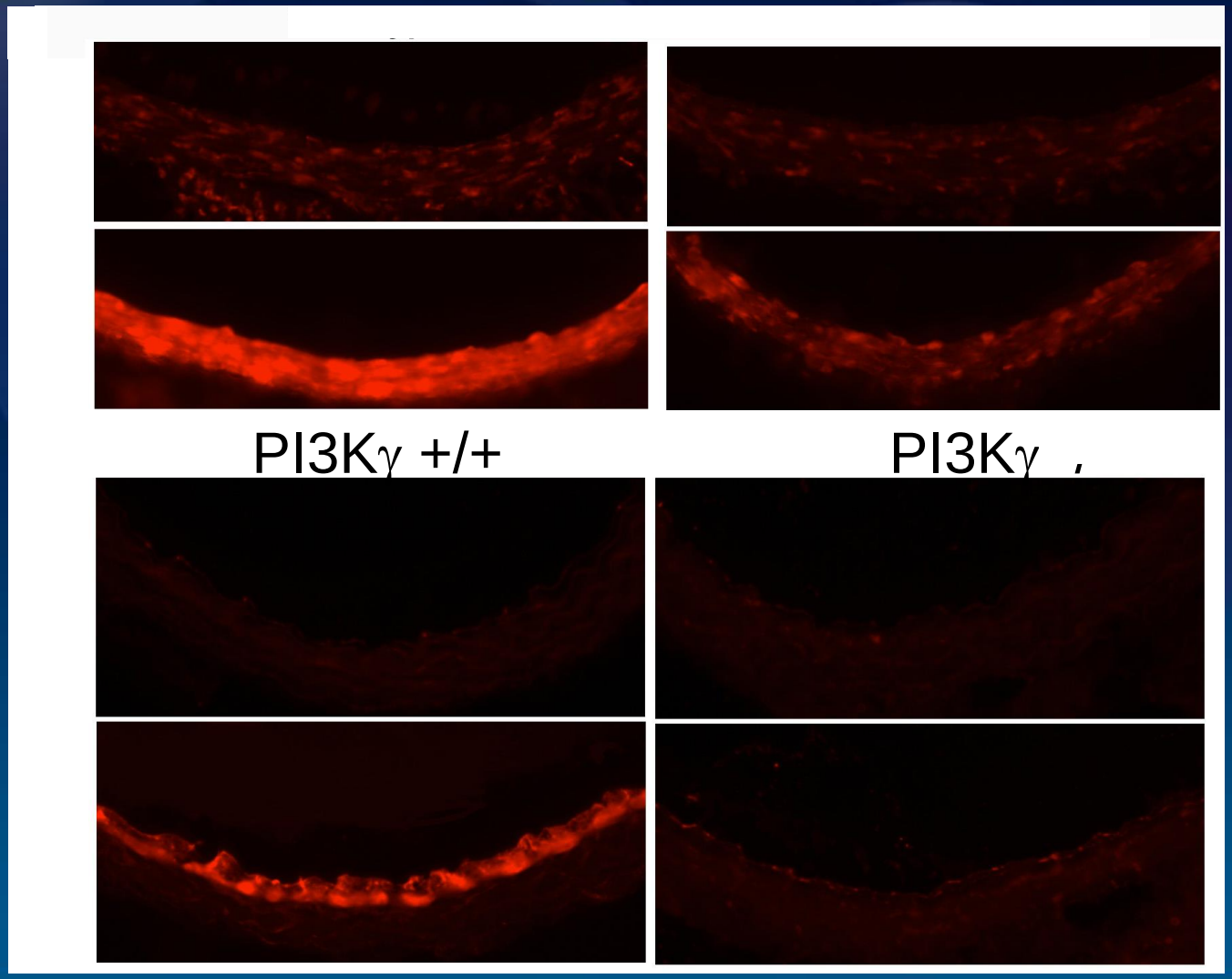
PI3K at the conjunction of GPCR- and TKR-dependent signalling pathways



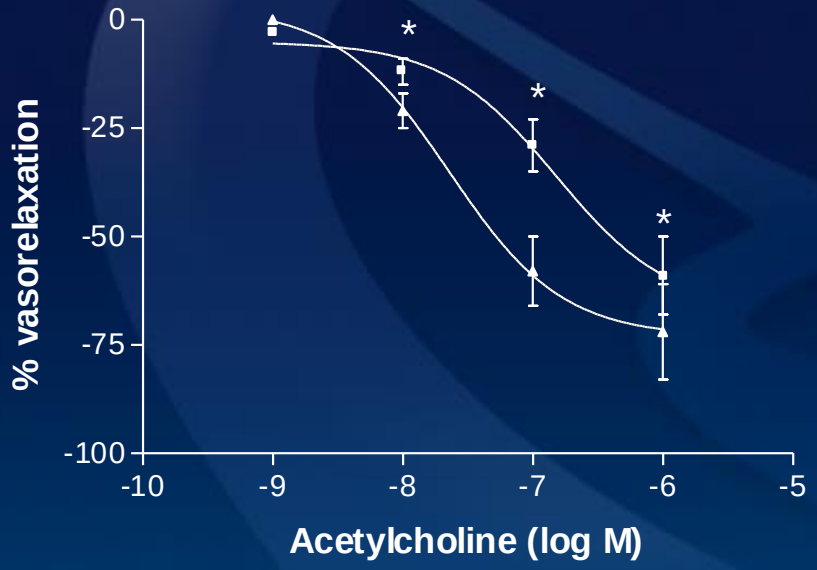
Rac-1 activity in PI3Kγ +/+ and PI3Kγ -/- mice after Angiotensin II



Angiotensin II-induced vascular oxidative stress

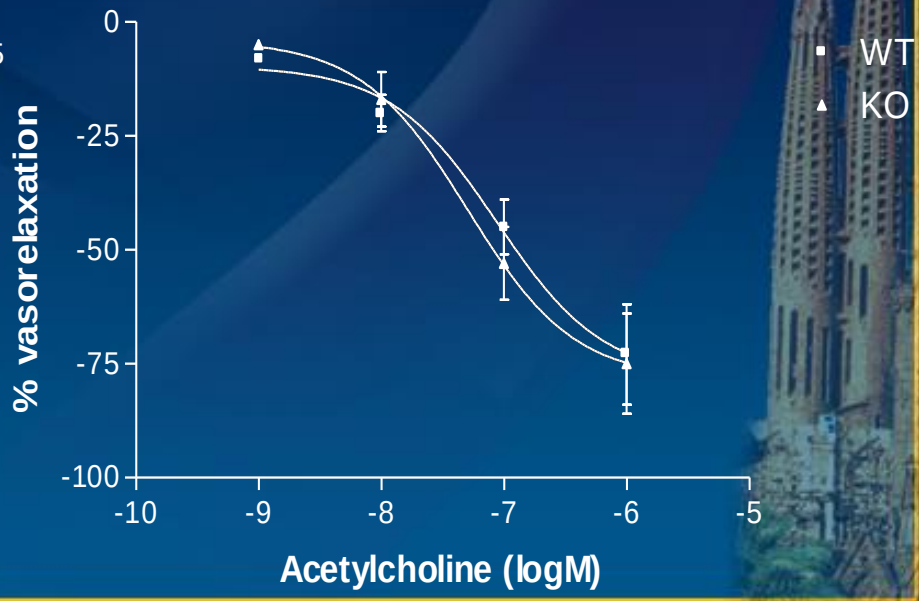


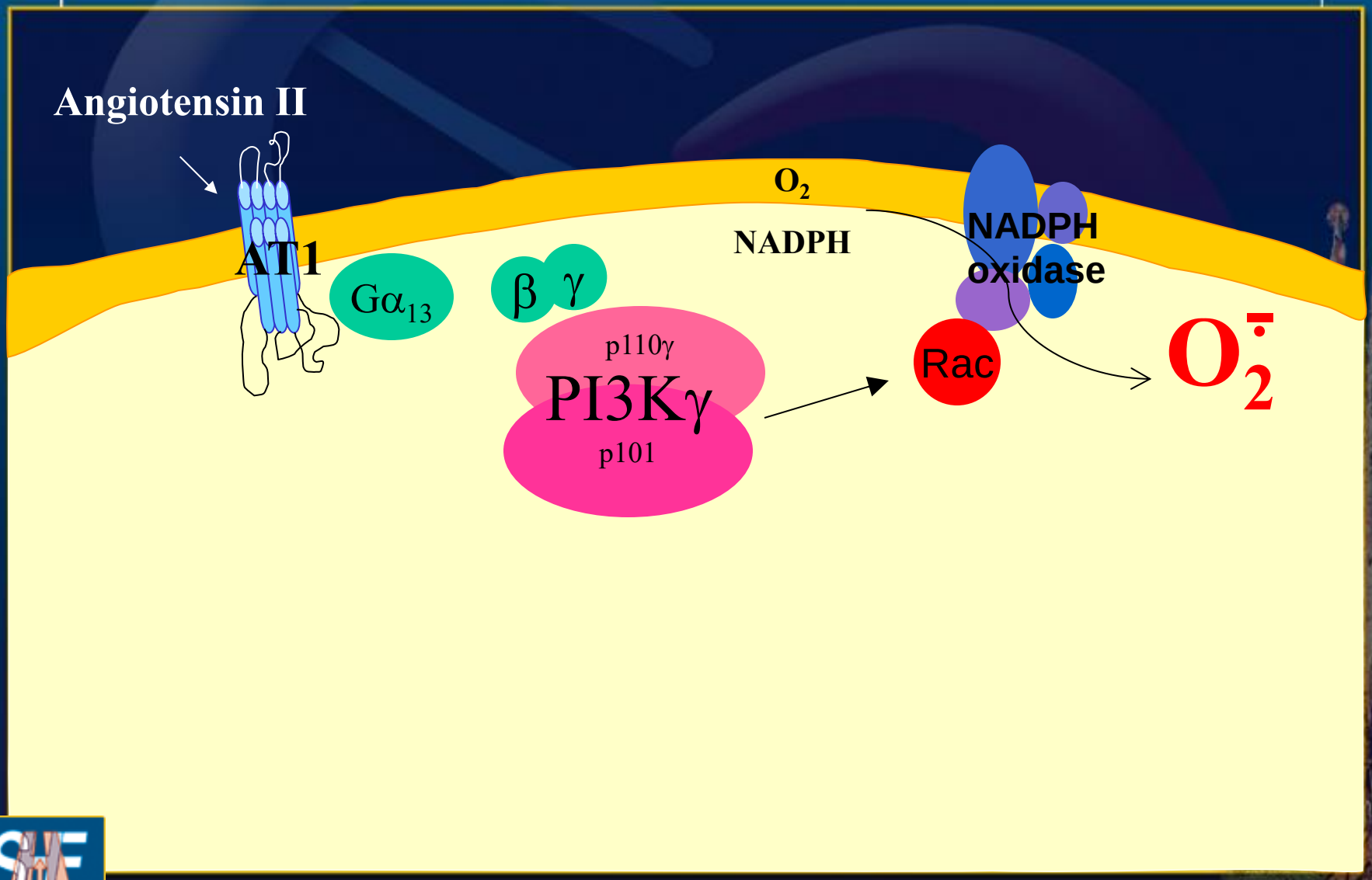
Effects of chronic Angiotensin II infusion on endothelial function of KO (PI3Kγ -/-) and WT (PI3Kγ +/+) mice



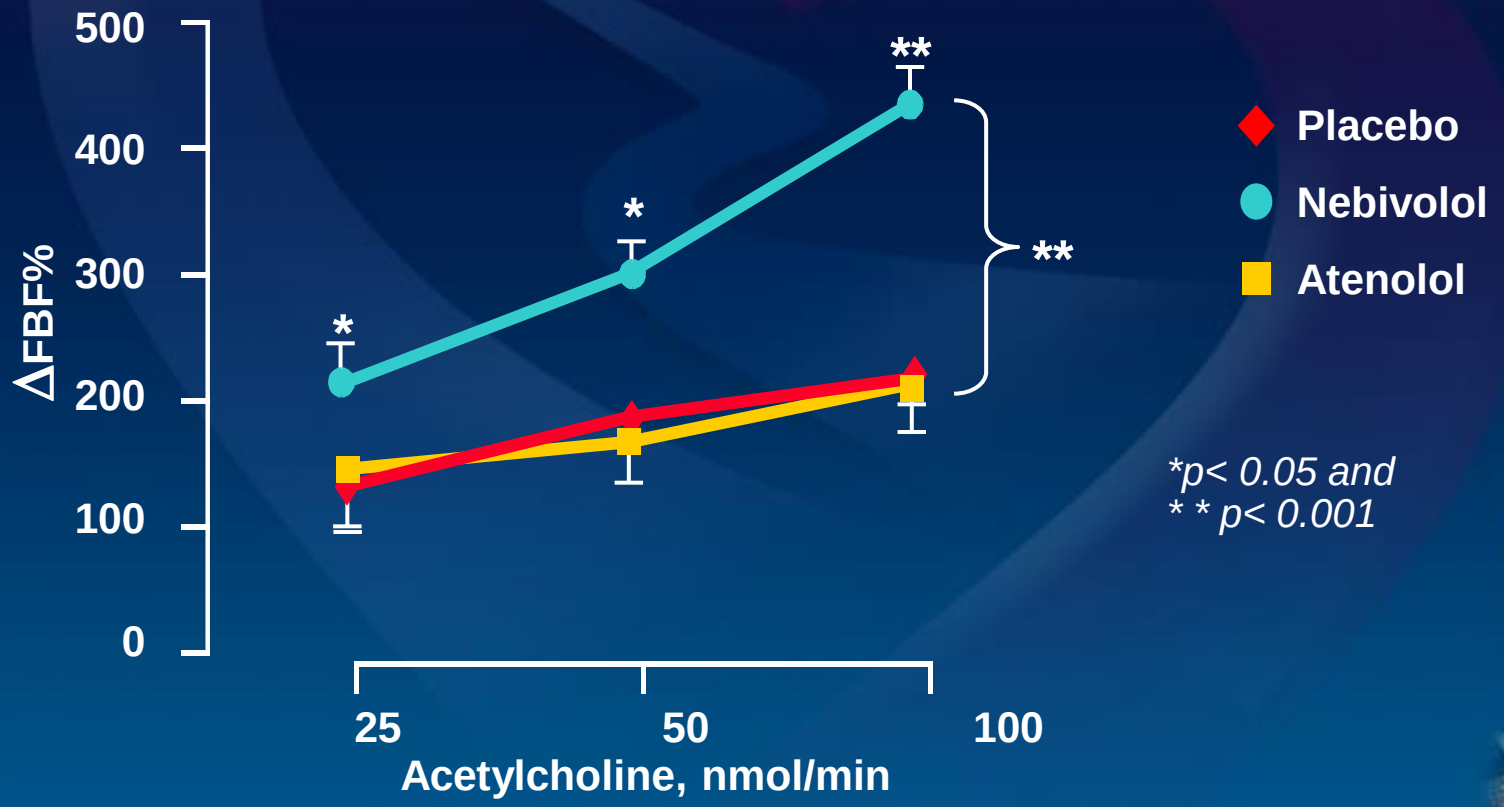
P<0.02 vs KO

Tiron



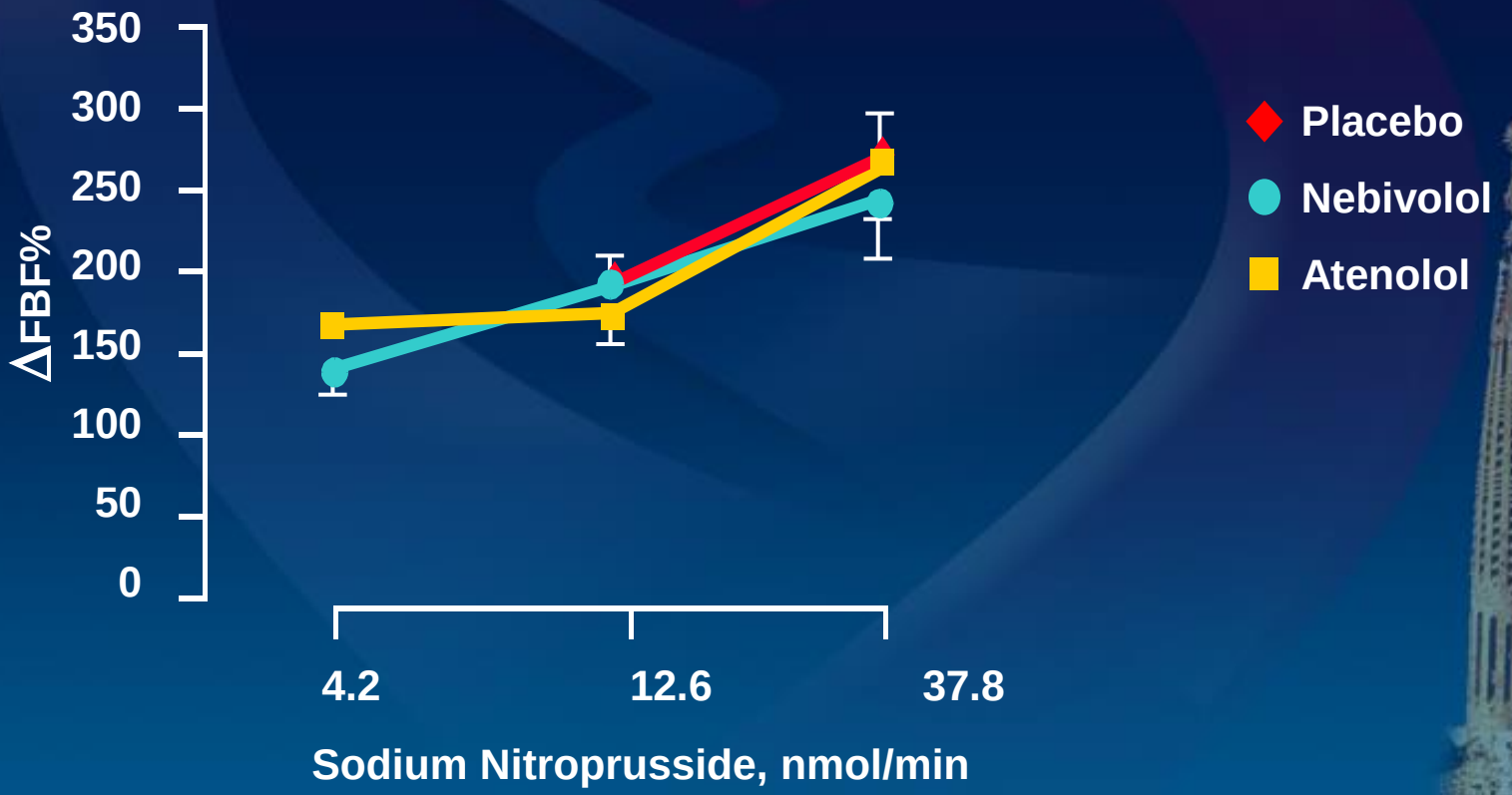

Angiotensin II
AT1
$G\alpha_{13}$
β γ
p110γ
PI3Kγ
p101
O_2
NADPH
NADPH oxidase
Rac
$O_2^{\cdot-}$

Nebivolol improves endothelial function in hypertensive patients



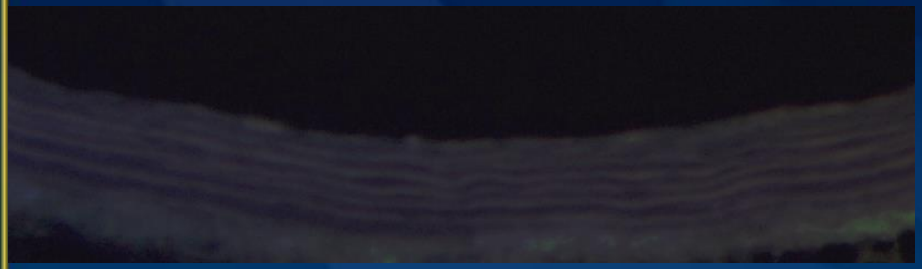
Tzemos N. et al. Circulation 2001; 104,5: 511-514

Nebivolol vasodilation in hypertensive patients

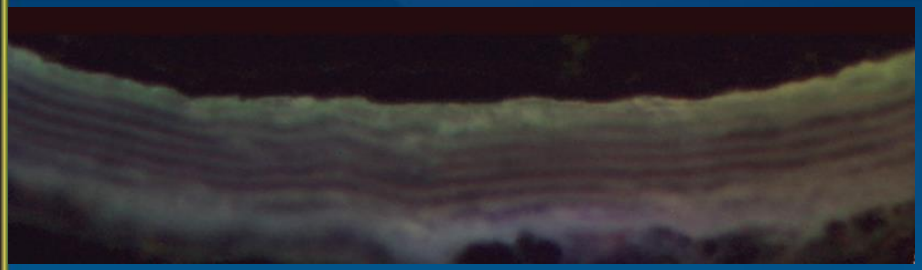


Tzemos N. et al. Circulation 2001; 104,5: 511-514

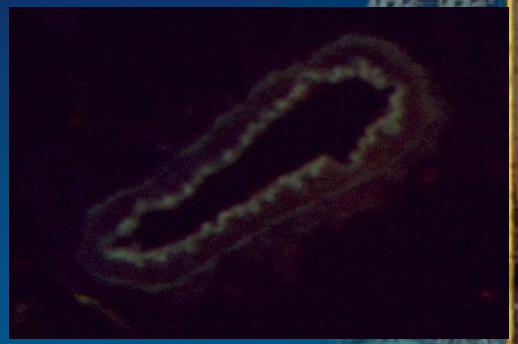
Nebivolol induces NO production in both aortic and mesenteric rings



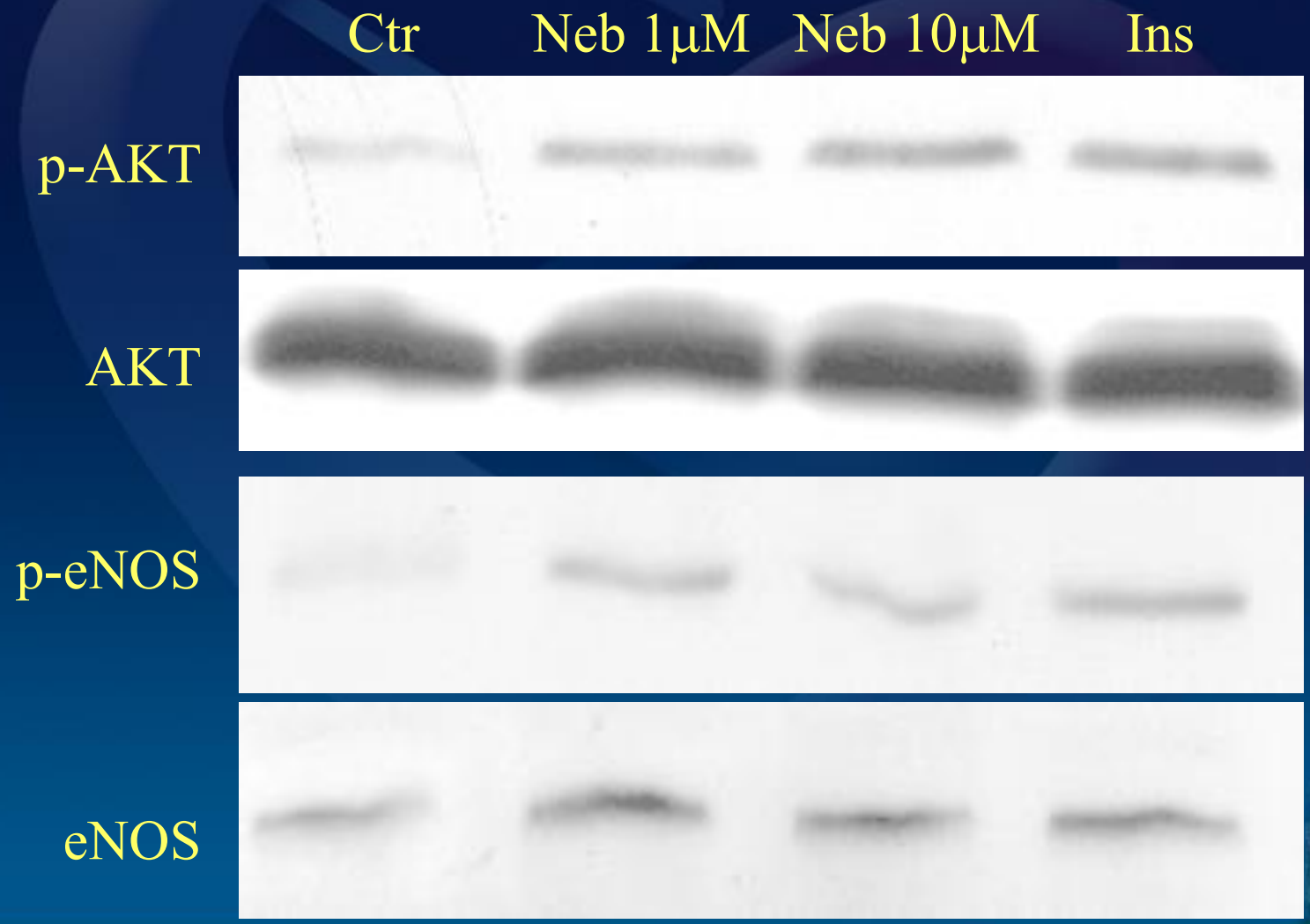
Control



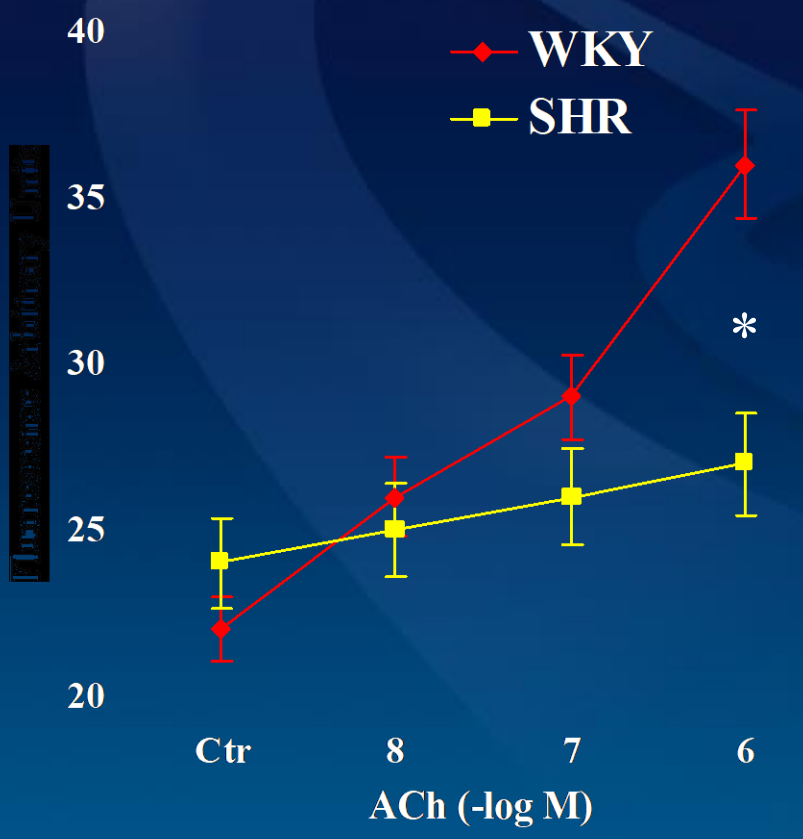
Nebivolol
10μM

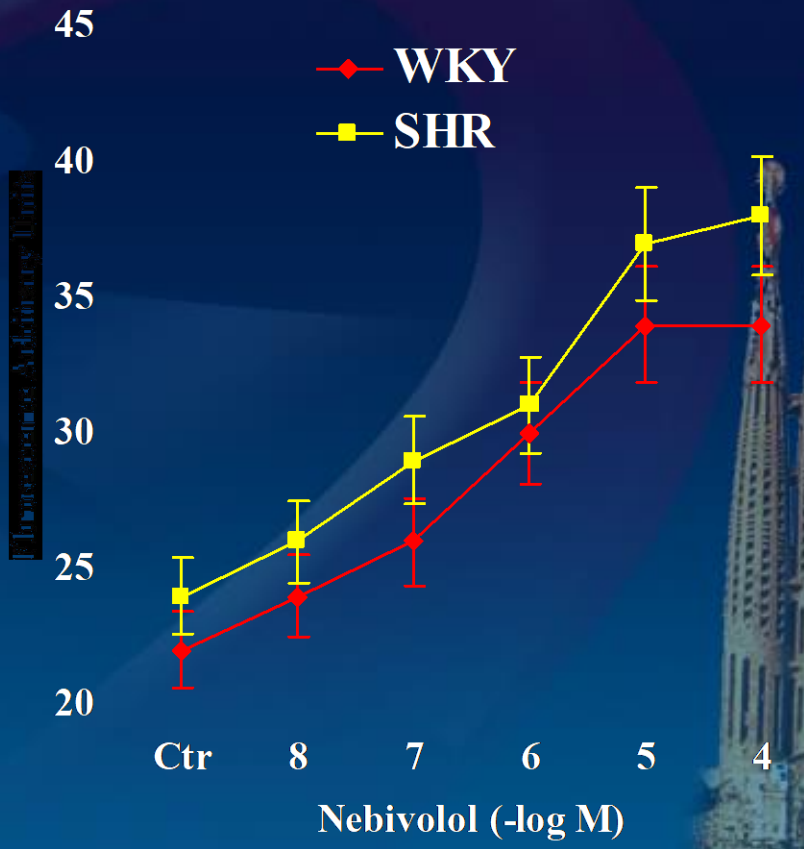


Nebivolol phosphorylates Akt and eNOS



Preserved vascular response Nebivolol in hypertension





*p<0.01

Nebivolol

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Increased NO synthesis

Reduction of oxidative stress