Aldosterone – beyond blood pressure

Eberhard Ritz
Heidelberg (Germany)

Aldosterone – beyond blood pressure

Aldosterone and blood pressure –
beyond Conn syndrome

Activation of mineralocorticoid receptor -
beyond aldosterone

Aldosterone action –
beyond classical mineralocorticoid receptor

Aldosterone –
blood pressure independent target organ damage

The permissive action of salt

Aldosterone and progression

Escape of proteinuria –
the role of aldosterone and consequences for treatment

Conn J.W.
Primary aldosteronism: a new syndro

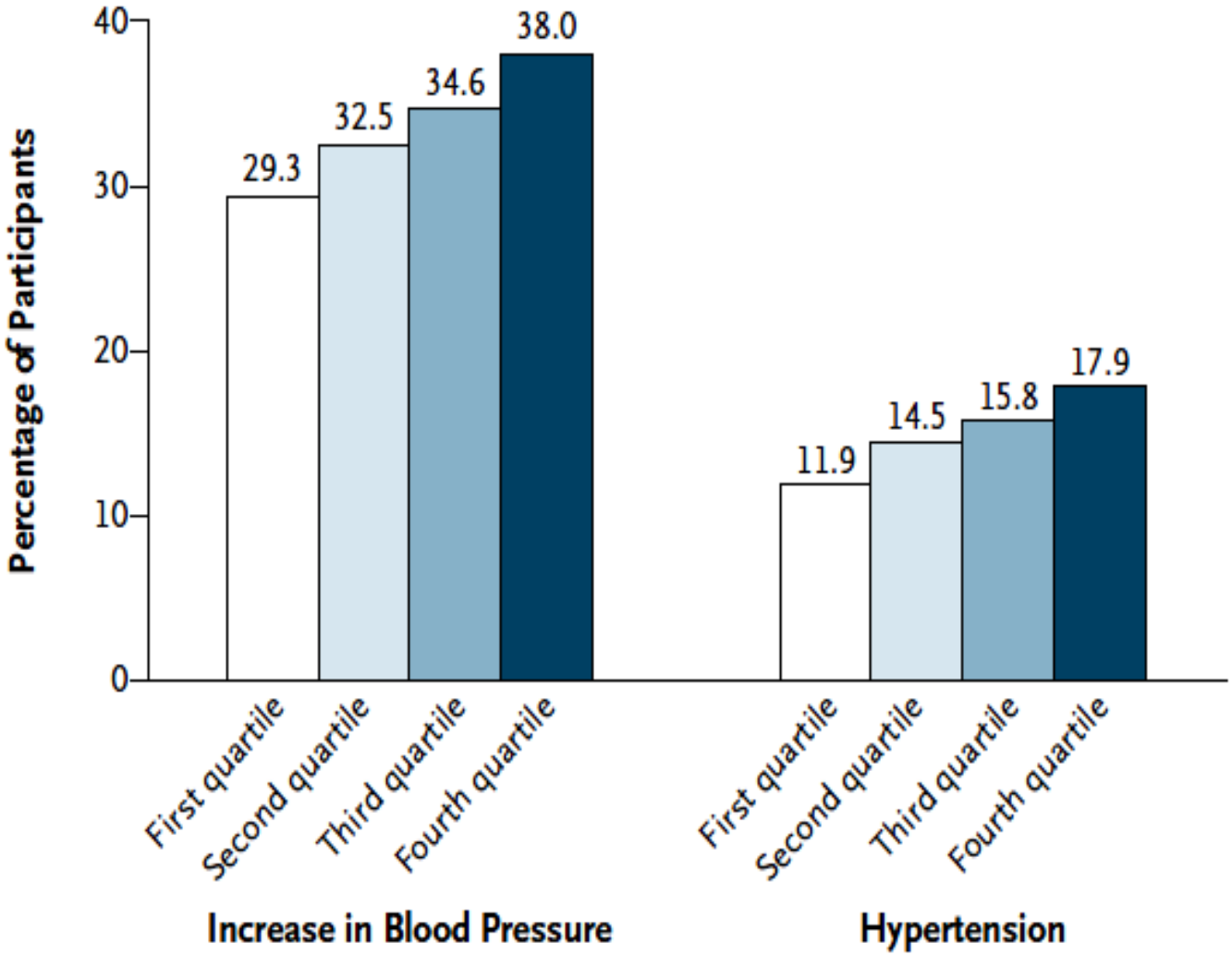
J.Lab.Clin.Med. *(1955) 45:3*

-adenoma
-bilateral hyperplasia

Colhoun, Hypertension (2007)50:447
Is there an unrecognized epidemic of primary aldosteronism?

Progressively higher blood pressure values and higher prevalence of hypertension in progressively higher quartiles of S-aldosterone concentration

Framingham study



Vasan, New Engl.J.Med.(2004) 351:33

Whether primary aldosteronism is as widespread as some believe may not be as relevant as whether the commonly prevailing level of aldosterone is too high for the amount of sodium we consume.

Aldosterone. ..contributes to the development of hypertension… more than even the moste generous estimate for the prevalence of primary hyperaldosteronism

Pratt, Hypertension (2008) 51:39

Salt sensitive blood pressure in mice with increased expression of aldosterone synthase

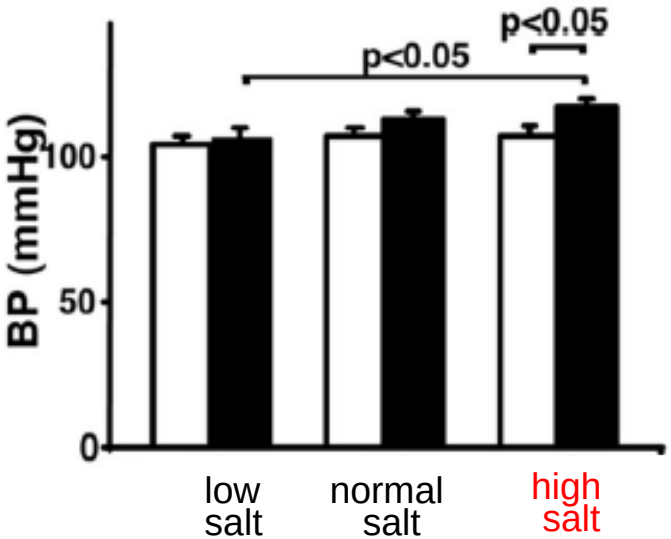
modification of the 3'untranslated region of aldosterone synthase (AS $^{high/high}$) in mice by causing stable activation of aldosterone synthase resulting from 1.5 times higher mRNA aldosterone synthase (AS)

on low salt diet: in AS $^{high/high}$ mice → normal blood pressure, but lower activity of RAS than in wild type

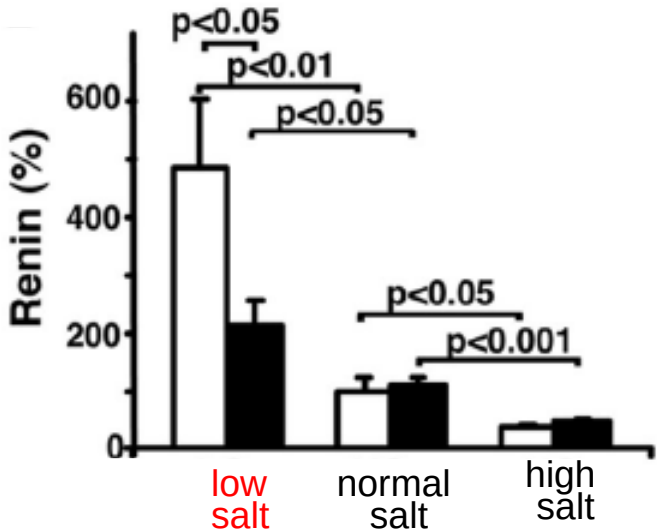
on high salt diet: wild type mice → no change of BP
AS $^{high/high}$ mice → BP increase by 10 mmHg and :
high aldo,
low K^+,
increased collecting duct sodium channel (ENaC)

Makhanova, Hypertension (2008) 51: 134

High blood pressure on high salt



Renin suppression even on low salt



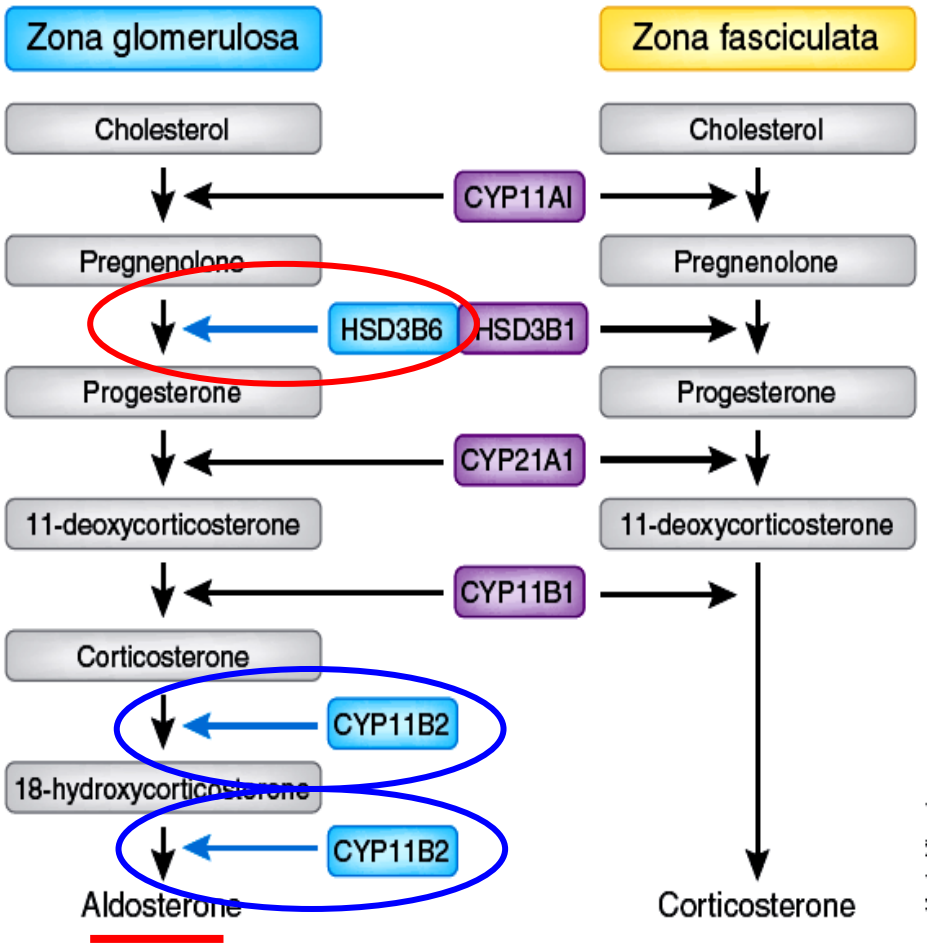
high aldosteron-synthase activity (mutation)

wildtype

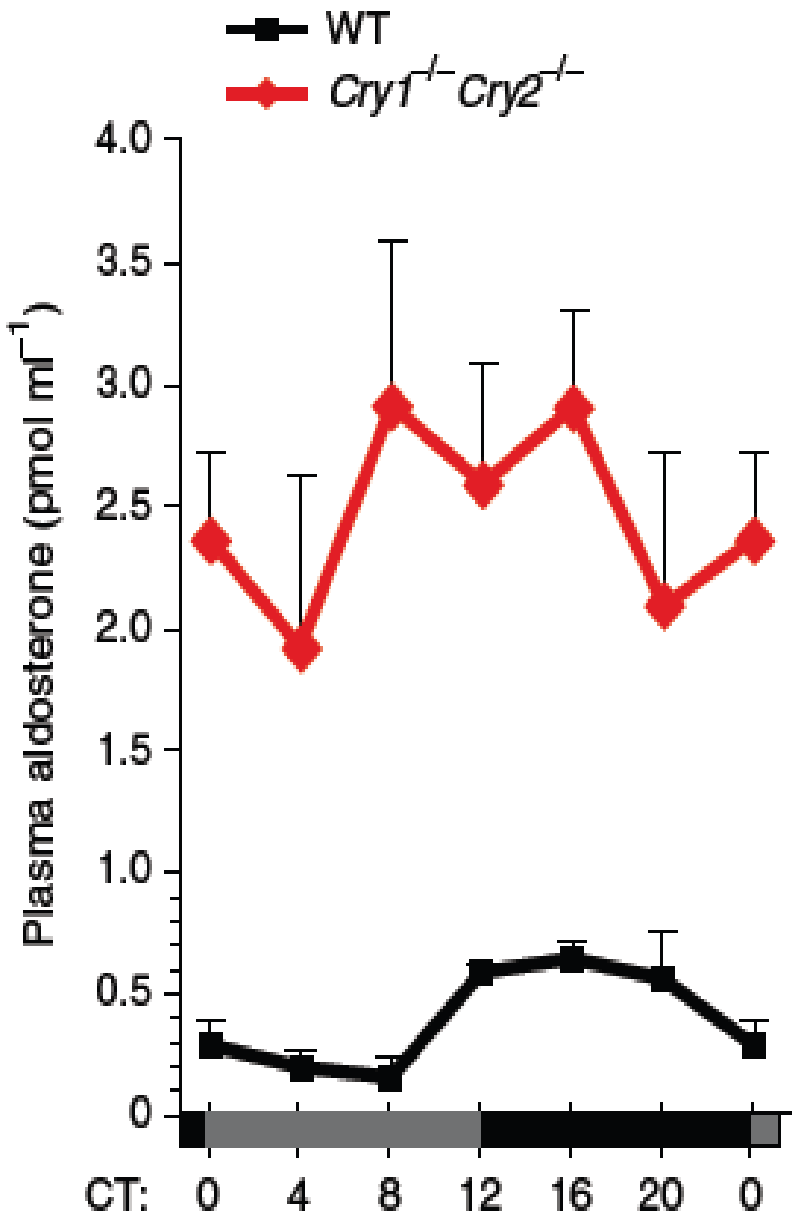
Makhanova, Hypertension (2008) 51:134

A periodicity gene (clock-gene)
Is responsible for aldosterone-synthesis (HSD3B6)

-/- mice → hypertension



Doi, Nature Med.(2010) 16:67



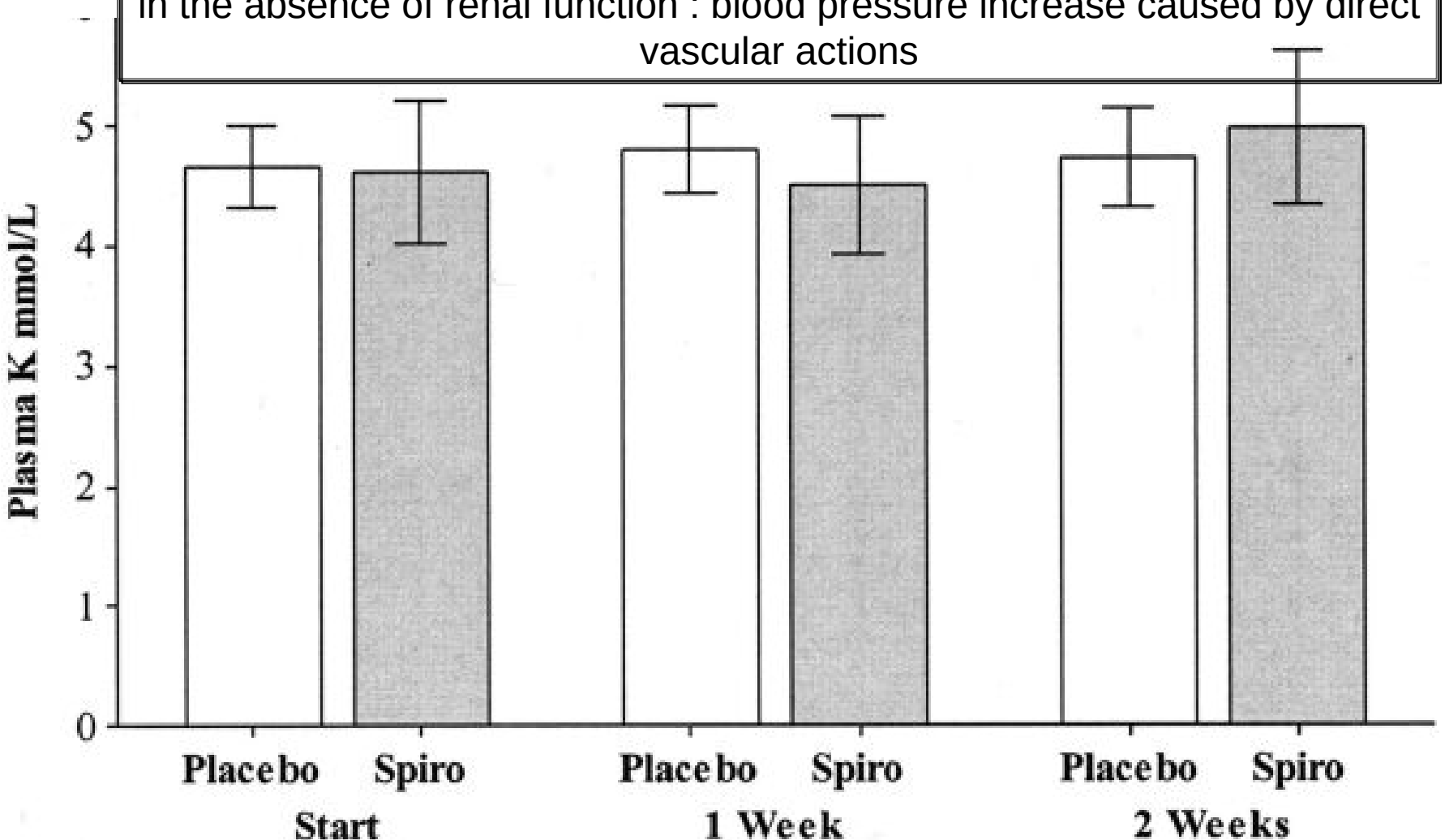
Mice with knock-out of
cryptochrome 1 and 2 genes
(driving circadian periodicity)
have
hypertension
and
high plasma aldosteron

Doi, Nature Medicine (2010) 16:67

Lowering of BP by 50 mg Spironolactone in anuric hemodialysis patients – *no change in S-K+*

Systolic blood pressure : Spironolactone 142→131 mmHg
Placebo 146→142 mmHg

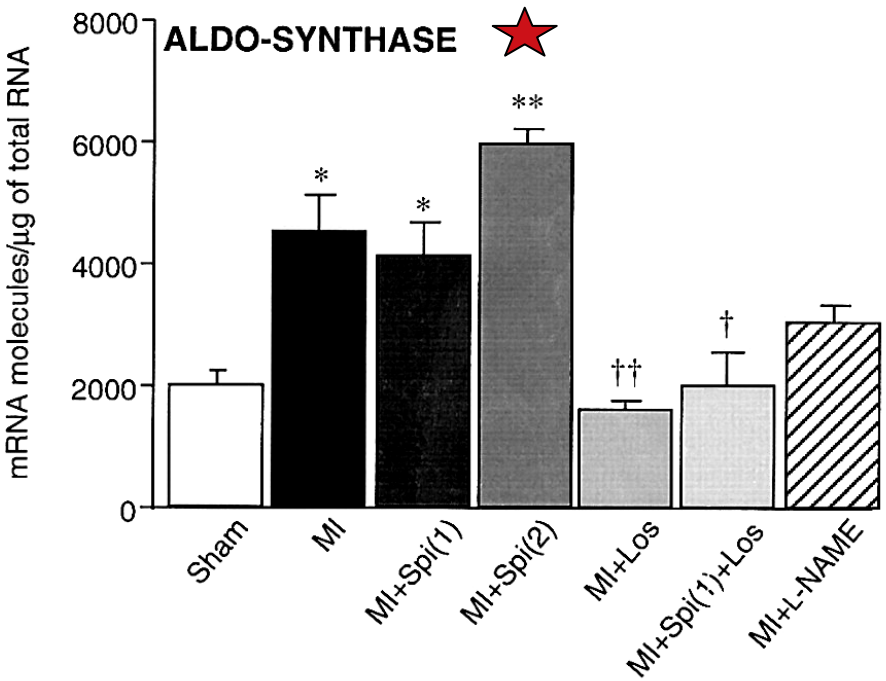
in the absence of renal function : blood pressure increase caused by direct vascular actions

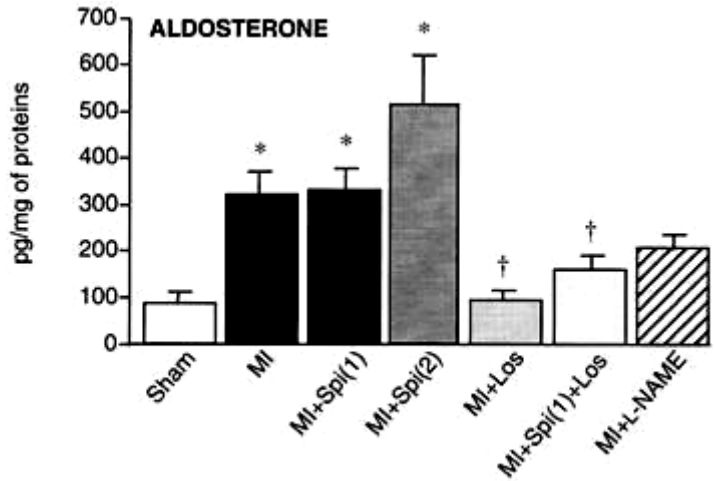


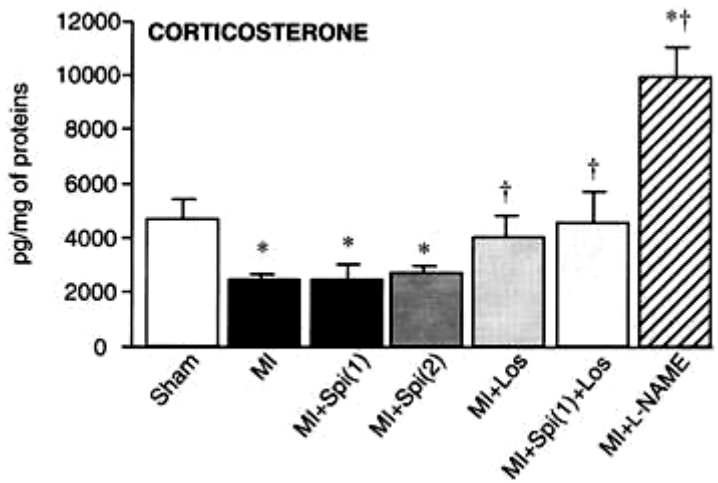
Gross, Am.J.Kidn.Dis (2005) 46:94

Local production of aldosterone in damaged target organs

e.g. rats with MI







Silvestre, Circulation (1999) 99: 2694

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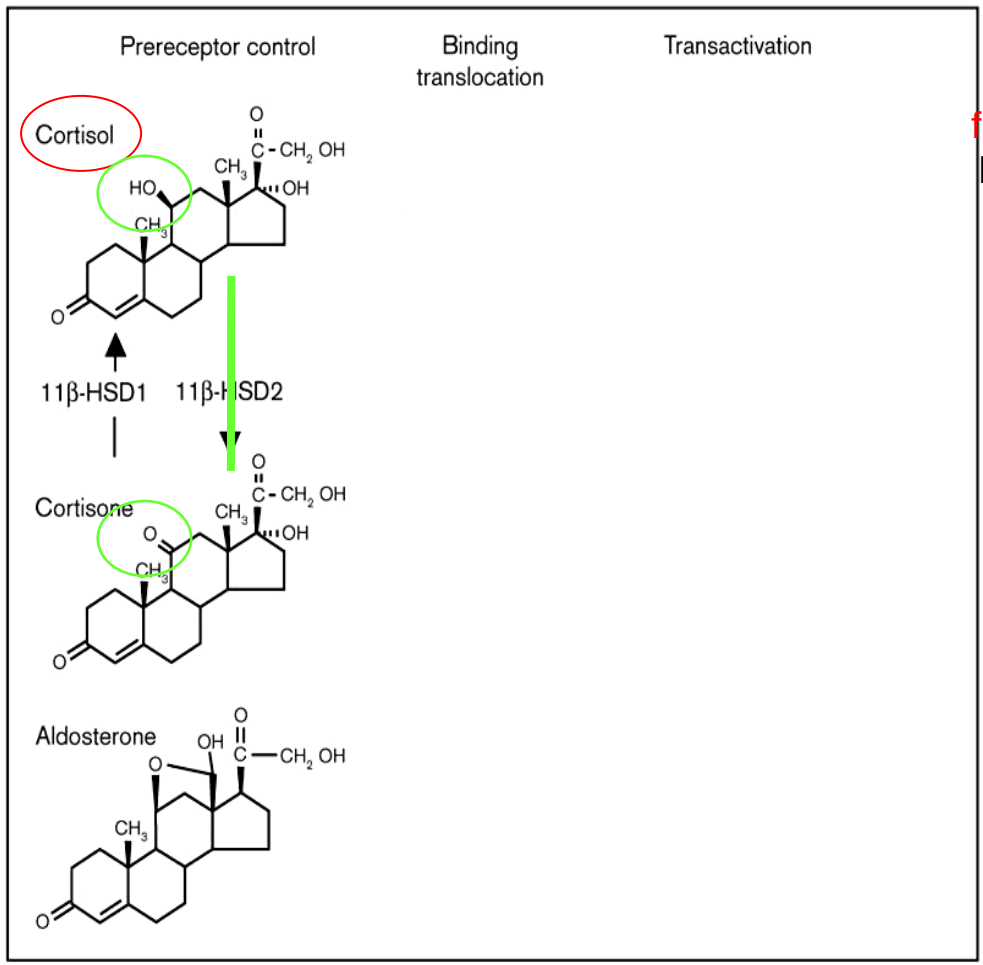
Isidore S.Edelman
(1920-2004)

Prereceptor metabolism (cortisol → cortisone) by cytoplasmic 11β hydroxysteroid dehydrogenase 2 prevents stimulation of the mineralocorticoid receptor by cortisol

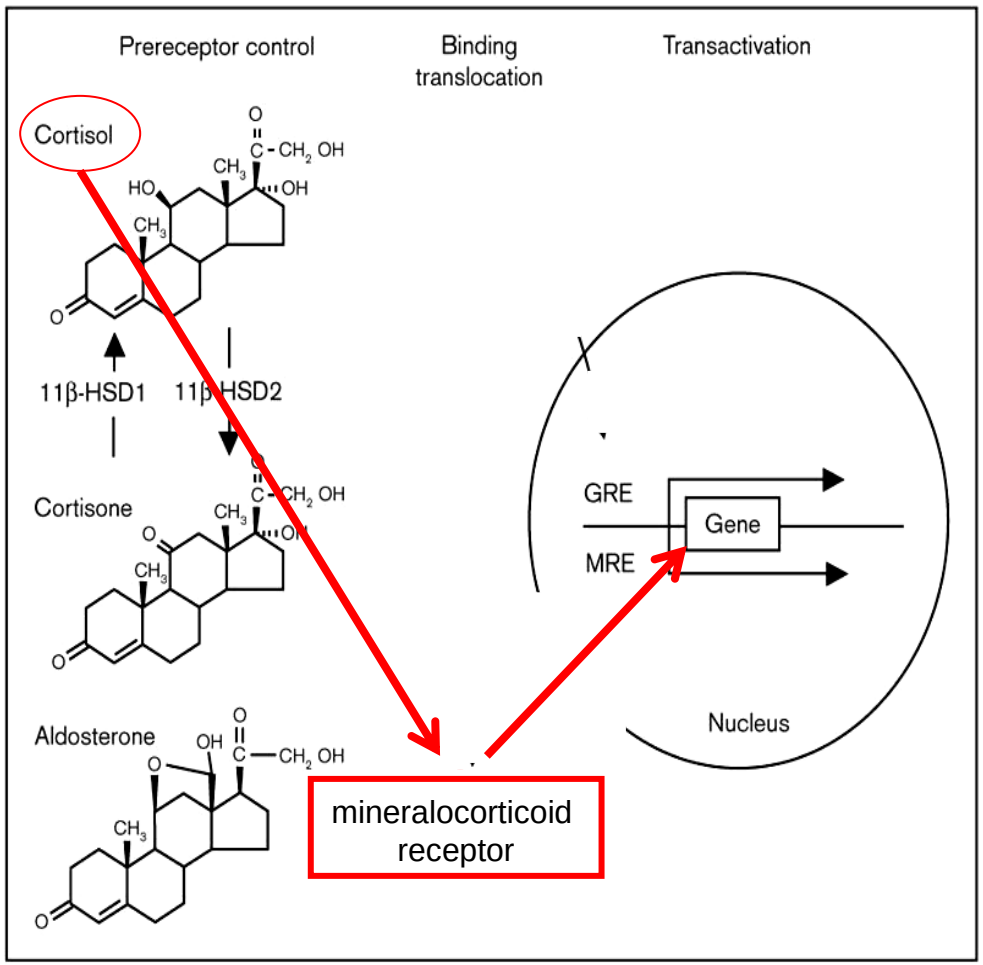


fish produce no aldosterone, but have a precursor of the mineralocorticoid receptor which is stimulated by glucocorticoids and was later hijacked by aldosterone

Frey, Curr.Opinion.Nephrol.Hypertens.(2004) 13:451

High intracellular cortisol *(e.g. inflammation)* → **aldosterone antagonists effective despite normal plasma aldosterone concentrations**

(recapitulates a phylogenetically ancient constellation)



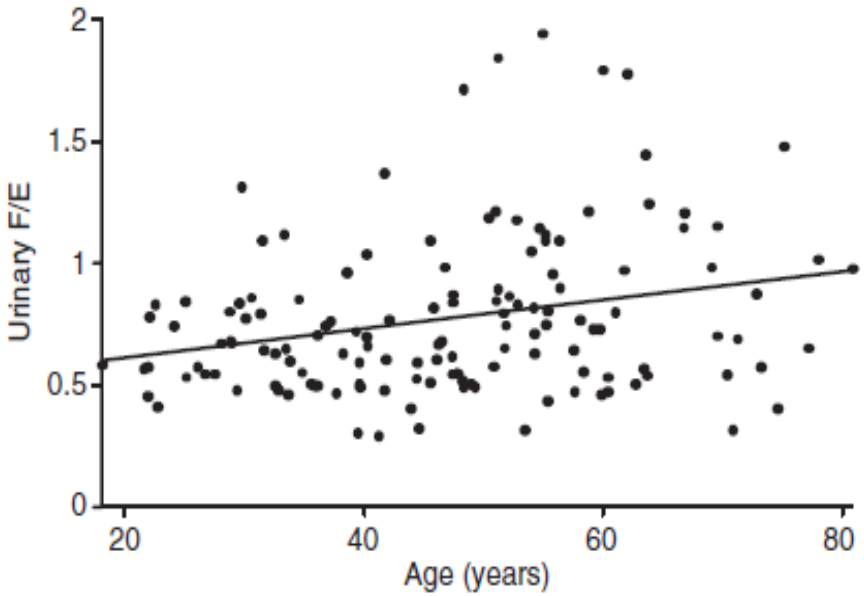
One reason for increased blood pressure in the elderly :

In the elderly increased urinary cortisol (F) / cortisone (E) ratio ➡ salt- sensitive hypertension

(faulty stimulation of the mineralocorticoid receptor)

low 11βHSD2 activity
i.e. low transformation of cortisol to cortison

→high cortisol stimulates mineralocorticoid receptor and causes hypertension



Henschkowski, Am.J.Hypertens.(2008) 21: 644

Metabolic syndrome – a role for aldosterone ?

- **frequently elevated aldosterone in obese individuals**

  Goodfriend, Endocrine Research (1998) 24:789

- **adipocytes produce aldosterone stimulating factor (?)**

  Ehrhart-Bornstein, Proc.Natl.Acad.Sci.USA(2003) 100:14211

- **potential role of fat derived factors and aldosterone in podocyte injury**

  Nagase, J.Am.Soc.Nephrol.(2006) 17:3438

- **in hypertensive rats with metabolic syndrome ROS production by podocytes as consequence of aldosterone overproduction**

  Shibata, Hypertension (2007) 49:355

- **Eplerenone → inhibition of podocyte injury and proteinuria**

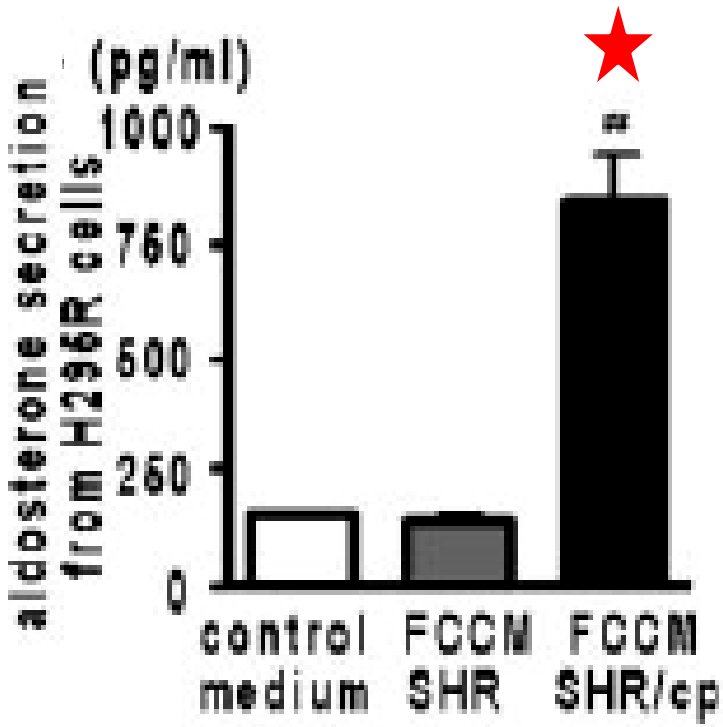
  Nagase, Hypertension (2006) 47:1084

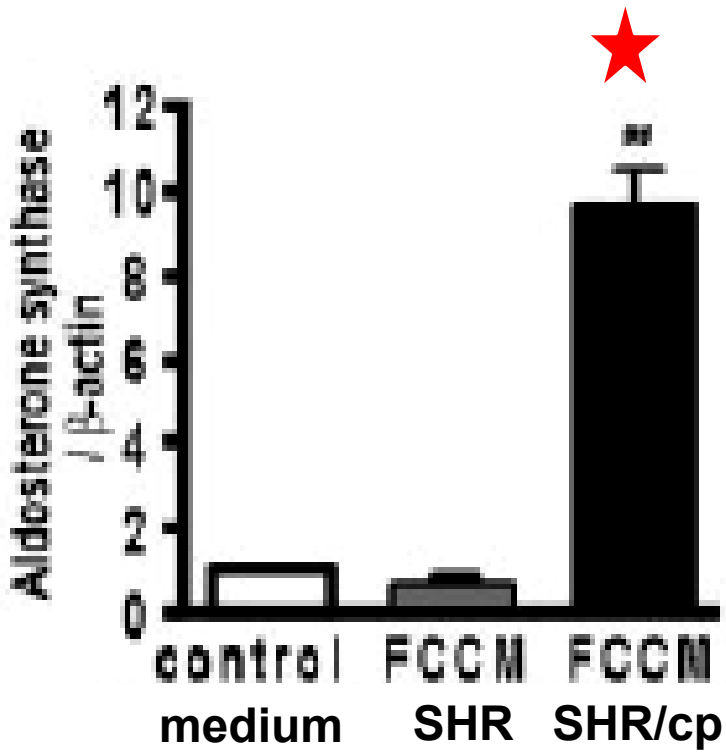
Epidydimal fat-cell conditioned-medium of SHR/Ncp *(metabolic syndrome)*

(but not SHR)

stimulates aldosterone secretion and activates aldosterone synthase in the adrenals

cross-talk - adipocytes talking toadrenal





Nagase, J.Am.Soc.Nephrol.(2006) 17:3438

REVIEW

PHYSIOLOGY IN MEDICINE: A SERIES OF ARTICLES LINKING MEDICINE WITH SCIENCE
Physiology in Medicine: Dale J. Benos, PhD, *Editor*; Edward Abraham, MD, *Associate Editor*; Peter D. Wagner, MD, *Associate Editor*

Annals of Internal Medicine: Harold C. Sox, MD, *Series Editor*

Narrative Review: The Emerging Clinical Implications of the Role of Aldosterone in the Metabolic Syndrome and Resistant Hypertension

James R. Sowers, MD; Adam Whaley-Connell, DO; and Murray Epstein, MD

Ann.Intern.Med.(2009) 150:776

"Inappropriately high Aldosterone concentrations in the circulation favour the appearance of the metabolic syndrome and hypertension refractory to treatment, of abnormal "insulin signalling" and disturbed endothelial cell function.

This results in

- *insulin resistance*
- *cardiovascular damage*
- *disturbed* ***renal*** *function (albuminuria, loss of GFR)*

This is associated with

- *disturbed β cell function of the pancreas*
- *reduced insulin sensitivity of muscles*
- *secretion of proinflammatory adipokines*"

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Aldosterone

classical concept (Isidore S.Edelman)

synthesis : adrenal cortex *(zona glomerulosa)*

action (endocrine) : transport epithelia

- *distal nephron*
- *colon*
- *salivary gland*
- *sweat gland*

Na+ absorption (vectorial transepithelial transport)

K+ secretion (indirectly)

⇨ mediated by : sgk-1 *(serum and glucocorticoid inducible kinase)*

Aldosterone

genomic effects — **mineralocorticoid receptor**

nuclear

ENaC (Epithelial **Na⁺ C**hannel**)**

(hours)

Rossier, Endocr Rev (1989) 15: 206

nongenomic effects — **plasma membrane receptor**

(seconds; not inhibited by actinomycin D)

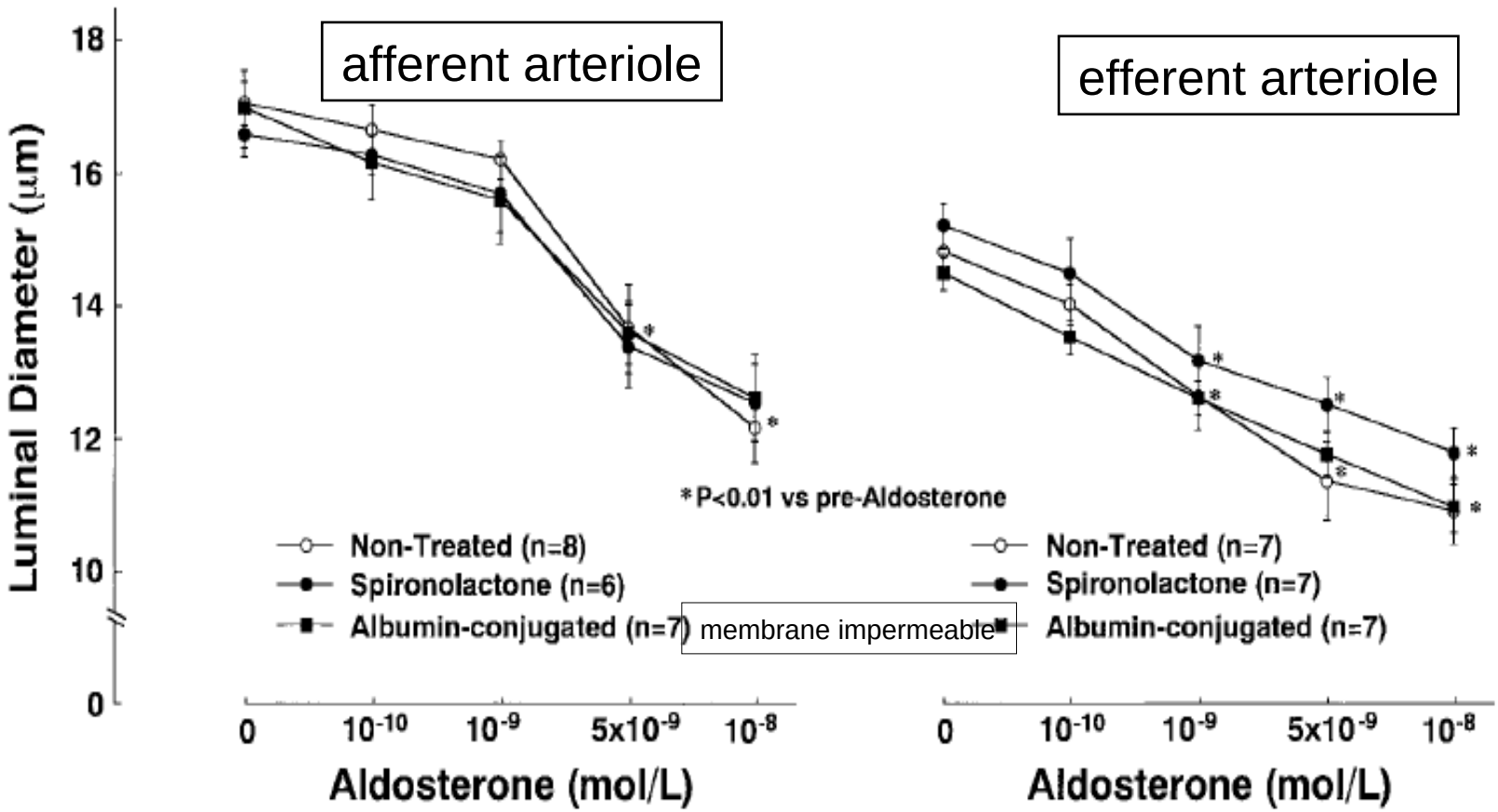
classical effects — **transport epithelia**

nonclassical effects — **interstitial tissue etc**

Wehling, JCEM (1998) 83: 3517

Renal afferent and efferent vessels vasoconstricted by aldosterone, but not reversed by Spironolactone or albumin-conjugated aldosterone

nongenomic effects



Arima, J.Am.Soc.Nephrol. (2003) 14:2255

Aldosterone and the cardiovascular system – the good, the bad and the ugly

the good : sodium retention and potassium homeostasis → avoidance of hypotension

the bad : persistent hypertension → blood pressure dependent target organ damage

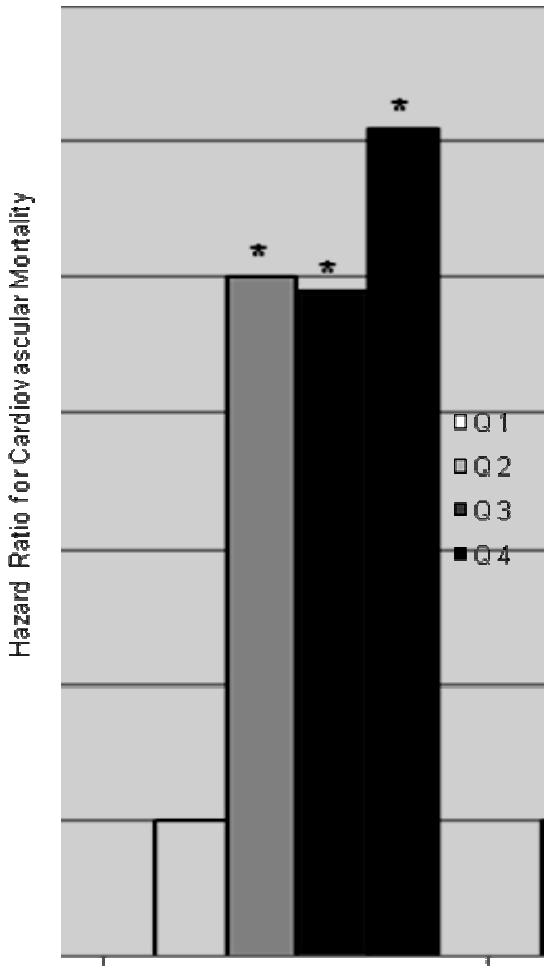
the ugly : in a permissive milieu → even normal aldosterone concentrations promote blood pressure independent target organ damage

(inflammatory, profibrotic etc pathways; oxydative stress…; NF_KB, AP1,NADPH-oxydase,ICAM,VCAM…)

Gekle and Grossmann, Plügers Arch-Eur.J.Physiol.(2008) 458: 231

Quartiles of plasma aldosterone- concentrations in the normal range – progressively higher "hazard ratio" for cardiovascular death

3153 patients with coronary heart disease (*LURIC Studie*)



Tomaschitz, Europ.Heart J. (2010) 31:1237

Renal aspirin: will all patients with chronic kidney disease one day take spironolactone?

Andrew S Bomback*, Abhijit V Kshirsagar and Philip J Klemmer

Nature Clin.Practice Nephrol. (2009) 5: 74

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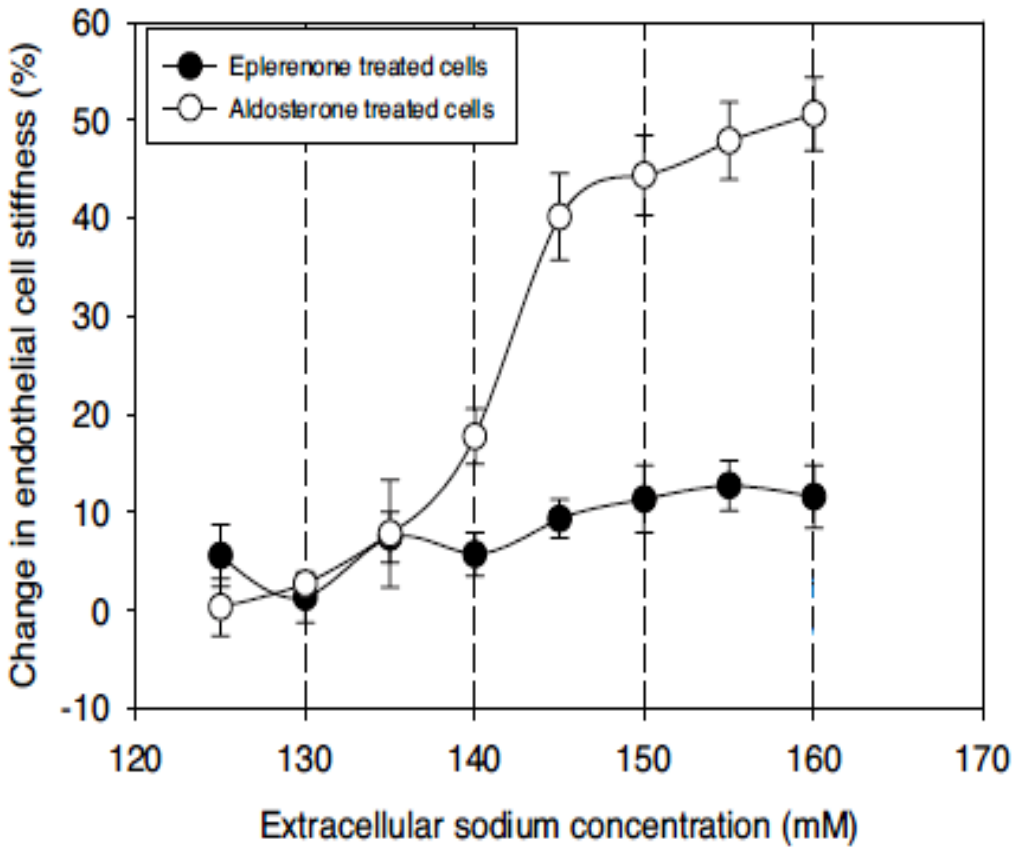
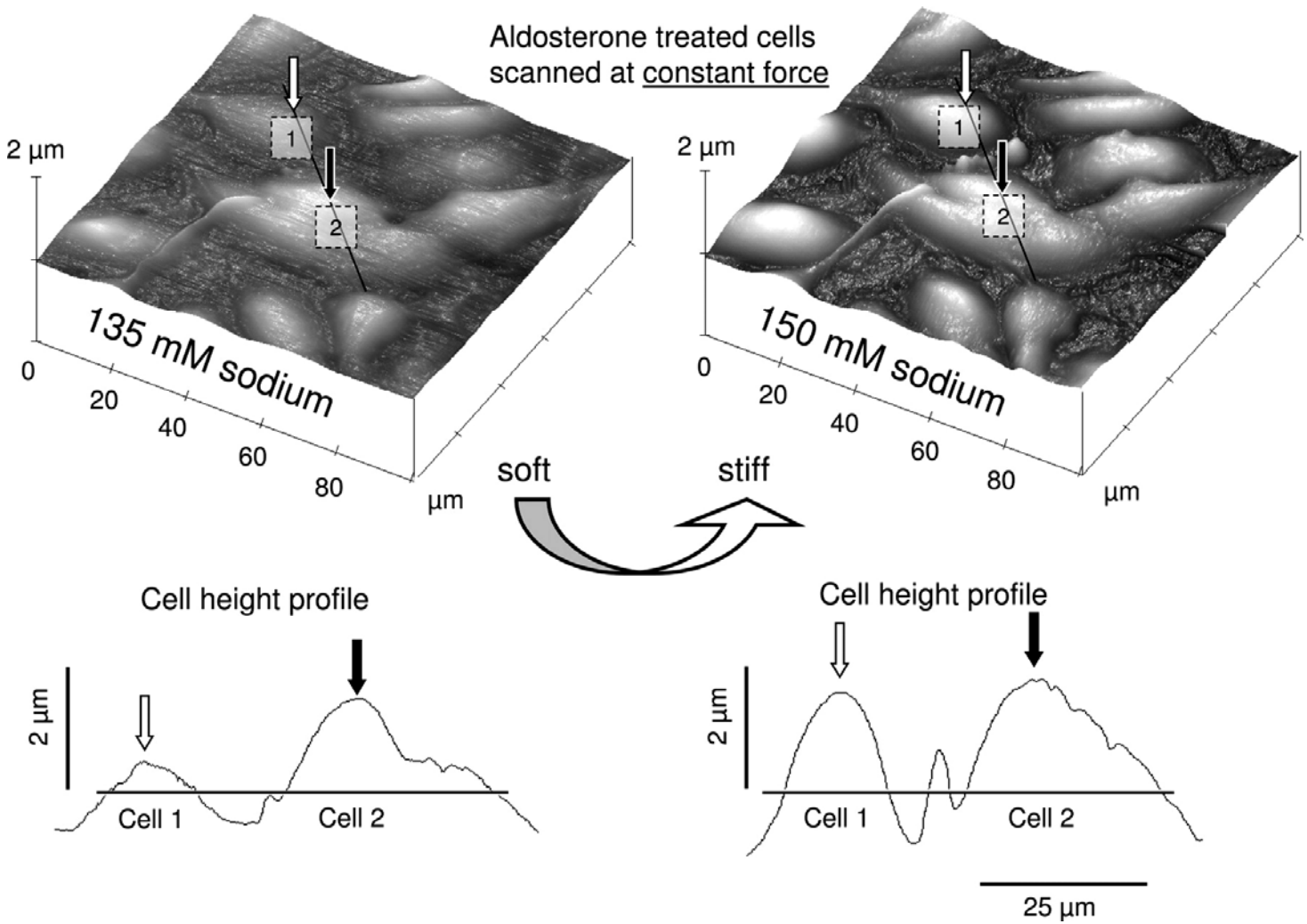
Plasma sodium concentration stiffens human vascular endothelium in vitro – effect of aldosterone and eplerenone



Oberleithner, Proc.Natl.Acad Sci USA (2007) 104:16281

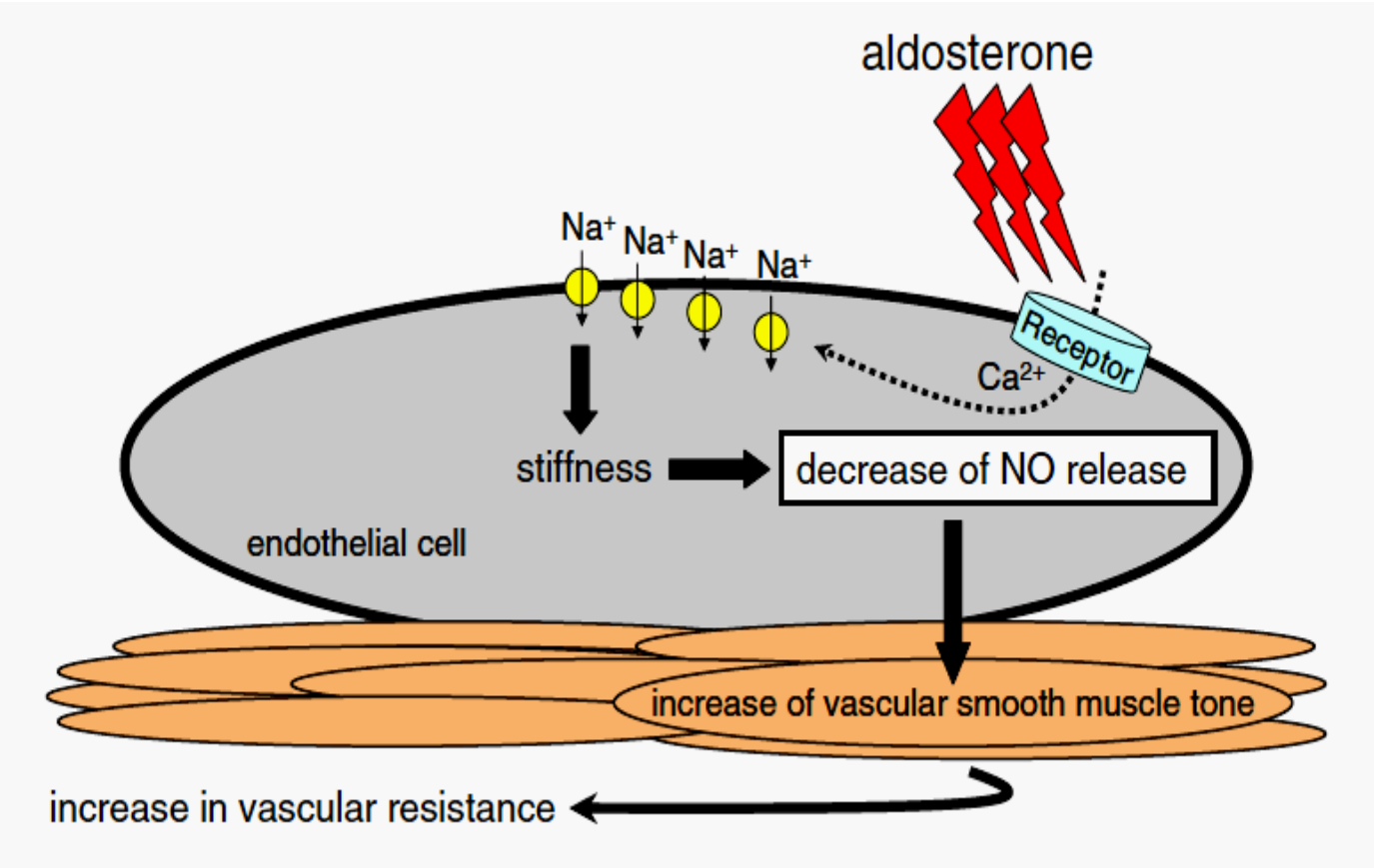
“Atomic force microscope“ :
shape change of vital aldosteron treated human endothelial cells



Oberleithner, PNAS (2007) 104: 16281

Nonclassical mineralocorticoid receptors on endothelial cell membranes –

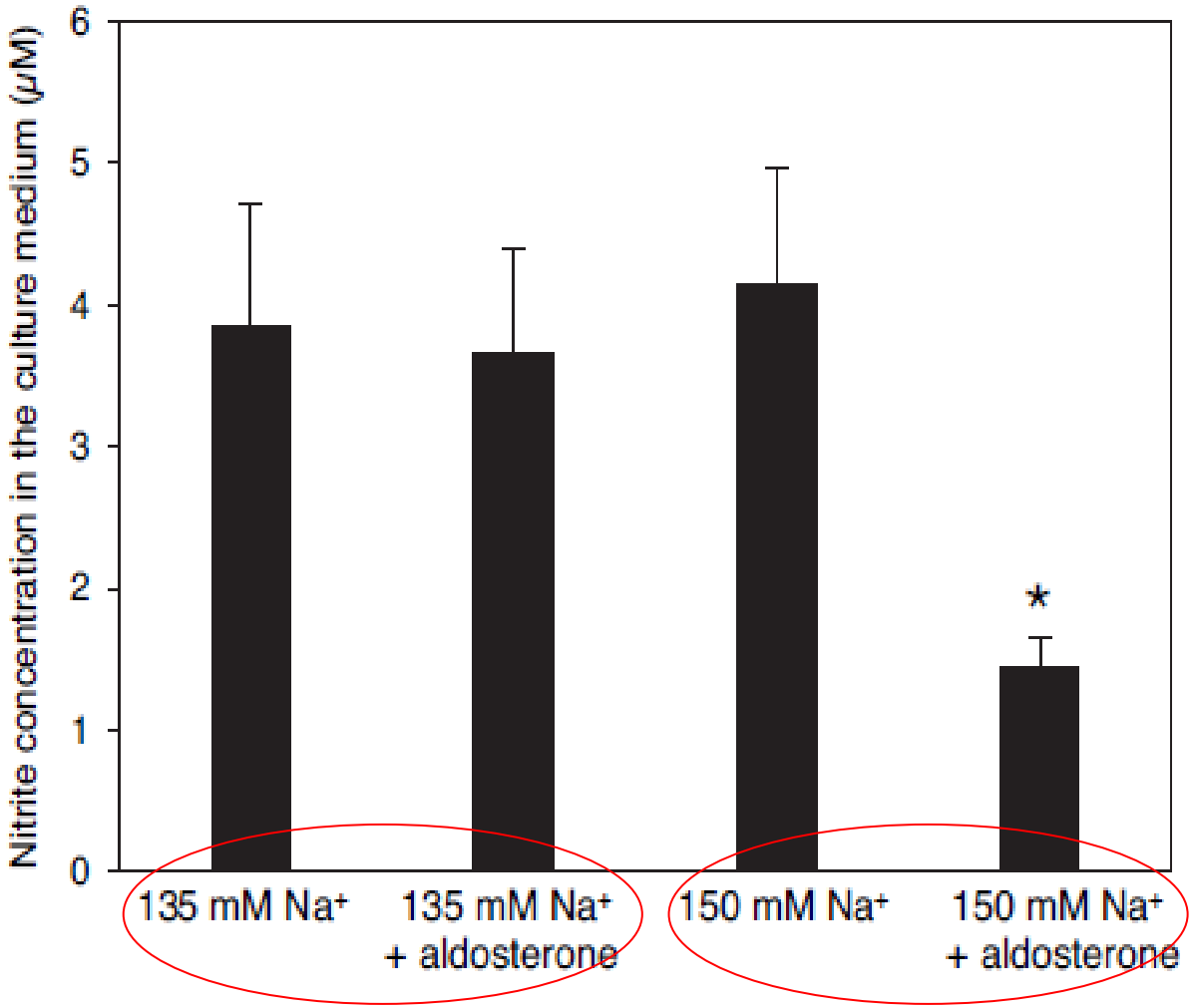
nongenomic effcts



Wildling, Pflügers Arch. (2008) 458: 223

High [Na^+] induced inhibition of nitrite production by eNOS in human endothelial cells –

but only in the presence of aldosterone *(permissive effect)*



Oberleithner, Proc.Natl.Acad Sci USA (2007) 104:16281

Arterial stiffness in essential hypertension – response to aldosterone antagonist

- *24 untreated patients (mean age 51 yrs)*
- *50 mg of spironolactone or 2.5 mg of bendroflumetazide for 4 weeks, washout period of 1 month*

➡ *both drugs reduced blood pressure,*

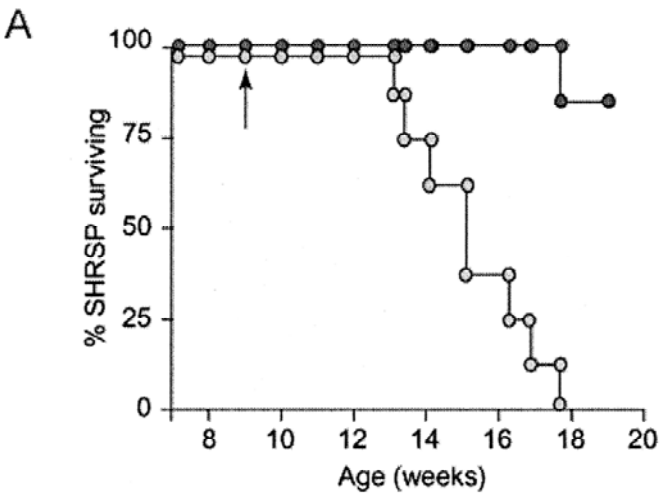
but only spironolactone reduced pulse wave velocity

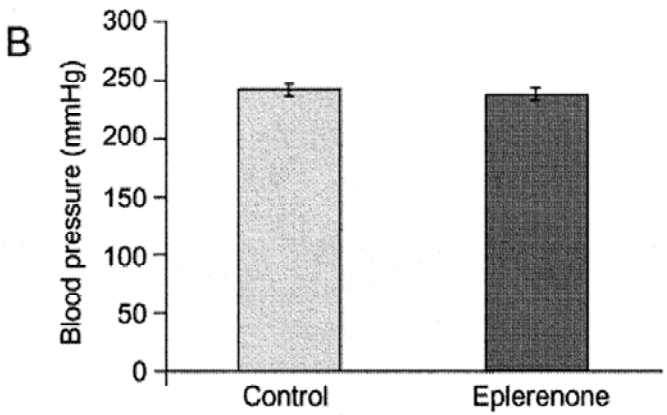
blood pressure independently

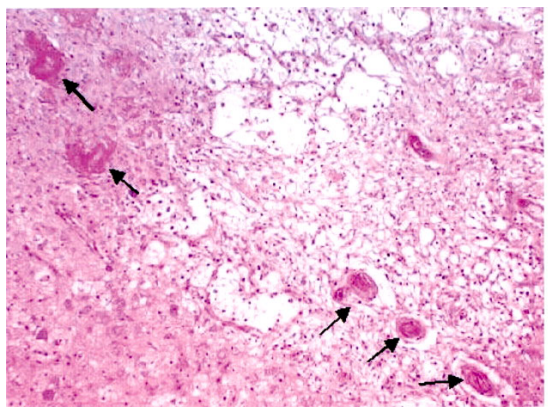
Mahmud; Am J Hypertens (2005)18 : 50

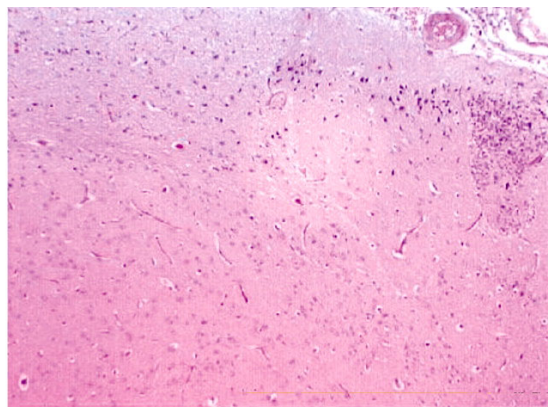
Aldosterone receptor blockade reduces mortality and target organ damage in the SHRsp despite no change in blood pressure

blood pressure independent target organ damage









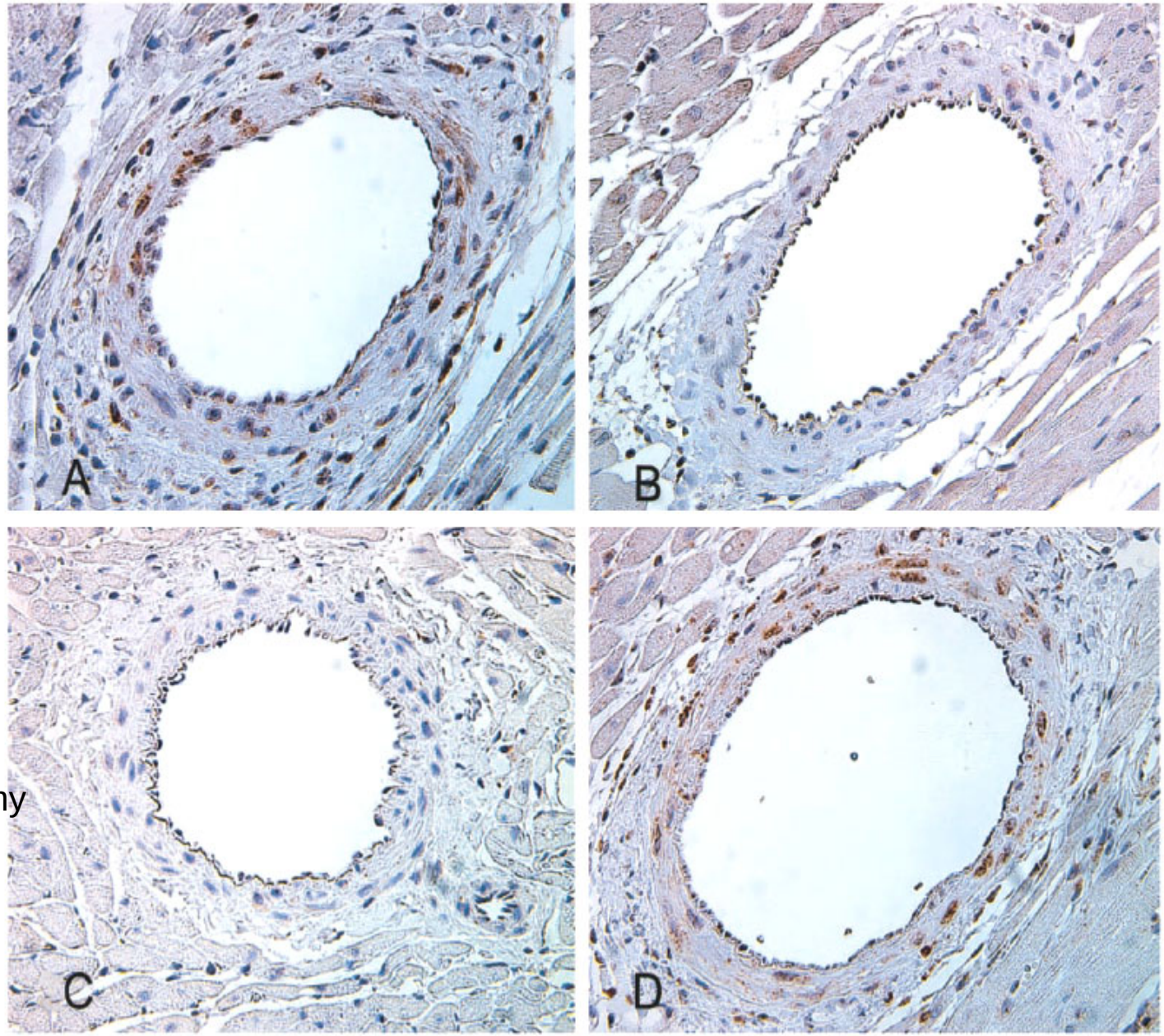
untreated *Eplerenone*

Rocha, Trends Endocr Metab (2001) 12:308

COX2 immunehistology – aldo dependent expression in vascular media

salt+ANGII

Eplerenone



adrenalectomy

adrenalectom
+aldosterone

Rocha, Endocrinology (2002) 143: 4818

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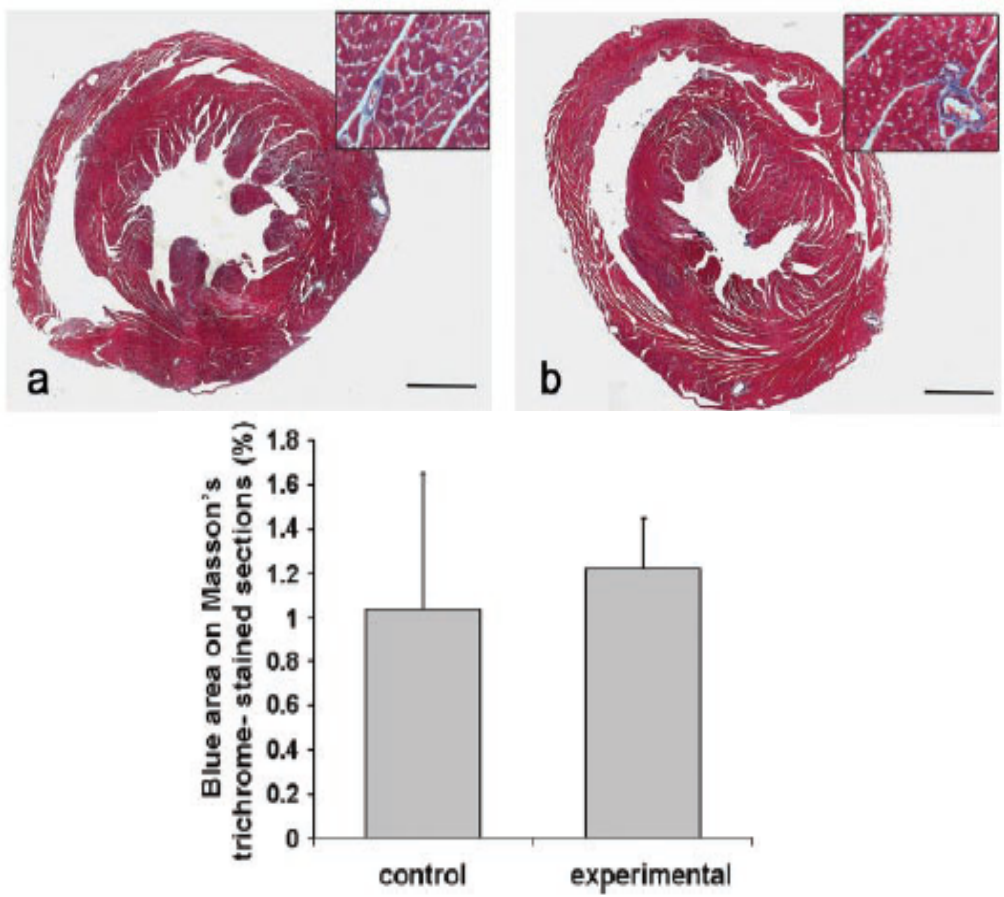
Low blood pressure (102/62 mmHg) **despite**
1±1.5 mmol/day NaCl and 203 ± 109 mmol K/day and S-aldosterone 85.6 ± 78 ng/dl

Nowaczynski, Clin.Physiol.Biochem.(1985) 3: 289

Low sodium diet + renal sodium loss no hypertension ➡ no cardiac hypertophy depite high aldosterone

(ENaC -/- mice on 0.3% salt diet – chronic renal Na+ loss)



Wang, Am.J.Physiol Renal Physiol.(2004) 286:F1178

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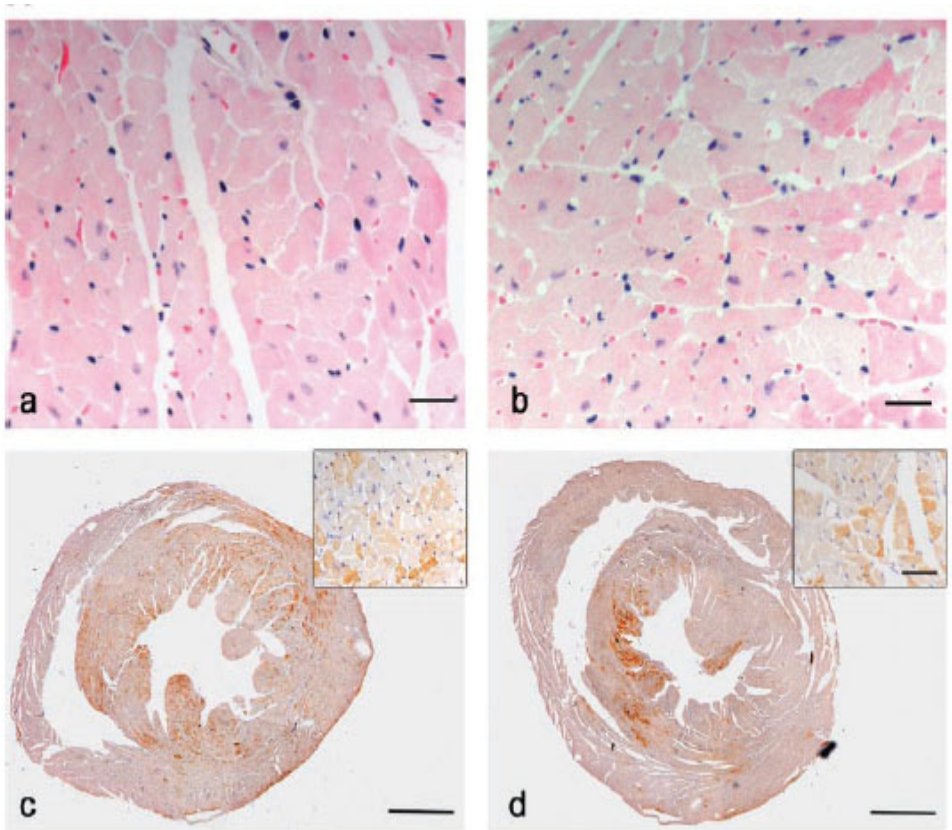
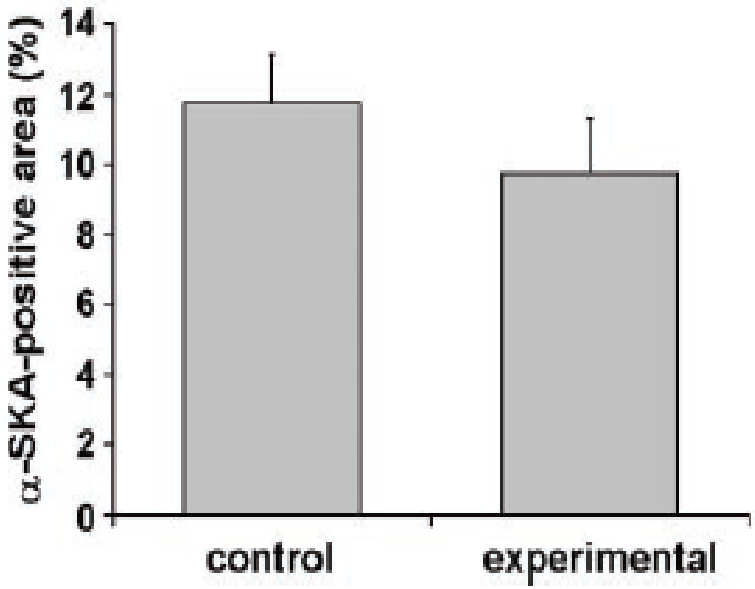




Wang, Am.J.Physiol Renal Physiol.(2004) 286:F1178

Aldosterone induced damage – high salt environment required

vascular inflammatory response (NFκB)

NO↓

leucocyte infiltration

remodelling

fibrinoid necrosis

ischemia

Rocha and Funder, Ann NY Acad Sc (2002) 970: 89

Rho family of small GTPases

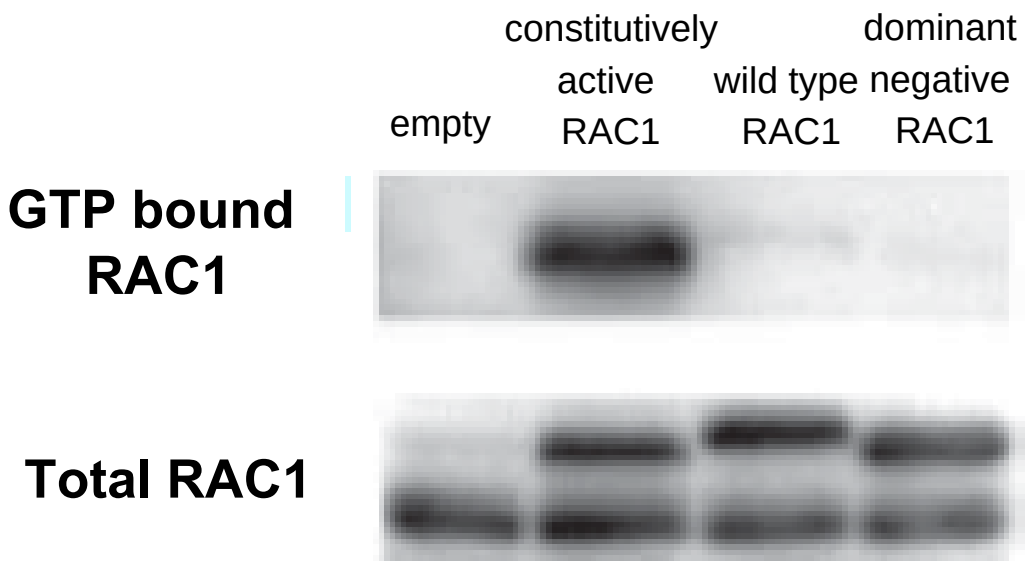
involved in transactivation of

several steroid receptors

including the mineralocorticoid receptor

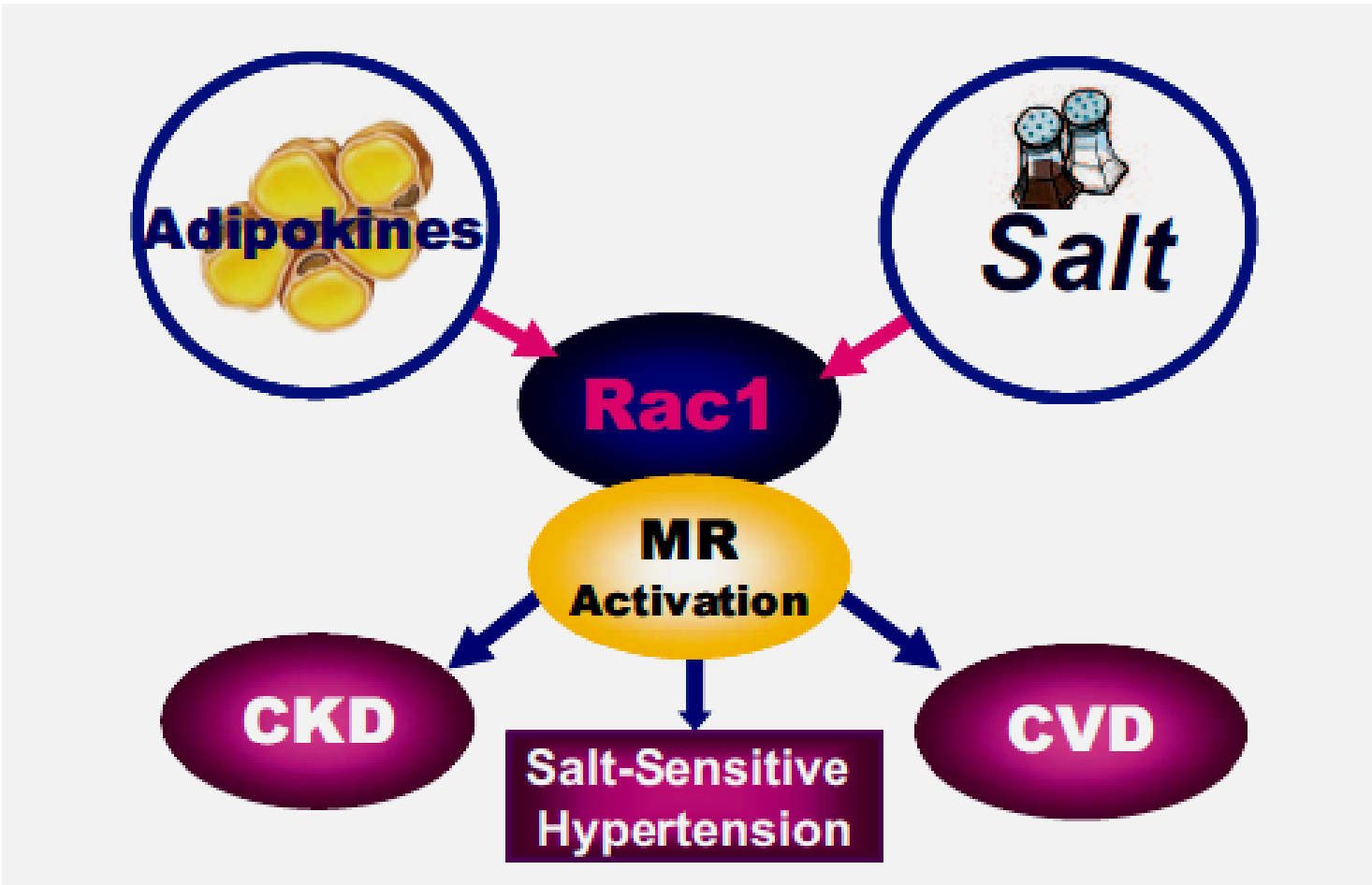
Shibata, Nature Medicine (2008) 14:1370

Constitutively active Rac1 GTP‘ase nuclear expression in human derived HEK 253 cells



Shibata, Nature Medicine (2008) 14:1370

The role of aldosterone independent mineralocorticoid receptor activation by high salt and/or metabolic syndrome



Fujita, Hypertension (2010) 55:813

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Aldosterone :

Blood pressure independent target organ damage (e.g.kidney) dependent on salt status :

“high salt” + aldosterone

kidney damage

malignant nephrosclerosis of SHRsp

double transgenic rat

- *adrenalectomy prevents renal and vascular necrosis*
- *eplerenone blocks vascular necrosis*

Rocha,Hypertension (1998) 31:451

Fiebeler Hypertension (2001) 37:787

Animal models of progressive renal damage

activation of adrenal gland after subtotal nephrectomy

10fold increase plasma aldosterone after SNX

Greene, J Clin Invest (1996) 98: 1063

adrenal hyperplasia (zona glomerulosa)

Morrison,Lab.Invest.(1962) 11:321

Kidney damage after subtotal nephrectomy

effects of

adrenalectomy

and

administration of mineralocorticoids

less hypertension, proteinuria, structural lesions

- **SNX vs**
- **SNX + adrenalectomy** *(glucocorticoid substitution)*

Quan, Kidney Intern (1992) 41: 326

DOCA salt → malignant nephrosclerosis

Gavras, Circ Res (1975) 36: 300

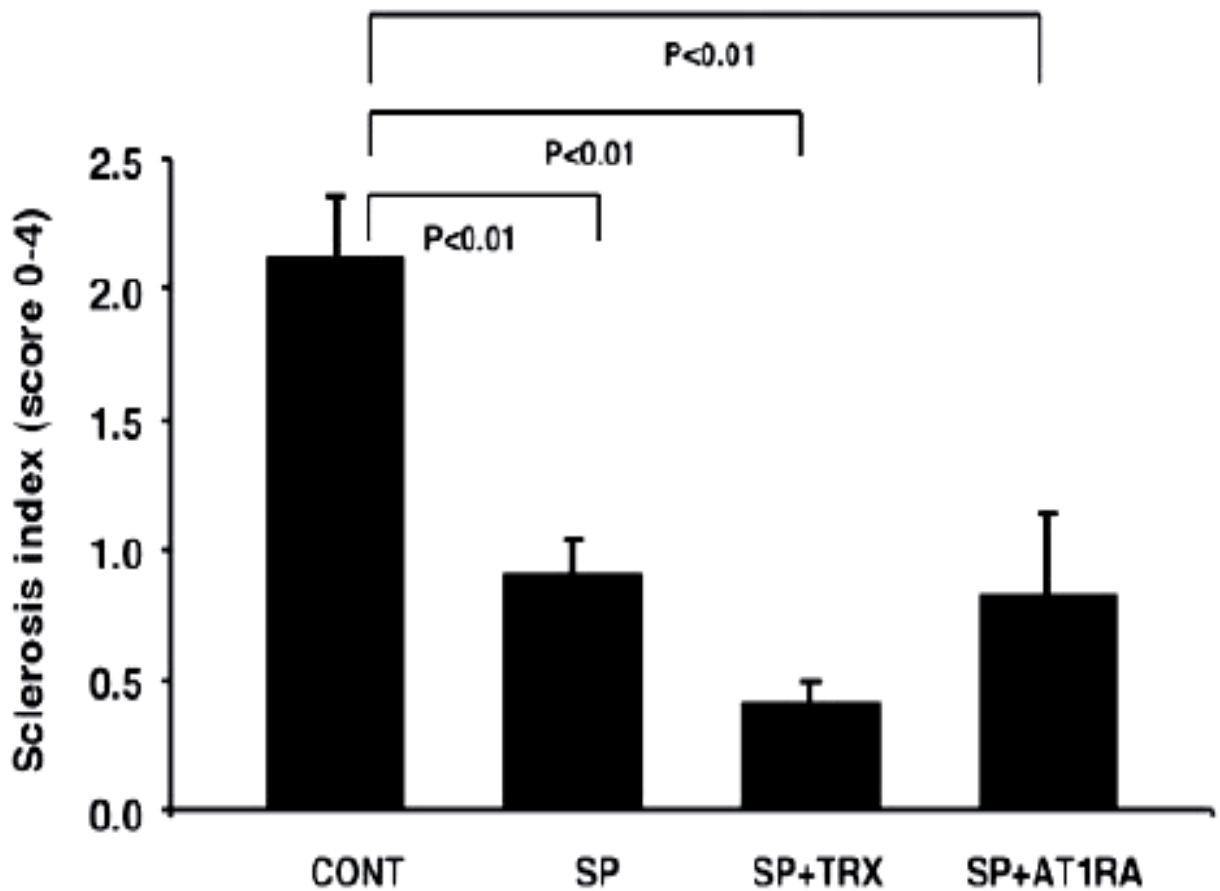
Subtotal nephrectomy – effect of RAS blockade (ACEi+ARB) and of additional Aldosteron

	p-Aldoste- (pg/ml)	Heart weight (g)	Proteinuria (mg/day)
- **sham-op**	50±12	1.03±0.05	19±6
- **SNX**	526±250	1.33±0.19	203±103
- **SNX + ACEi+ARB**	181±124	0.88±0.11	30±15
- **SNX + ACEi+ARB+ Aldosteron**	487±114	1.28±0.12	217±71

Spironolacton little effect - nongenomic effects of aldosteron?

Greene,J.Clin.Invest,(1996) 98:1063

Spironolactone causes regression of established glomerulosclerosis after subtotal nephrectomy



Aldigier, J.Am.Soc.Nephrol.(2005) 16:3306

Aldosterone and renal lesions even without subtotal nephrectomy

Unopposed aldosterone in the presence of high salt intake → thrombotic and proliferative lesions in glomeruli and renal vessels

Green, Journal Clinical Investigation (1996) 98:1063

Rocha, Hypertension (1999) 33:232

Rocha, Endocrinology (2000) 141:3871

Aldosterone and progression – clinical observations

p-aldosterone elevated when GFR < 70 ml/min

Hené,Kidn.Intern (1982) 21:98

correlation p-aldosterone and rate of progressior

Walker,Am.J.Kid.Dis.(1993) 22:164

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A first proposal of using Spironolactone to limit renal injury

Spironolactone in Addition to ACE Inhibition to Reduce Proteinuria in Patients with Chronic Renal Disease

- **8 pts with CKD and proteinuria > 1g/24h, despite ACE-inhibitor treatment**
- **25 mg spironolactone added on top of ACEi**
- **decrease of proteinuria from mean of 3.81 to 1.75 g/24 g (54% reduction)**
- **without significant change in blood pressure or creatinine clearance**

Chrysostomou and Becker, New Engl.J.Med.(2001) 345:925

Effect of Eplerenone on proteinuria in type 2 diabetes

Urinary albumin/creatinine ratio
>100mg/g

mild to moderate hypertension

Enalapril 40mg/day

Eplerenone 200mg/day

combination

by 24 weeks

albuminuria decrease

Enalapril 45%

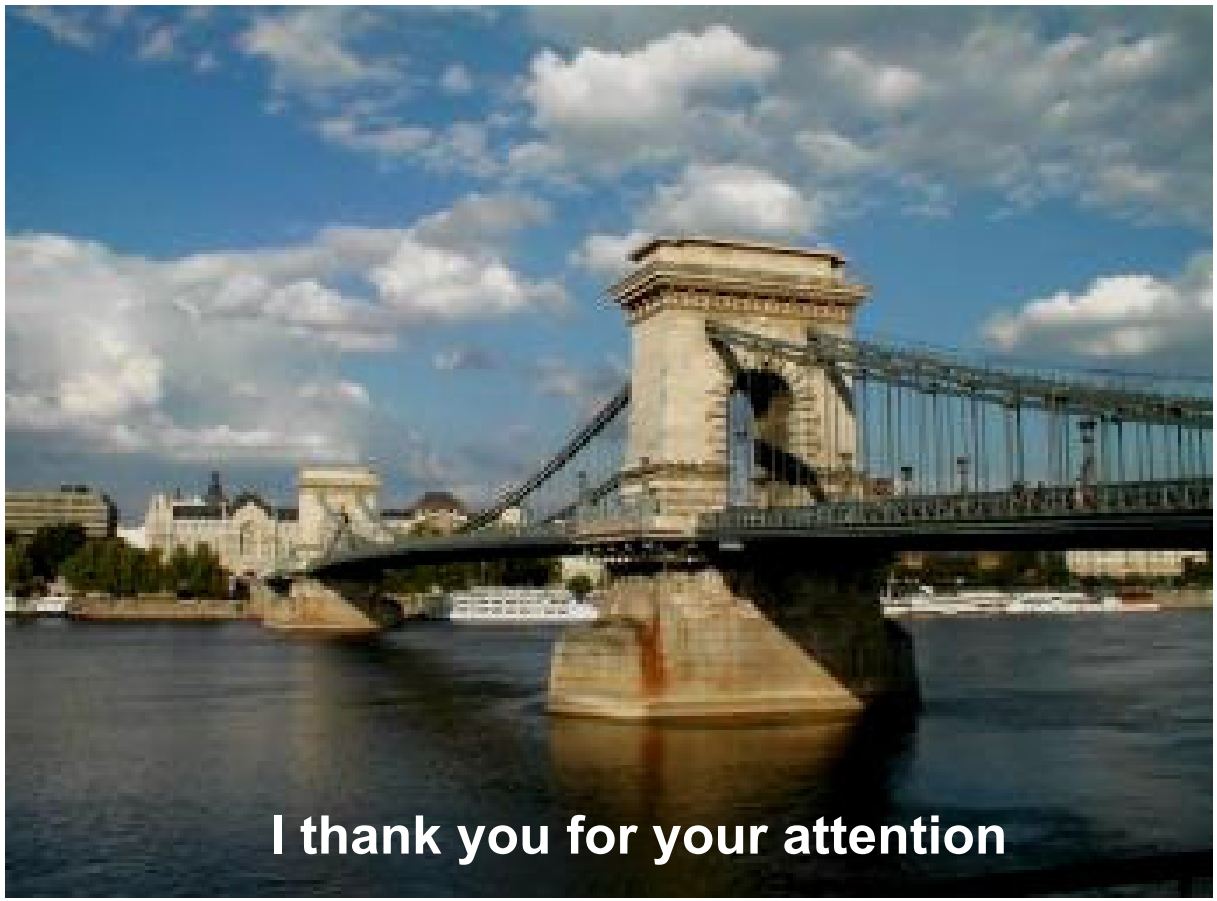
Eplerenone 62%

combination 74%

(p<0.018)

despite similar systolic BP

Epstein, Am J Hypertens (2002) 15: 24a


I thank you for your attention