The kidney and hypertension

Eberhard Ritz
Heidelberg (Germany)

The "epidemic" of hypertension in the USA

Hypertensives
(% of population throughout the 20th century)

1939: 10.0%

1975: 25.3%

1990: 28.9%

2000: 31.3%

Causal factors in the genesis of hypertension

- **Genetic** factors
  (Lifton)

- **Congenital** factors (e.g. low birth weight)
  (Barter and Brenner)

- **Acquired** factors
  (Goldblatt, Tracy, Johnson)

REPORTS

OF

MEDICAL CASES,

SELECTED

WITH A VIEW OF ILLUSTRATING

THE SYMPTOMS AND CURE OF DISEASES

BY A REFERENCE TO

MORBID ANATOMY.

By RICHARD BRIGHT, M.D. F.R.S. &c.

LECTURER ON THE PRACTICE OF MEDICINE,

AND ONE OF THE PHYSICIANS TO

GUY'S HOSPITAL.

LONDON:

PRINTED BY RICHARD TAYLOR, RED LION COURT, FLEET STREET.

PUBLISHED BY LONGMAN, REES, ORME, BROWN, AND GREEN.

1827.

Hypertension: The kidney is the culprit even in the absence of kidney disease

Kidney International (2007) **71**, 371–372. doi:10.1038/sj.ki.5002142

Why is World Kidney Day an occasion to raise the issue of whether or not the kidney is involved in the genesis of high blood pressure? High blood pressure affects approximately 30% of the adult population in Western countries,[1] tendency rising, and even 80% of people older than 80 years, so that a cynic stated, "The only safeguard against hypertension is to die early." The burden of high blood pressure is a major, if not *the* major, public health problem.[2]

a polygenic disorder that is dependent on the interaction among several genetic defects, all rare monogenic forms of hereditary hypertension have one common denominator: increased sodium reabsorption by the kidney at different sites and by different mechanisms along the tubules.[9]

Recently, more insight into the link between a kidney abnormality and hypertension in 'run-of-the-mill' essential hypertension has been provided by anatomical studies of the kidney. The number of glomeruli, and, by implication, of tubules, in

Ritz, Kidn.Internat.(2007) 71: 371

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3. The renal mechanisms leading to hypertension
4. Salt sensitivity in renal hypertension
5. Hormonal mediation of salt effects

High urinary albumin excretion precedes onset of overt hypertension

- Brantsma A.H. et al
  Urinary albumin excretion as a predictor of the development of hypertension
  J.Am.Soc.Nephrol.(2006) 17:331

- *Wang T.J. et al.*
  Low-grade albuminuria and the risks of hypertension and blood pressure progression
  Circulation (2005) 111: 1370

Albuminuria in the normoalbuminuric range predicts future hypertension

(postmenopausal, Nurses Health study)

quartiles of albumin/creatinine ratio (mg/g)
median and range

1.0	**2.2**	**3.4**	**6.5**
(0-1.7)	*(1.7-2.7)*	*(2.7-4.3)*	*(4.3-24.2)*

risk of incident hypertension

1.1	**2.0**	**2.9**	**5.4**
(0-1.6)	*(1.6-2.4)*	*(2.4-3.7)*	*(3.7-23.8)*

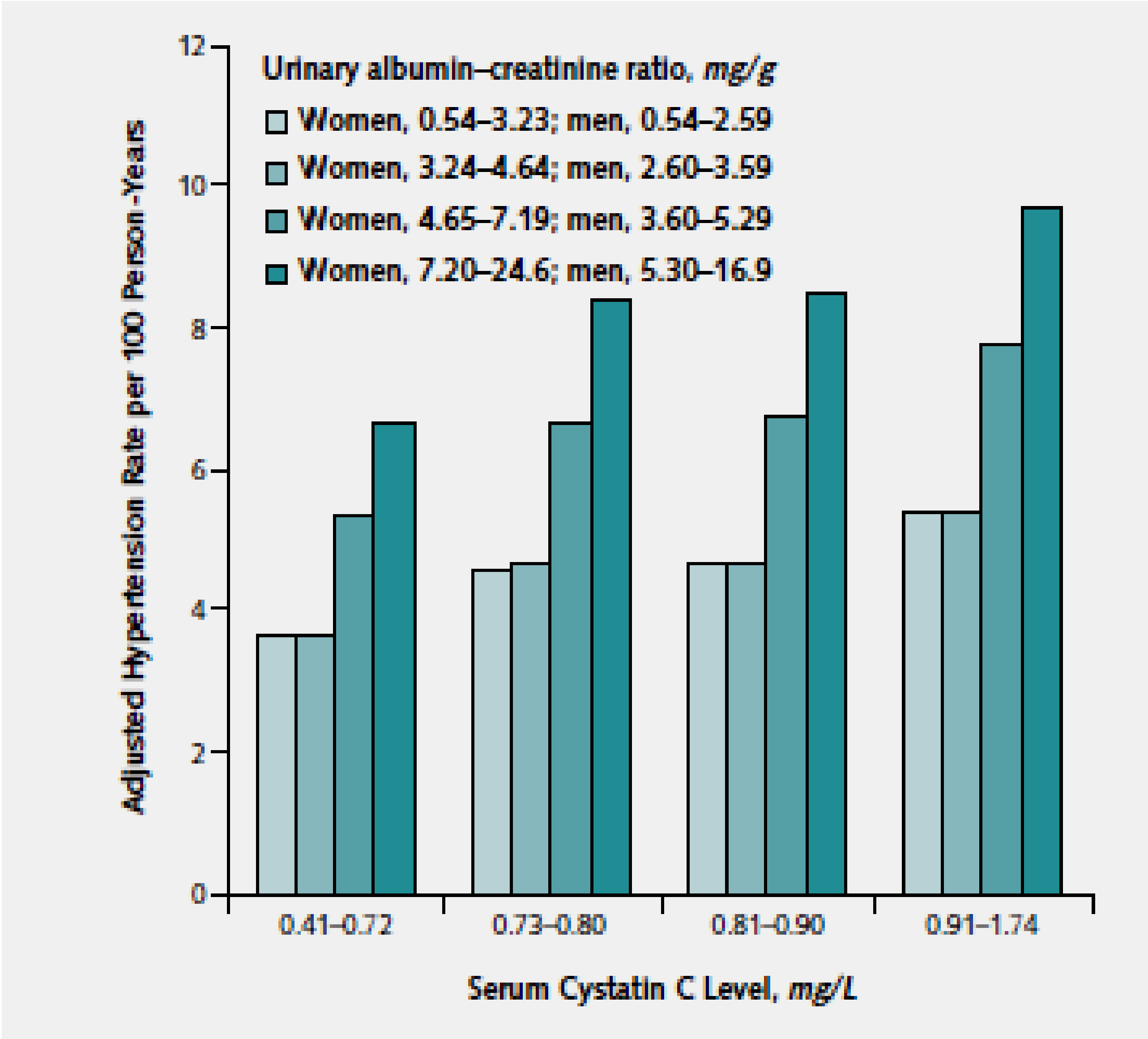
$\mathbf{p_{trend} < 0.004}$

Forman, J.Am.Soc.Nephrol.(2008) 19:1983

Higher serum cystatin C as well as higher urinary albumin precede the onset of hypertension

MESA study

(multiethnic study of atherosclerosis)



Kestenbaum, Ann.Int.Med.(2008) 148:501

Animal experiments:
blood pressure
“goes with the kidney”

kidney genetically programmed for hypertension,
transplanted into a normotensive recipient animal with no immunerejection

→ **persistent hypertension**

Rettig R, Am J Physiol (1980) 258, F606

Persistent normotension after kidney graft from normotensive donor

6 black patients
dialysis dependent because of "essential hypertension"
nephrosclerosis by histology
kidney graft from normotensive donor

➡ after 4.5 years follow-up
all normotensive
normal BP response to Na loading / deprivation

Curtis, New Engl J Med (1983) 309, 1009

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Pregnancy and early childhood – critical periods for cardiovascular and renal risk in adult life ?

Prenatal programming

***Epigenetics* :**

nutritional deprivation, placental malfunction, hyperglycemia, smoking…
in pregnancy

hypertension
renal disease
metabolic syndrome

Barker, Nat.Clin.Pract.Nephrol.(2006) 2: 700

Abnormalities of kidney structure
("nephron underdosing")

hypertension
susceptibility to renal damage

Brenner, Am J Hypert (1988) 1, 335

Initiation of hypertension in utero and its amplification throughout life

C M Law, M de Swiet, C Osmond, P M Fayers, DJP Barker, AM Cruddas, CHD Fall

Abstract

***Objective*—To determine whether the relation between high blood pressure and low birth weight is initiated in utero or during infancy, and whether it changes with age.**

***Design*—A longitudinal study of children and three follow up studies of adults.**

***Setting*—Farnborough, Preston, and Hertfordshire, England, and a national sample in Britain.**

***Subjects*—1895 children aged 0-10 years, 3240 men and women aged 36 years, 459 men and women aged 46-54 years, and 1231 men and women aged 59-71 years. The birth weight of all subjects had been recorded.**

***Main outcome measure*—Systolic blood pressure.**

***Results*—At all ages beyond infancy people who had lower birth weight had higher systolic blood pressure. Systolic blood pressure was not related to growth during infancy independently of birth weight. The relation between systolic pressure and birth**

sion can persist even after the primary cause, the tumour or stenosis, has been removed.[2 3]

Recent work has shown that raised blood pressure in adults is associated with reduced growth in early life.[4 5] Mean systolic and diastolic pressures of men and women in middle and late life fall progressively from those with the lowest birth weights to those with the highest. Blood pressure is also higher in those whose birth weights were low in relation to that expected from their placental weights.[4] Children show similar relations.[6] These findings could indicate that high adult blood pressure is initiated in utero. Alternatively, healthy infants of low birth weight may have accelerated growth, so called catch up growth, during the first six months of life.[7 8] If this accelerated early growth were accompanied by an accelerated rise in blood pressure, then the values would be set on a higher than expected plane when tracking of blood pressure becomes established after 6 months of age.[9 10]

We examined the timing of initiation of high blood

Brit.Med.J.(1993) 306: 24

“Nephron underdosing”

(less nephrons)

→ *developmental plasticity : same genes,*
different phenotypes

- *In early life humans are “plastic”, moulded by their environment*
- *The critical periods mostly coincide with periods of rapid cell division*
- *For final nephron number the critical period is 34-36 weeks – later nephrons are no longer formed*
- *frequently associated with insulin resistance, cardiovascular risk, propensity to renal damage*

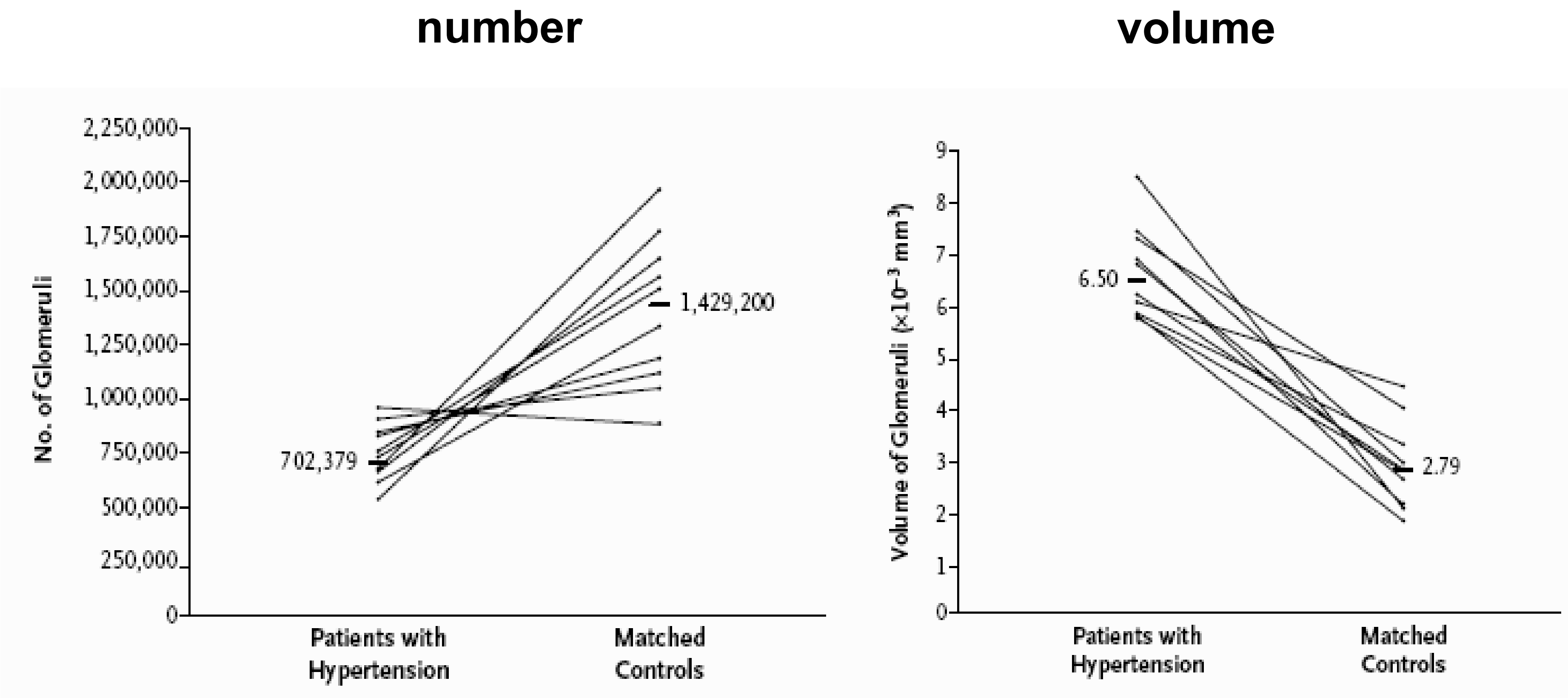
Barker, Nature Clin.Pract. Nephrology (2006) 12: 2

	hypertensive individuals (n=10)	normotensive individuals (n=10)
number of glomeruli	890,869 ± 158,110	1,666,805 ± 411,690
		$p < 0.001$
volume of glomeruli	5.67 ± 0.85	2.41 ± 0.71
		$p < 0.001$

► ***no evidence of obsolescent glomeruli as evidence of hypertension induced loss of glomeruli***

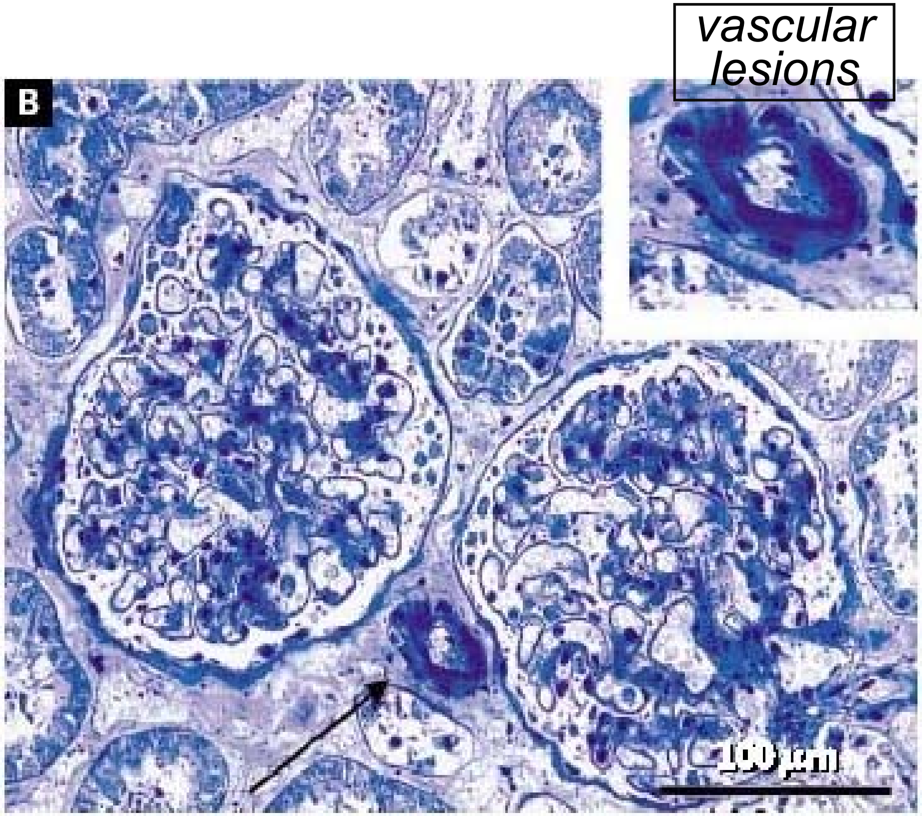
Keller , New Engl J Med (2003) 348: 101

“Oligomeganephrony“

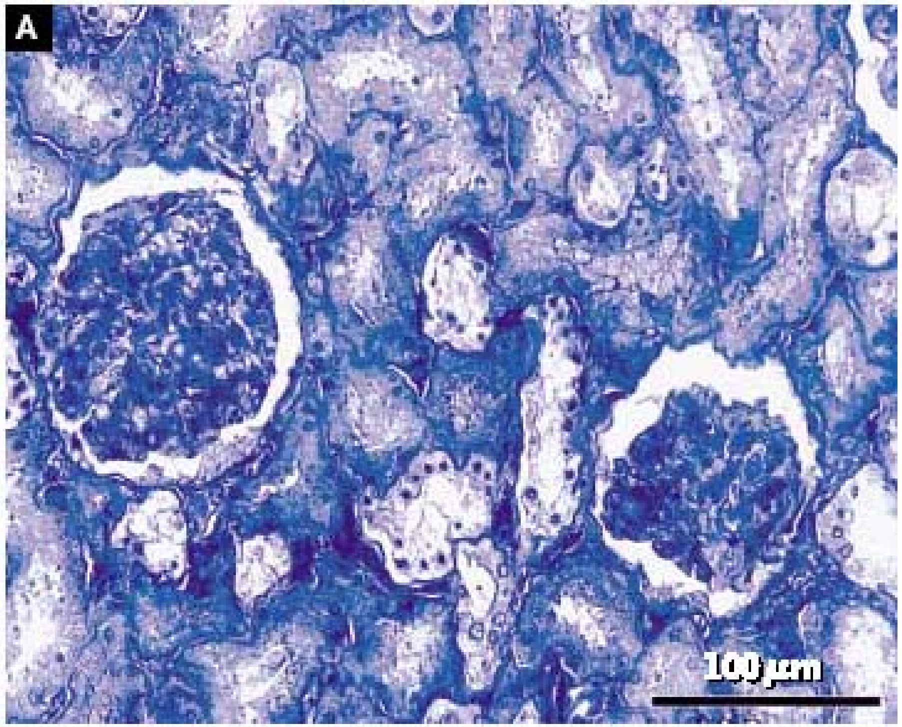


Keller , New Engl J Med (2003) <u>*348*</u>*: 101*

hypertension



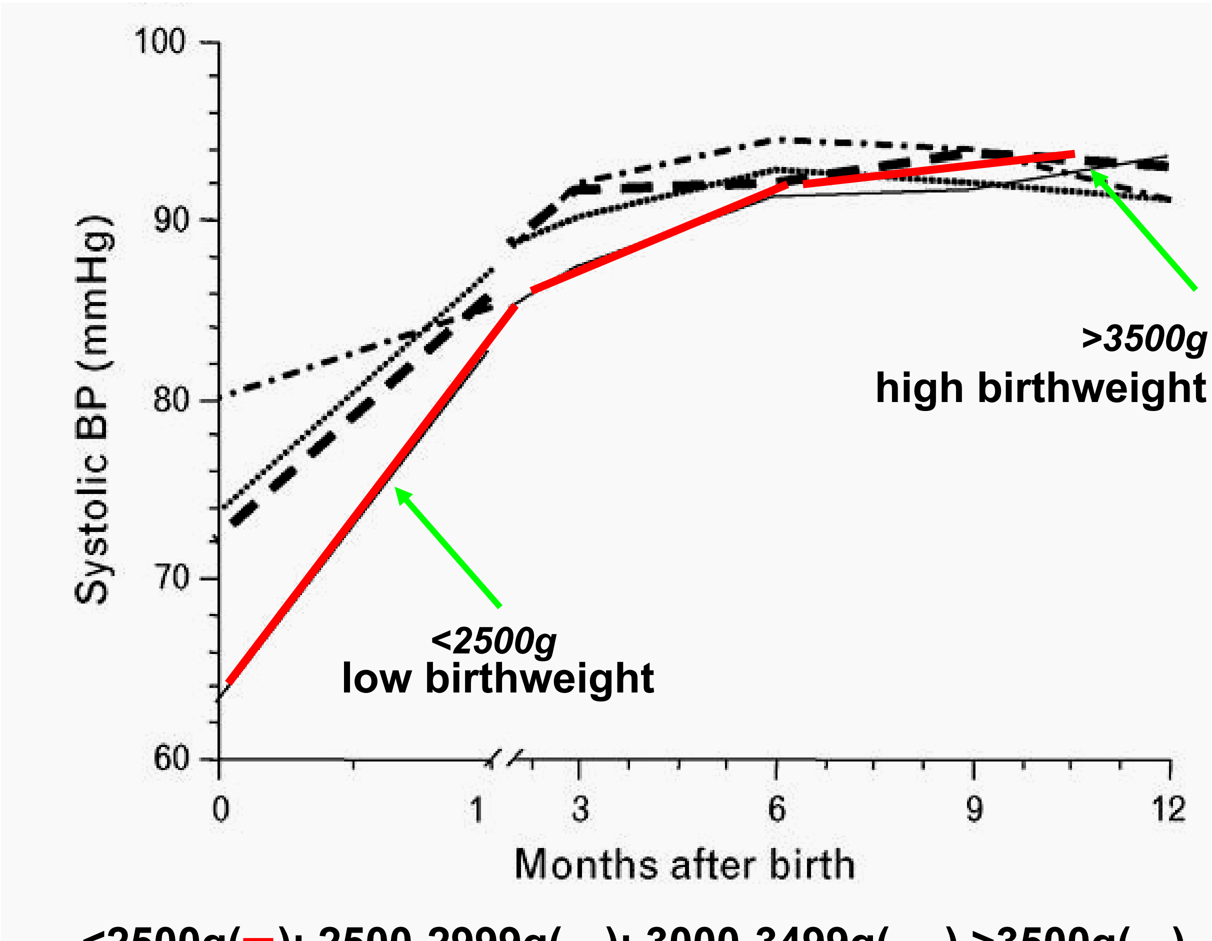
normotension



Keller, New Engl.J.Med.(2003)348:101

Low birthweight –

lower blood pressure at birth→
*more rapid increase during **1st year !***

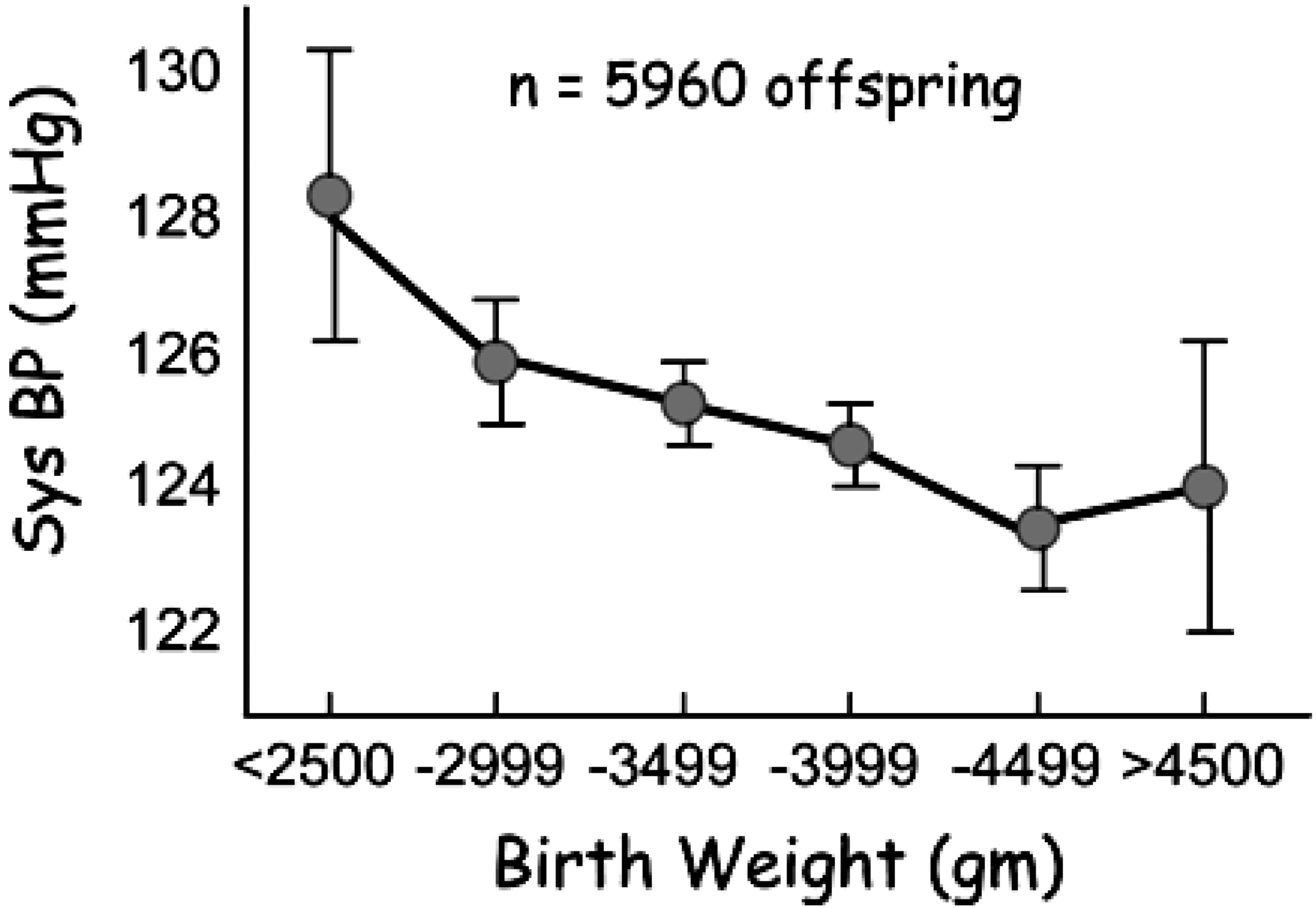


<2500g(▬); 2500-2999g(---); 3000-3499g(….) >3500g(-.-)

Lurbe,J.Hypertens.(2007) 25:81

Inverse correlation between birthweight and systolic blood pressure

(with and without adjustment for current weight)



Järvelin, Hypertension (2004) 44:838

Less and bigger nephrons in kidneys of low birthweight newborns

- 35 neonates
- coronal sections of renal cortex

	birth weight low	birth weight high
glomeruli per 0.6 mm^2	92.9 ± 4.85	106 ± 3.91
glomerular volume ($\mu^3 x10^{-3}$)	529 ± 188	158 ± 50

correlation between birthweight and :

glomerular numbers (r=0.87) and volume (r= - 0.821)

Mañalich, Kid.Intern (2000) 58:770

In vivo evaluation of kidney growth

- low birth weight → low kidney volume

Silver, Am.J.Obstetr.Gynecol.(2003) 188:1320

- smaller kidneys in fetuses with intrauterine growth retardation

Spencer, Am.J.Kidn.Dis. (2001) 37:915

- “sausage shaped” of fetal kidneys –

evidence of impaired cell/tissue migration

Konje, Ultrasound Obstet Gynecol. (1997) 10: 22

Low birth weight ⇨
higher adolescent blood pressure (2~3mmHg)

Rotterdam study :Uiterwaal, Hypertension (1997) 30:267
ALSPAC study :Fattal-Valevski ,Isr.Med.Ass. (2001) 153:779
Israel study :Whincup, Am.J.Epidemiol (1999) 149:730

Higher catch up growth ⇨ adult fatness
⇨ obesity related blood pressure

Horta, J.Epidemiol.Community Health (2003) 57: 226
Huxley, J.Hypertens. (2000) 18:815

Birth weight is inversely correlated with adult systolic blood pressure and pulse pressure in type 1 diabetes

Finnish diabetic nephropathy study
1225 patients born at term,
birth weight records

age-and sex adjusted regression coefficients for systolic BP
in males : - 1.90 mmHg/kg (-3.71 to -0.09)
in females : - 3.34 mmHg/kg (-6.06to-0.62)

Fagerudd, Hypertension (2004) 44:832

No gross excess hypertension in live kidney donors

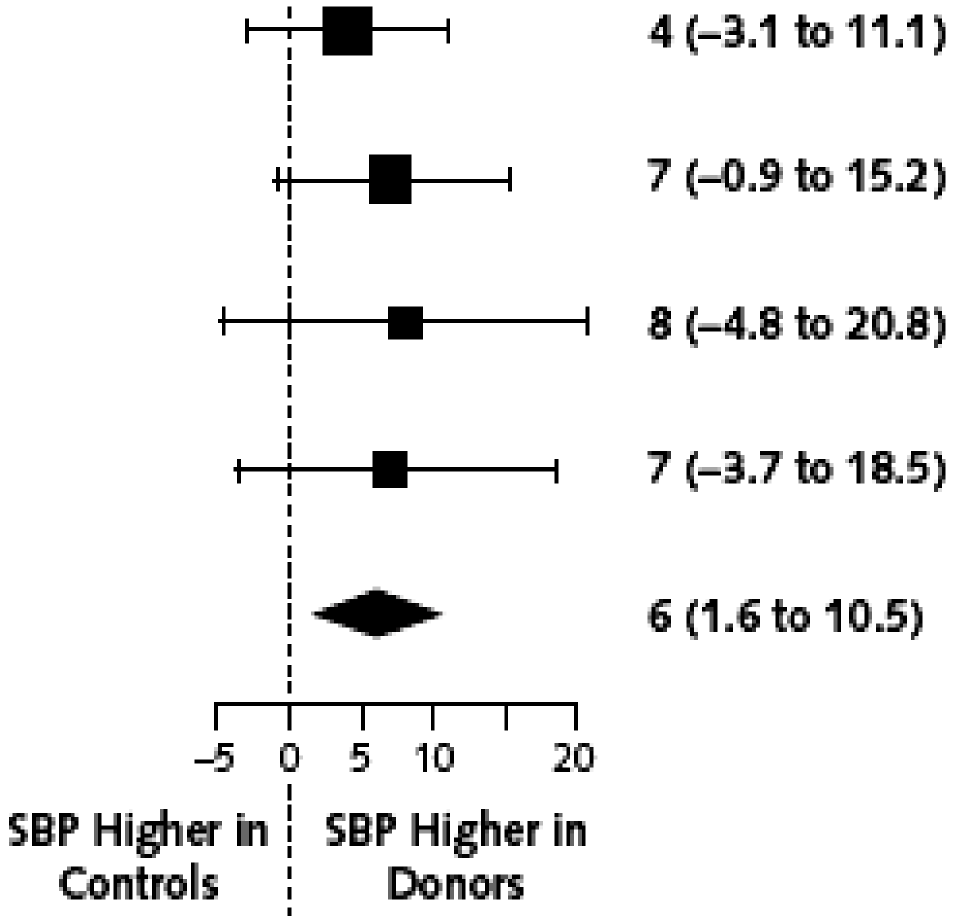
- *402 alive kidney donors 1964-1995*
- *proteinuria 12 %*
- *hypertension 38% -*

  → *not exceeding rate in matched background population*

Fehrman-Ekholm, Transplantation(2001) 72:444

Metaanalysis –

only slightly higher risk of hypertension in living kidney donors



Boudville, Ann.Intern.Med.(2006) 145:185

less glomeruli, but glomeruli bigger

calculated index of filtration surface was normal

▶ Hypothesis

- *high blood pressure not result of low glomerular number per se*

  (less, but bigger glomeruli → normal filtration surface)

- *but result of developmental changes in postglomerular segments*

  (→ higher sodium reabsorption)

Main mechanisms contributing to hypertension from prenatal programming

- *upregulation of sodium channels*
- *upregulation of RAS (AT1-R)*
- *cortisol (11βHSD2↓) → mineralocortocoid receptor*
- *sympathetic overactivity*

Outcome after unilateral renal agenesis (pre/perinatal)

- 157 patients with unilateral agenesis and normal contralateral kidney
- mean age 37 years

 # proteinuria 150 mg/day 19%

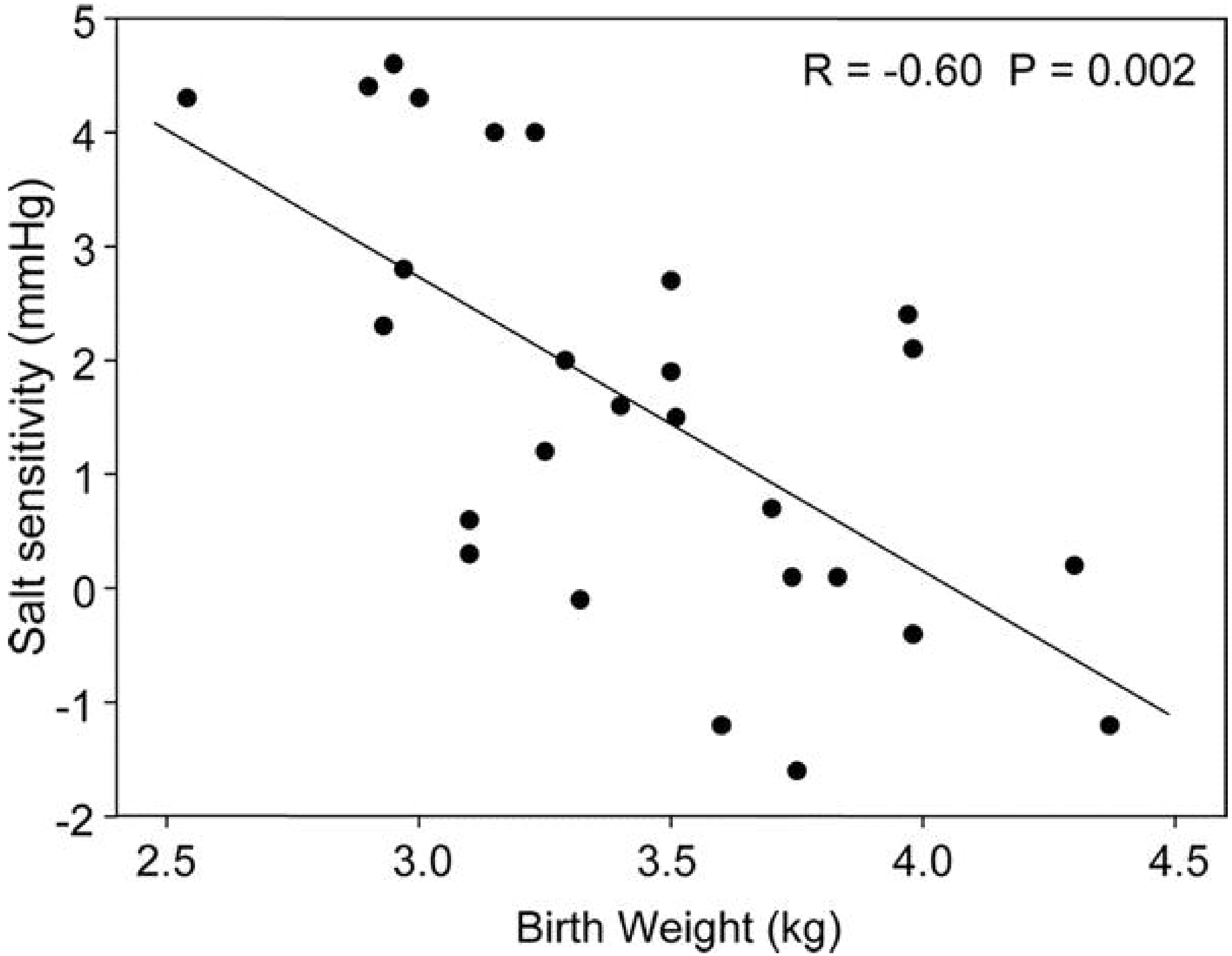
 # high blood pressure 47%

 # reduced renal function 13%

 # 6 deaths from renal failure

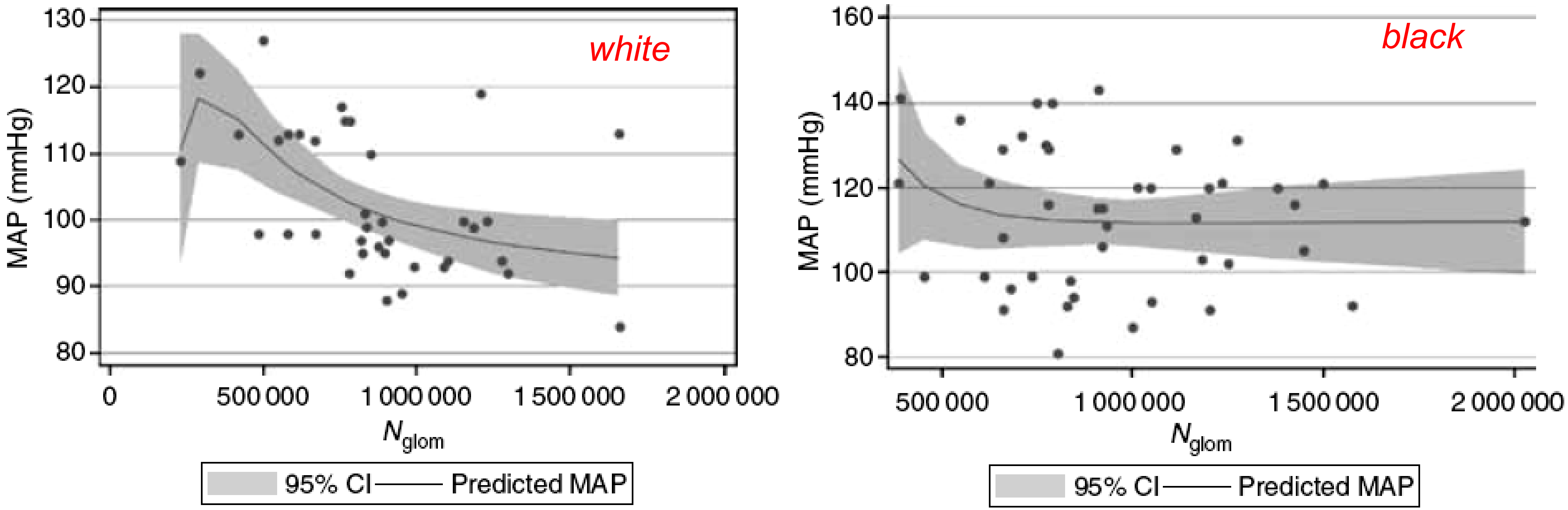
Argueso, Ped.Nephrology (1992) 6:412

Low birth weight – salt sensitivity of blood pressure in healthy adults



de Boer, Hypertension (2008) 51: 928

Hypertension and low number of glomeruli – in whites, but not in blacks



Hughson, Kidn.Intern.(2006) 69:671

Causes of reduced glomerular numbers in animal experiments–

maternal pathology →impaired nephrogenesis of offspring

- **low protein intake**

  Woods, Pediatr.Res.(2001) 49:460

- **uterine underperfusion**

  Wlodek, Kidn.Intern.(2008) 74:187

- **maternal hyperglycemia**

  Amri.Diabetes (2001) 50:1069

- **maternal hyperinsulinemia**

  Bursztyn, Hypertension (2006) 48:717

- **high and low maternal salt intake**

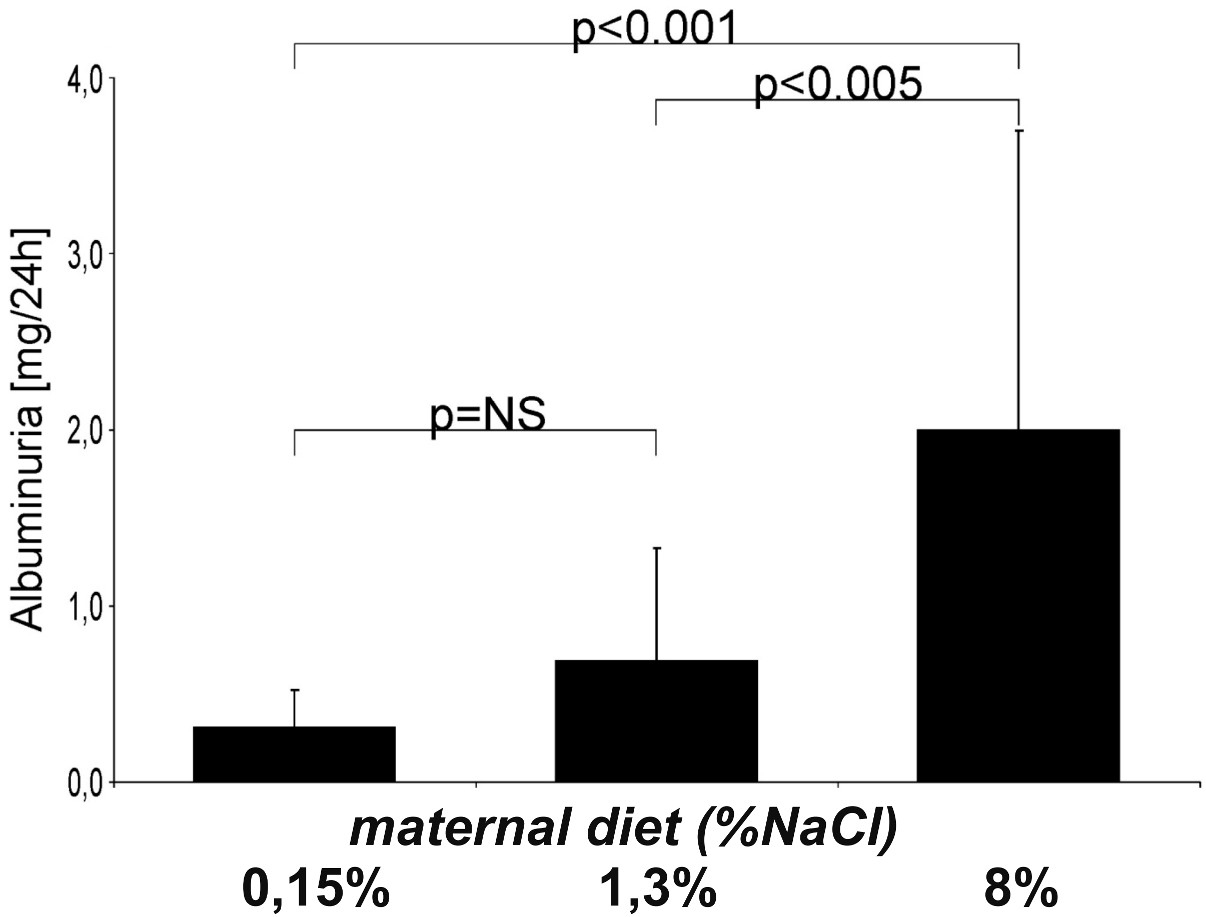
  Balbi, Pediatr.Nephrol (2004) 19:1212

- **corticosteroids**

  Woods, Am.J.Physiol. (2005) 289:R955

one example :

High salt diet in pregnant rats
→ high albuminuria in offspring



Kollagenova, Piecha, Ritz, Gross

High salt diet in pregnant rats

→*lower number and greater volume of glomeruli in offspring*

NaCl content of maternal diet (%)

		0.15%	1.3%	8%	
Glomeruli	**number**	**17,159** ±2,632	**22,760** ±8,8270	**14,310** ±2,573	⬇
	volume ($\mu^3 x 10^6$)	**2.59** ±0.43	**4.10** ±1.62	**4.83**↑ ±1.19	⬆
kidney	**weight (g)**	**2.34** ±0.22	**2.33** ±0.24	**2.66**↑ ±0.45	⬆

Piecha, Koleganova, Ritz, Gross

High salt diet in pregnant rats (8%)

→ *despite low salt diet for offspring after weaning and independent of blood pressure in offspring by telemetry*

Cardiovascular abnormalities in offspring

increased wall thickness :

aorta	**central arteries**
carotis	**central arteries**
mesenteric	**muscular arteries**
intrapulmonary	**muscular arteries**

- *eNOS ↓*
- *ADMA↑*
- *oxydative stress (8-isoprostane↑)*
- *endothelial cell proliferation↑)*

….

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“There is no hypervolemia in essential hypertension,
so there is no rationale to study tubular sodium transport“

Lifton
NIH grant application,
1978

Monogenic (Mendelian) forms of human hypertension → increased renal sodium reabsorption → salt-sensitivity

- *Glucocorticoid remediable aldosteronism -*
  excess production of aldosterone under ACTH control

- *Apparent mineralocorticoid excess*
  (11 β-hydroxysteroid dehydrogenase-2 deficiency)

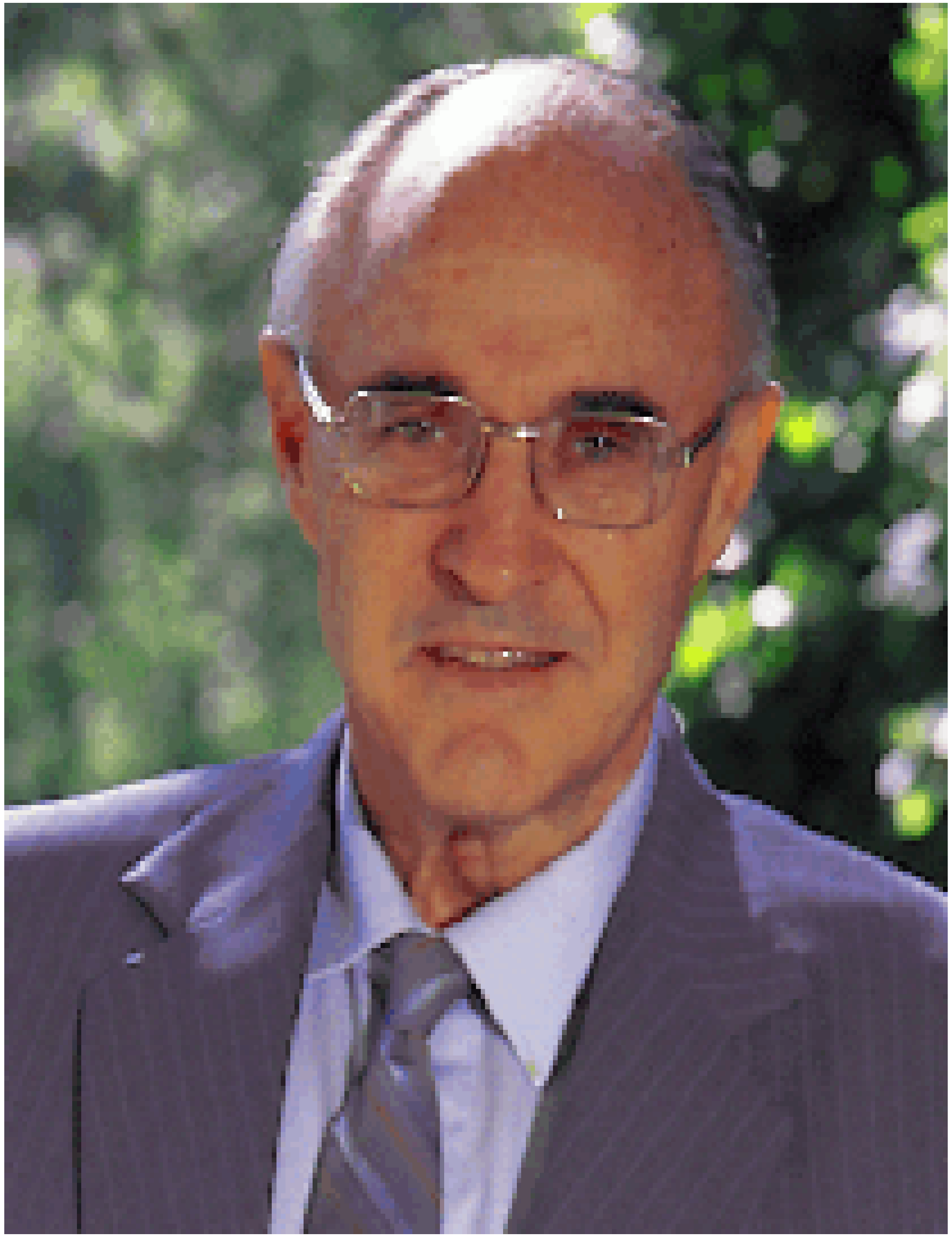
- *Gain of function mutations of mineralocorticoid receptors*

- *Excess ENaC activity (e.g. Liddle's syndrome)*

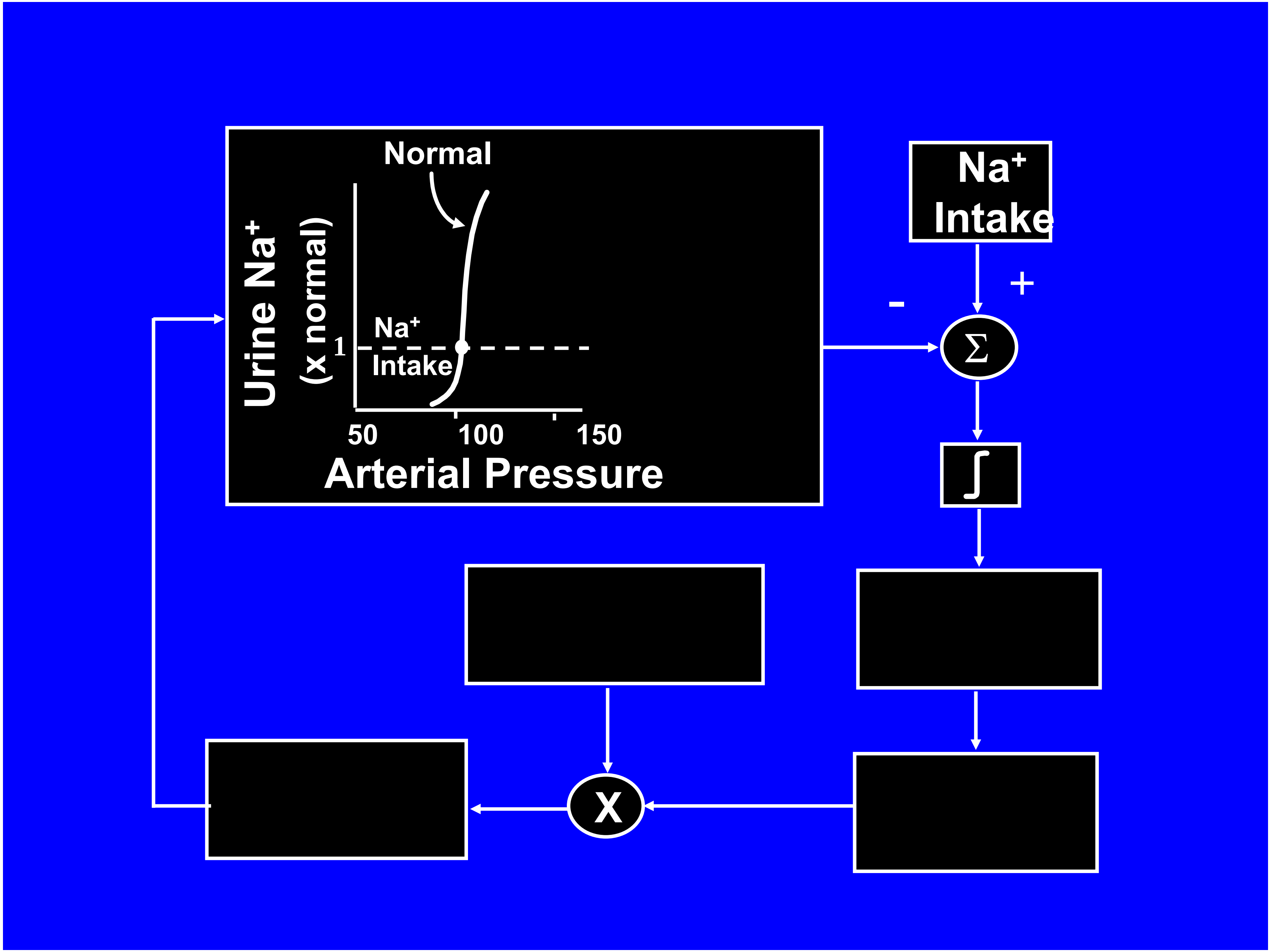
The kidney is involved in the genesis of any type of hypertension

All forms of hypertension are ultimately the consequence of resetting of the

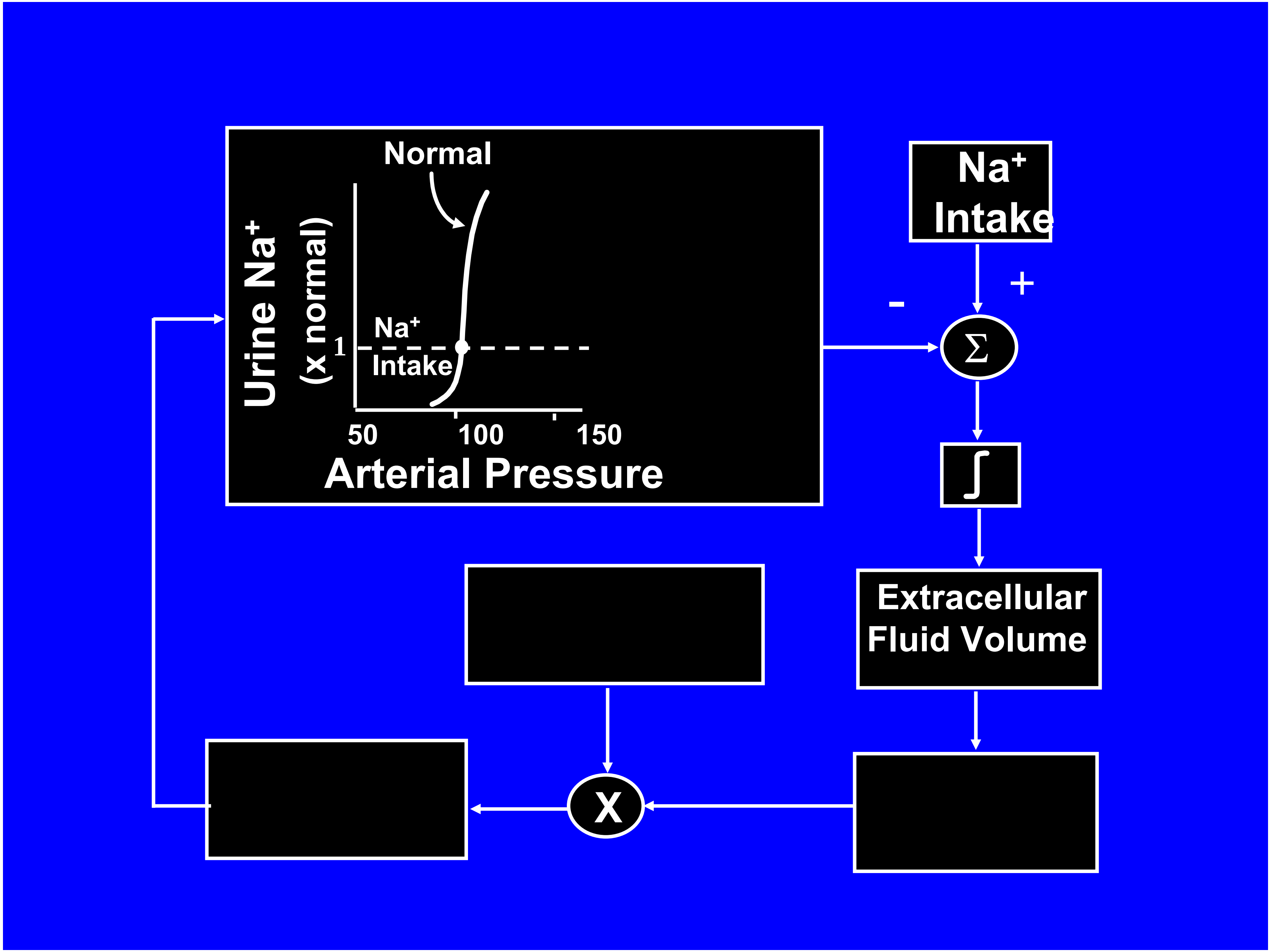
pressure natriuresis relationship

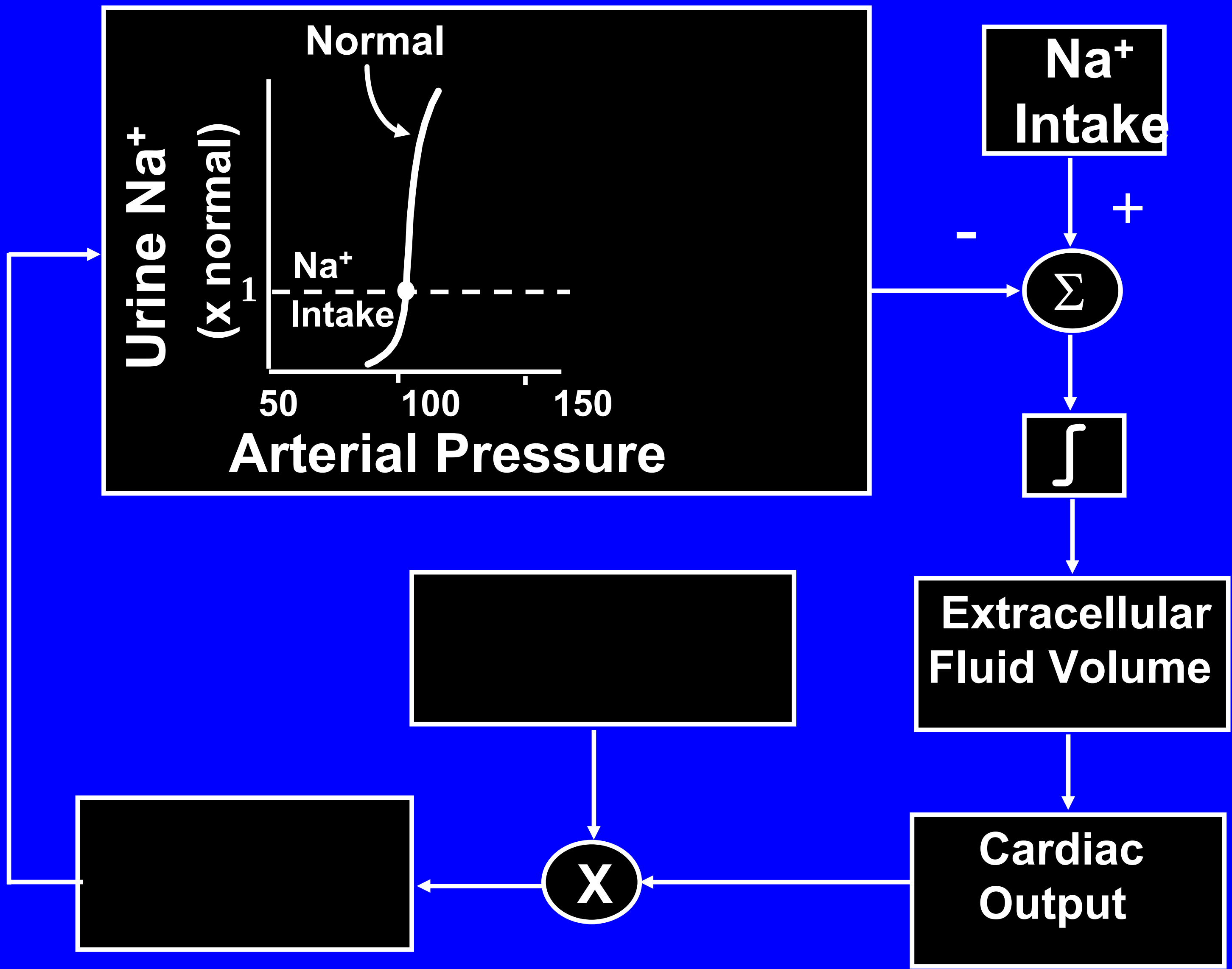


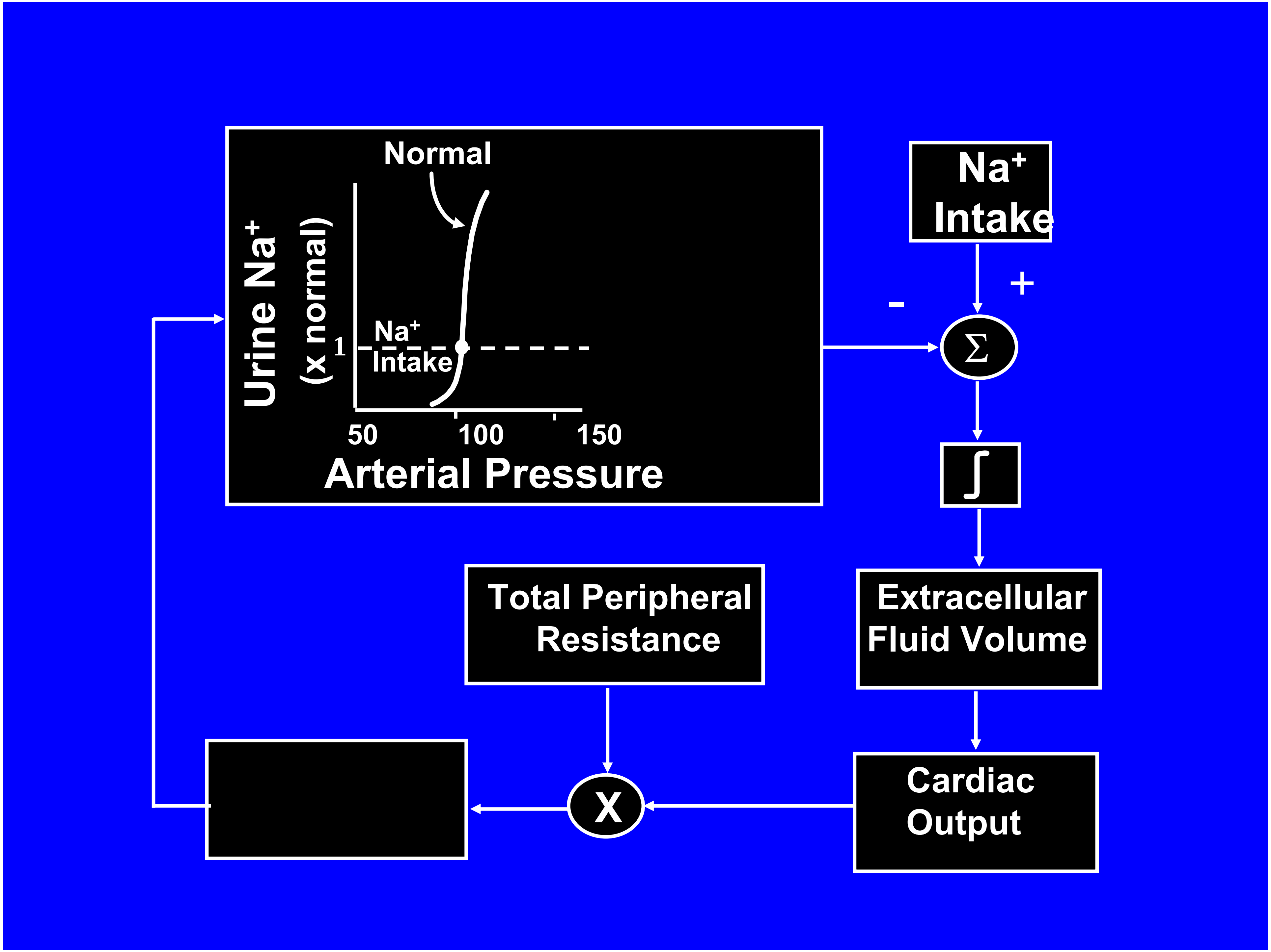
Arthur C. Guyton
1919 - 2003

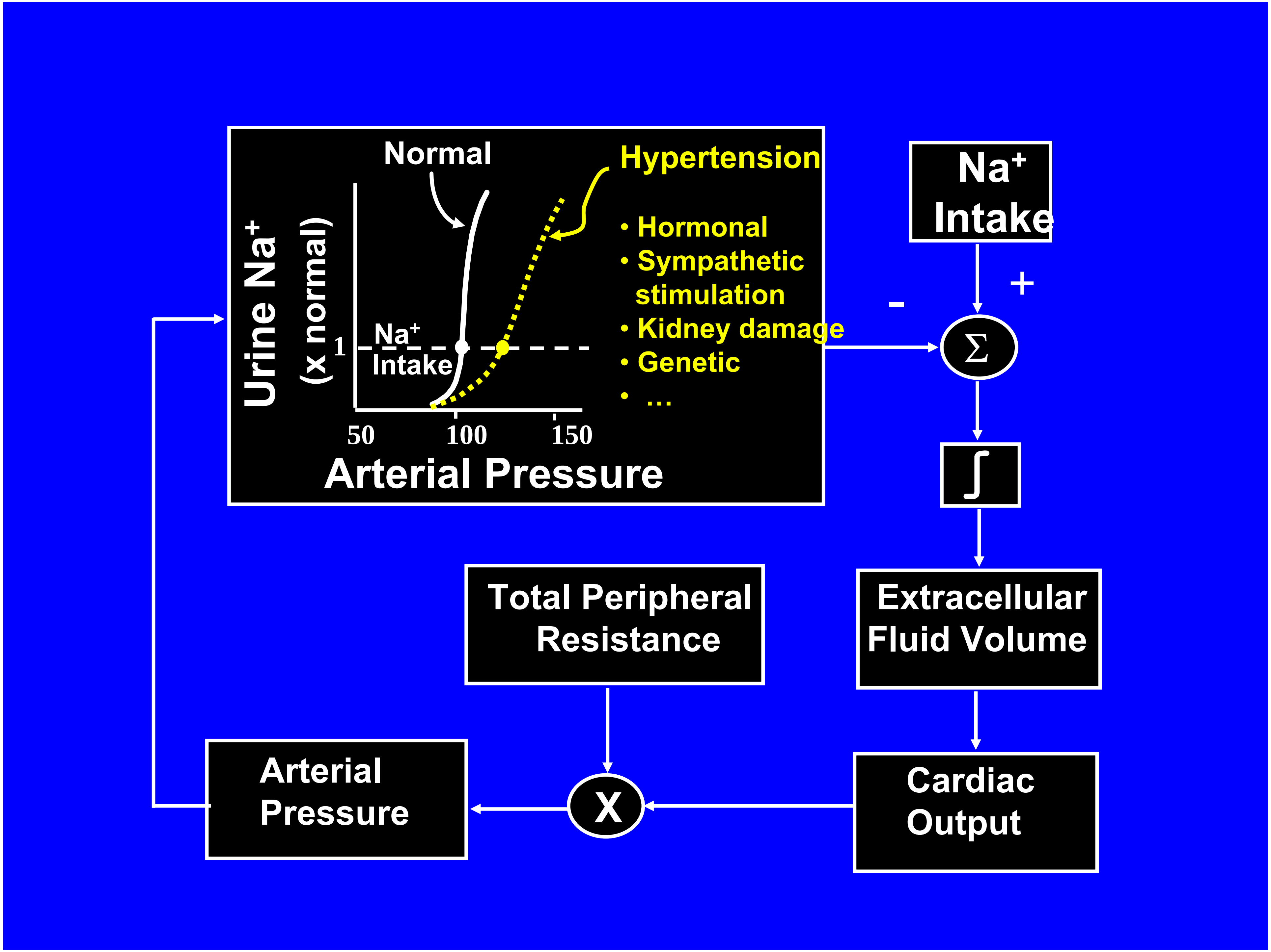


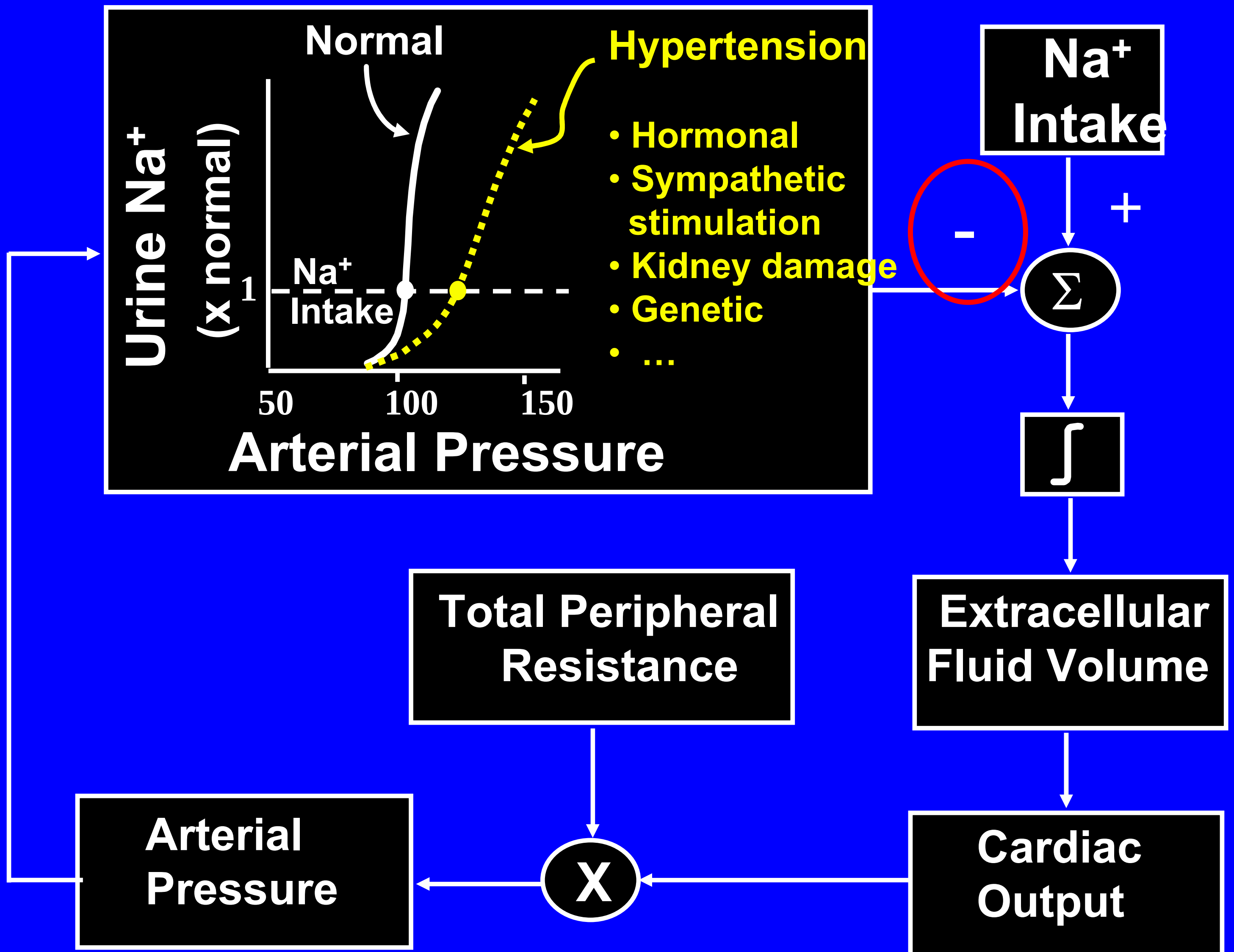
Normal
Urine Na+
(x normal)
Na+
1
Intake
50
100
150
Arterial Pressure
Na+
Intake
+
-
Σ
∫
X


Normal
Urine Na+
(x normal)
Na+
1
Intake
50
100
150
Arterial Pressure
Na+
Intake
+
-
Σ
∫
Extracellular
Fluid Volume
X

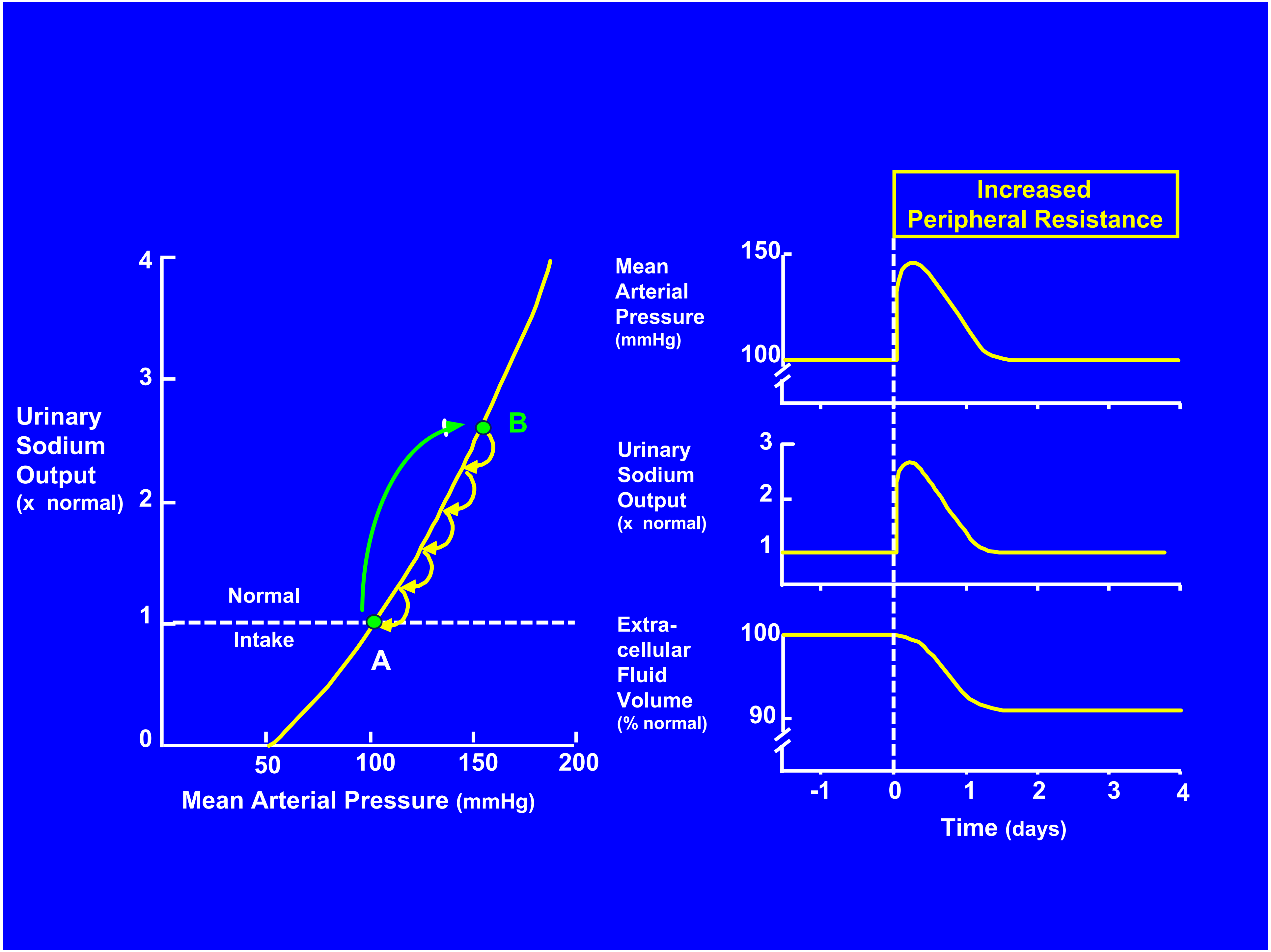

Normal
Urine Na+
(x normal)
1
Na+
Intake
50
100
150
Arterial Pressure
Na+
Intake
-
+
Σ
∫
Extracellular
Fluid Volume
Cardiac
Output
X


Normal
Urine Na+
(x normal)
1
Na+
Intake
50
100
150
Arterial Pressure
Na+
Intake
-
+
Σ
∫
Total Peripheral Resistance
Extracellular Fluid Volume
X
Cardiac Output


Normal
Hypertension
Urine Na+ (x normal)
1
Na+ Intake
50
100
150
Arterial Pressure
• Hormonal
• Sympathetic stimulation
• Kidney damage
• Genetic
• …
Na+ Intake
-
+
Σ
∫
Extracellular Fluid Volume
Total Peripheral Resistance
Cardiac Output
X
Arterial Pressure



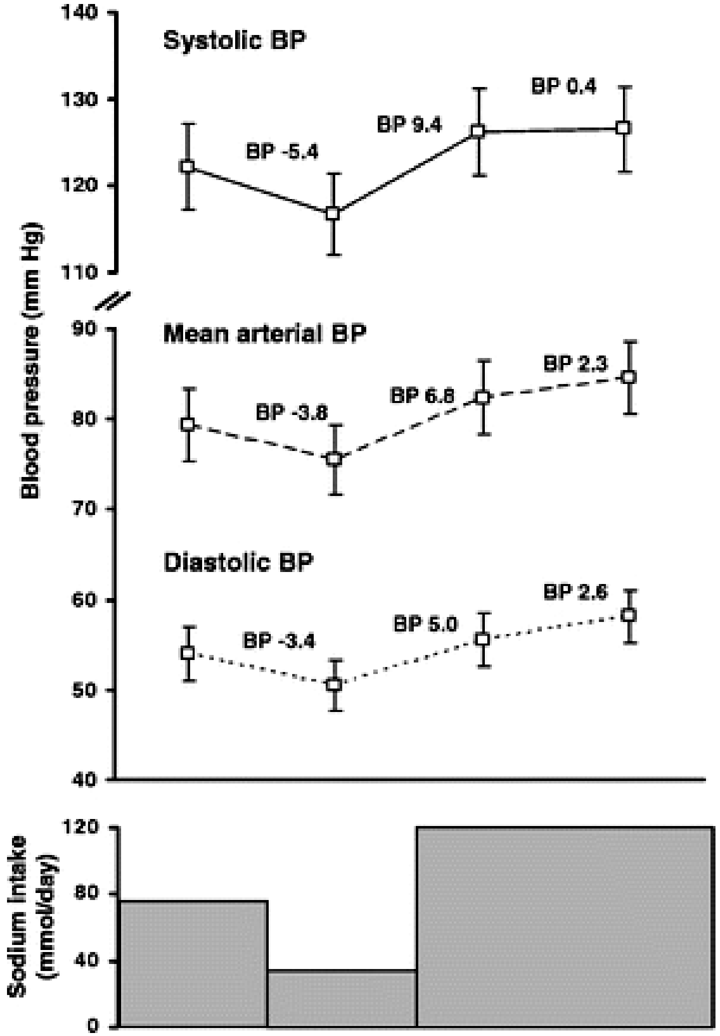
Normal
Hypertension
Urine Na^+ (x normal)
1
Na^+ Intake
50
100
150
Arterial Pressure
• Hormonal
• Sympathetic stimulation
• Kidney damage
• Genetic
• …
Na^+ Intake
-
+
Σ
∫
Extracellular Fluid Volume
Total Peripheral Resistance
Cardiac Output
X
Arterial Pressure


Increased
Peripheral Resistance
Urinary
Sodium
Output
(x normal)
4
3
2
1
0
50
100
150
200
Mean Arterial Pressure (mmHg)
Normal
Intake
A
B
Mean
Arterial
Pressure
(mmHg)
150
100
Urinary
Sodium
Output
(x normal)
3
2
1
Extra-
cellular
Fluid
Volume
(% normal)
100
90
-1
0
1
2
3
4
Time (days)

Variation of blood pressure in Chimpanzees with changes in salt intake corresponding to human intakes

blood presure reaction

sodium intake



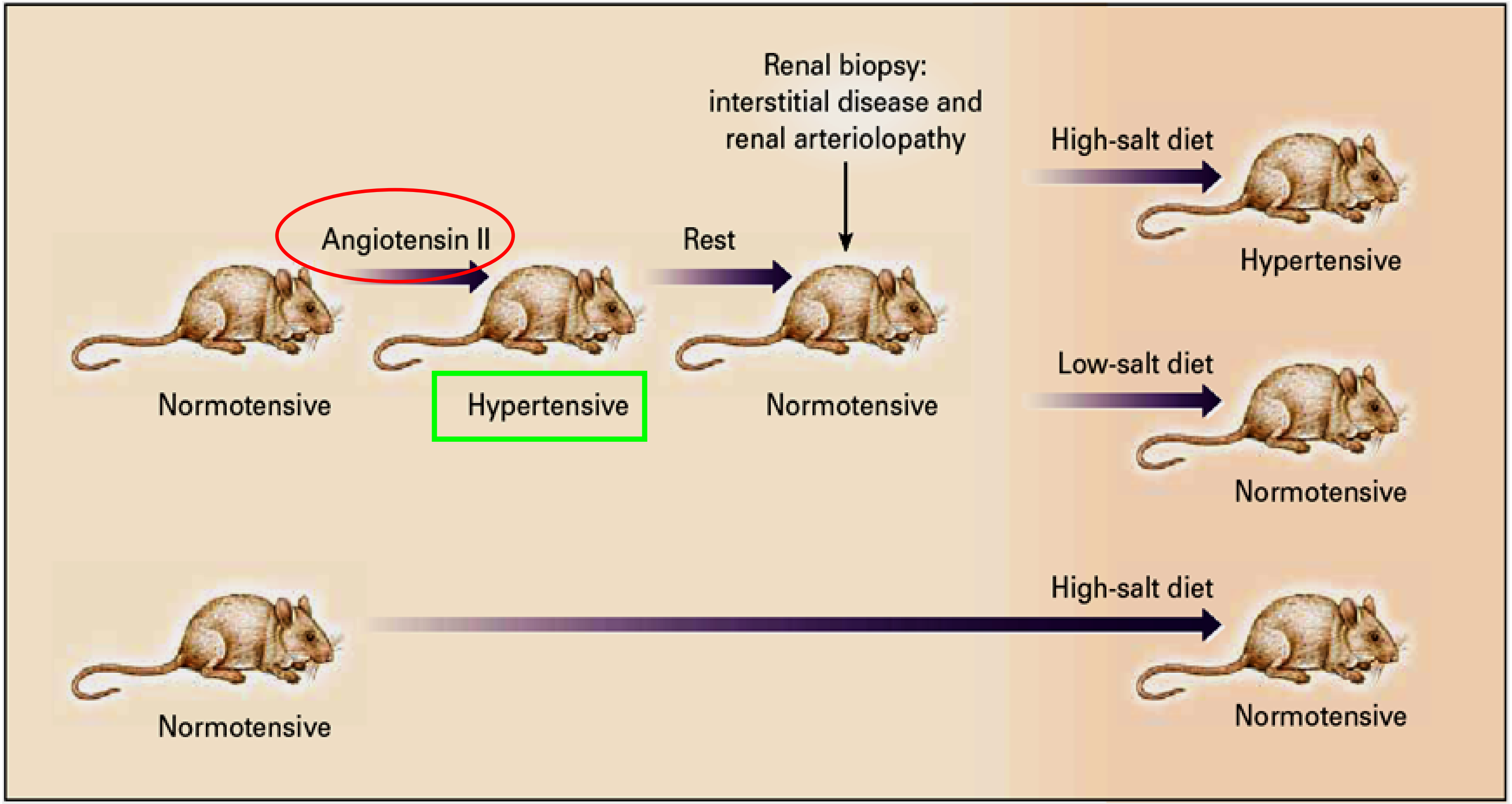
Elliott, Circulation (2007) 116:1563

Causes of salt-sensitive blood pressure

- ***low birth weight** (nephron underdosing)*
- ***primary glomerular diseases***
- ***aging***
- ***obesity***
- ***diabetes mellitus***

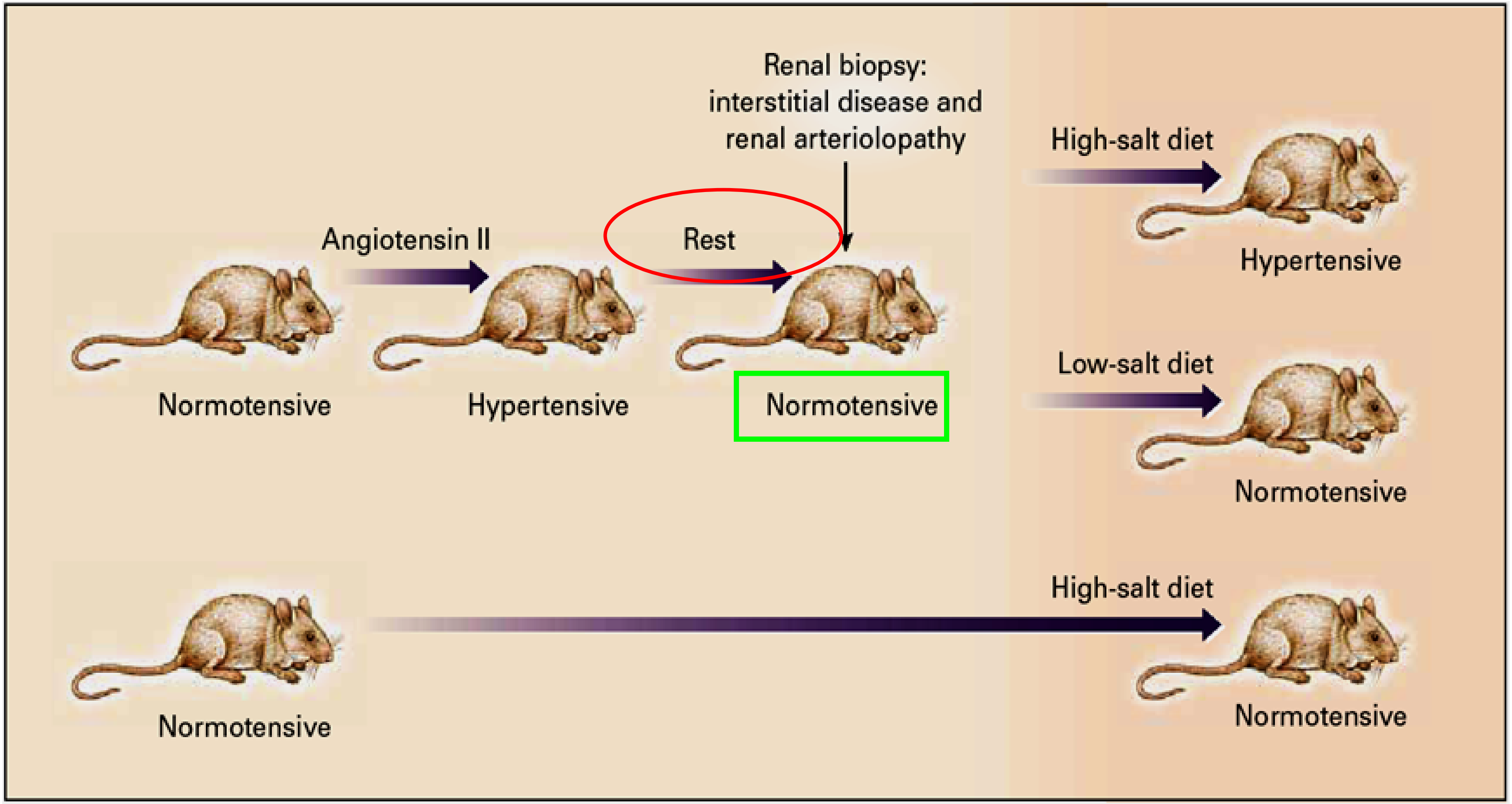
- ***consequence of hypertension***

Development of salt-sensitive hypertension in rats after exposure to angiotensin II



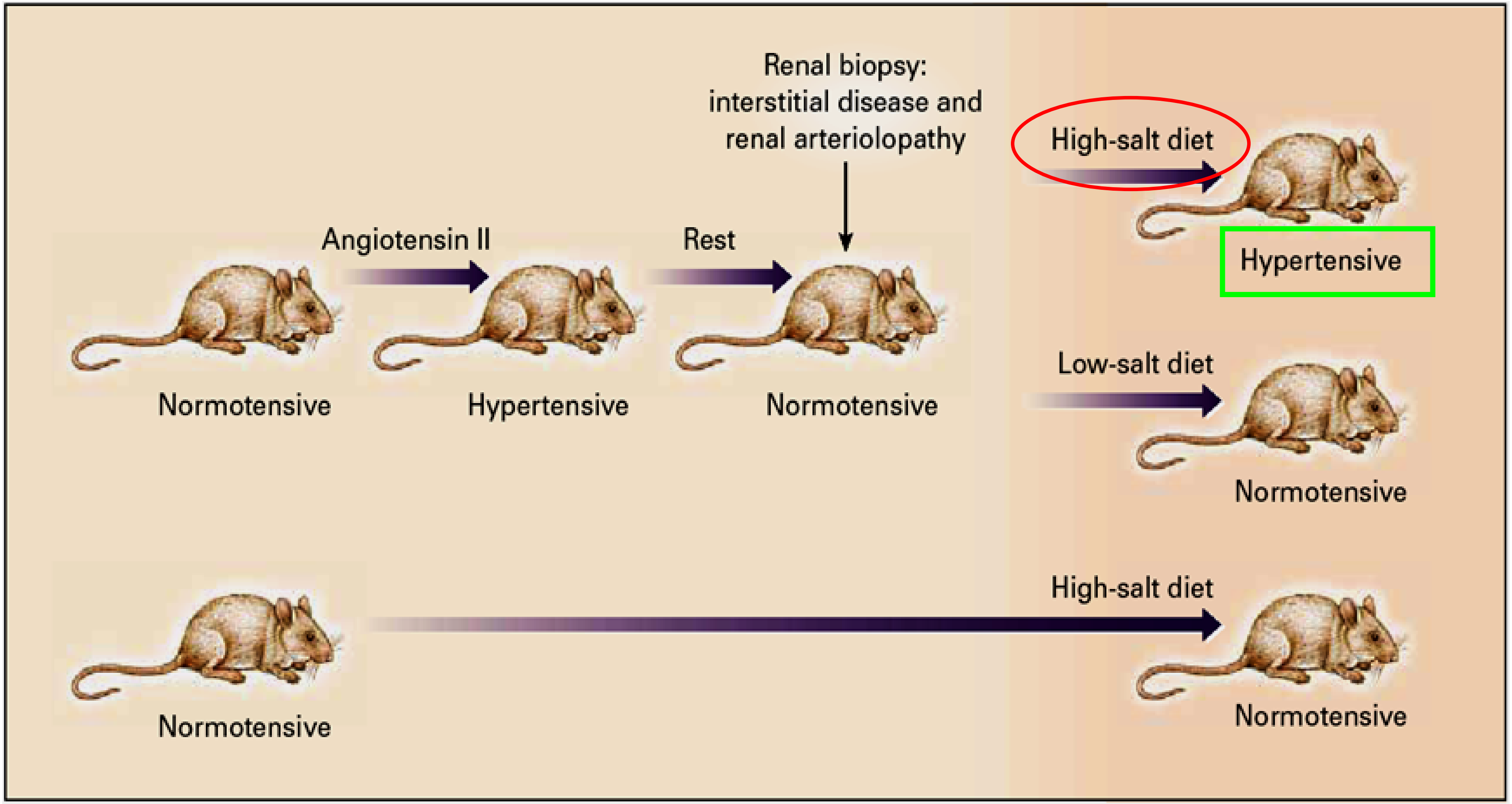
Johnson, New Engl.J.Med.(2002) 346:913

Development of salt-sensitive hypertension in rats after exposure to angiotensin II



Johnson, New Engl.J.Med.(2002) 346:913

Development of salt-sensitive hypertension in rats after exposure to angiotensin II



Johnson, New Engl.J.Med.(2002) 346:913

Sea water comparison –
salt content in 1 g food vs 1 ml Atlantic water

Smoked fish	**190%**
Sweet pickle	**170%**
Processed cheese	**130%**
Tomato Ketchup	**110%**
Cornflakes	**100%**
Lasagne	**40%**
....	

➪ *Pastrami, chicken soup, pickles ...*
excellent if you happen to have Addison's disease
bad if you have hypertension or renal disease

Sources of salt in food

• table salt	10%	under direct control of patient
• salt added during cooking	5%	
• salt contained in commercial food items	85%	

Sanchez-Castillo, Clin.Sci.(London) (1987) 72:95

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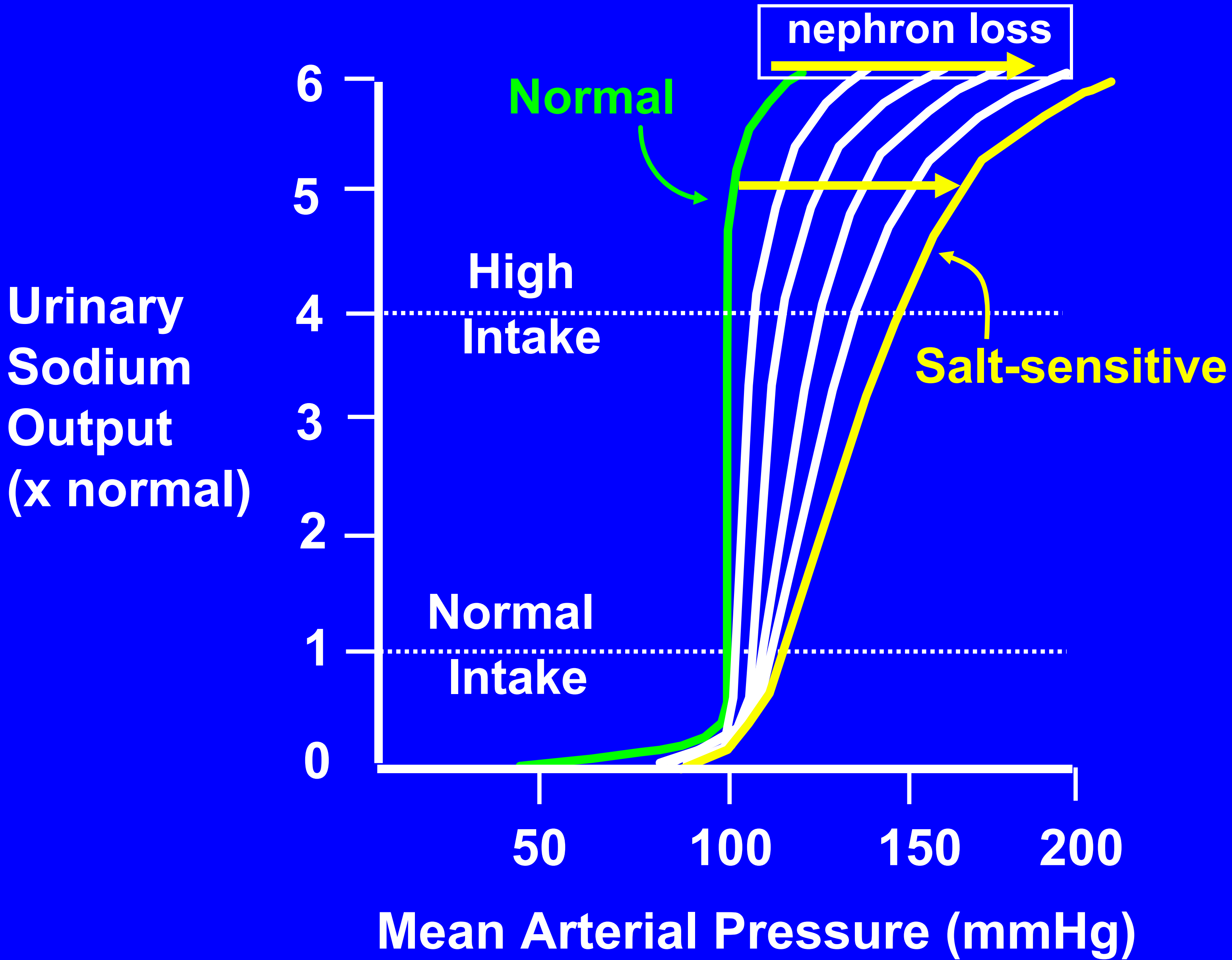
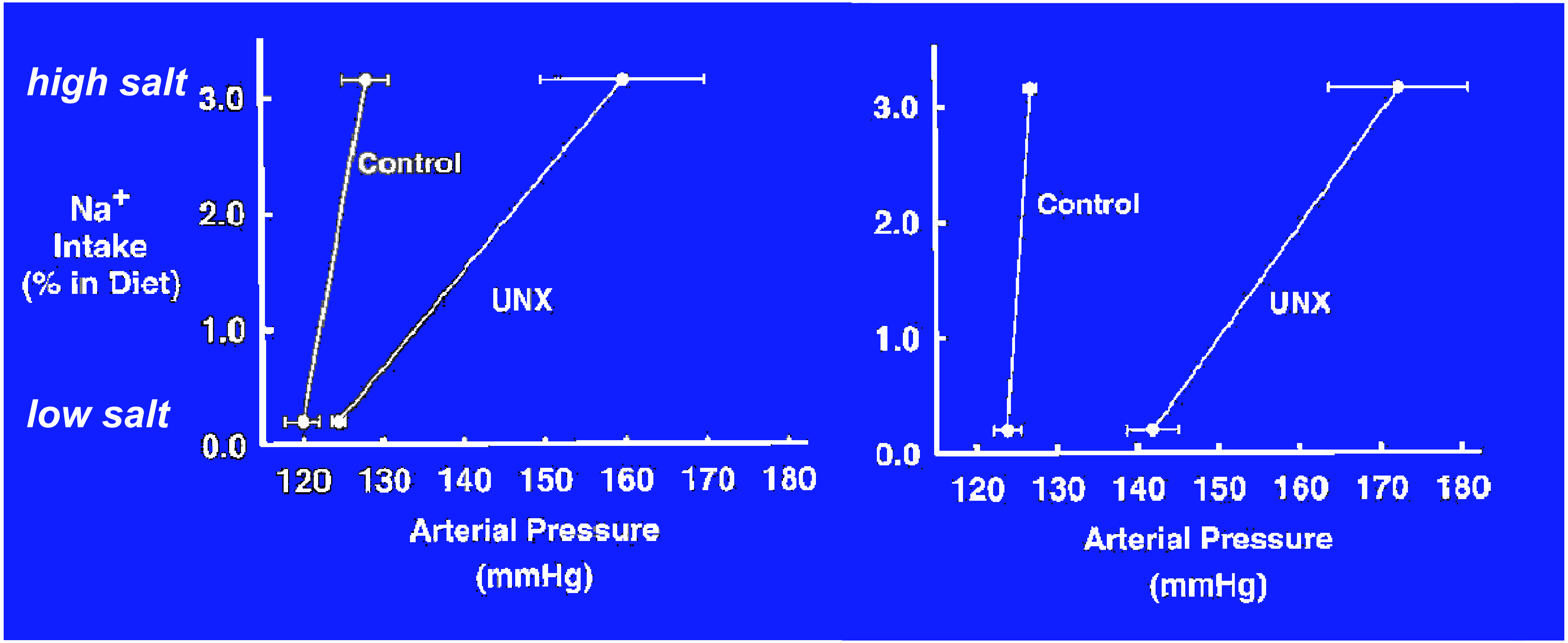
Decreased nephron number shifts pressure natriuresis relationship to the right



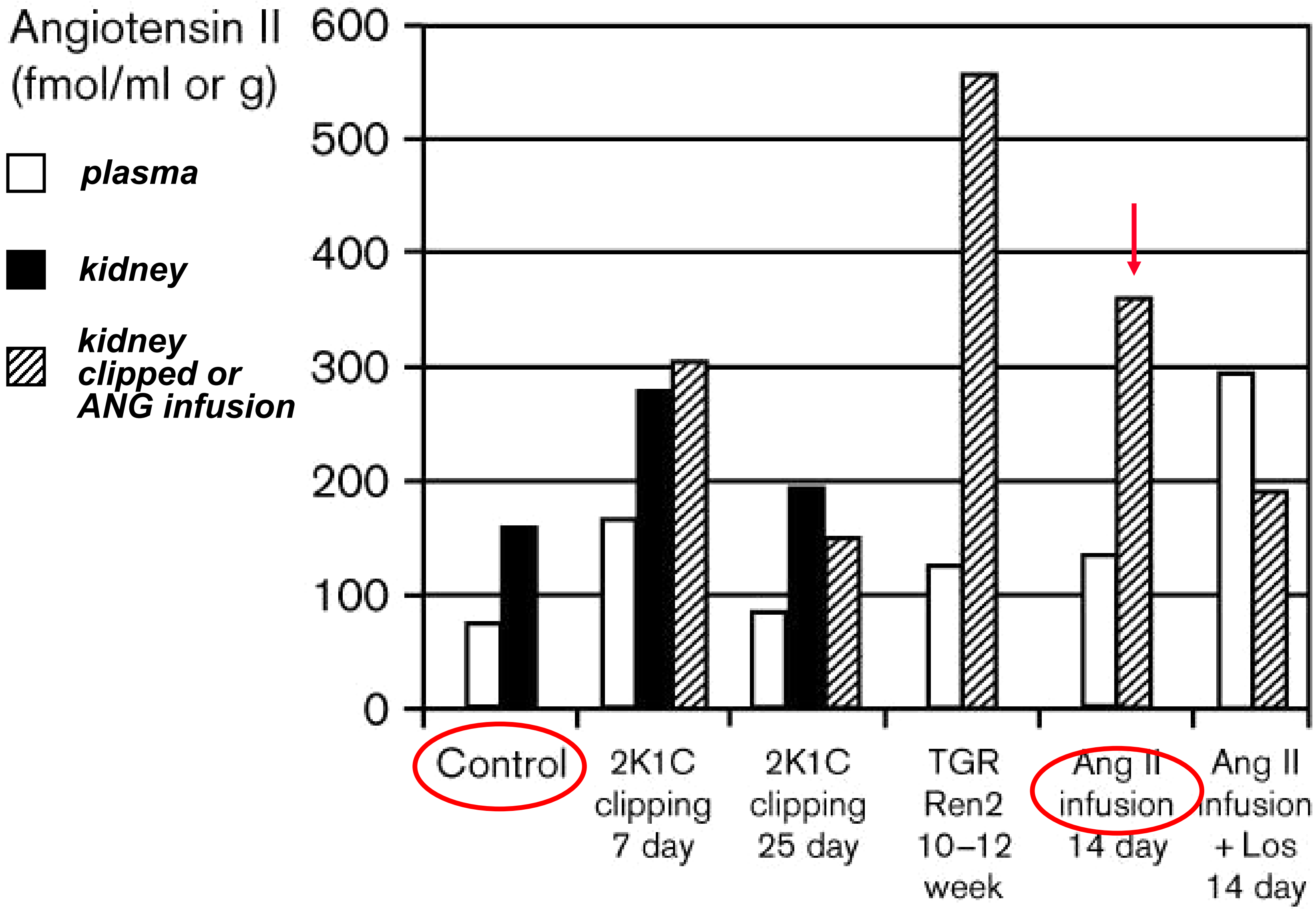
BP response to Na^+ loading after neonatal uninephrectomy



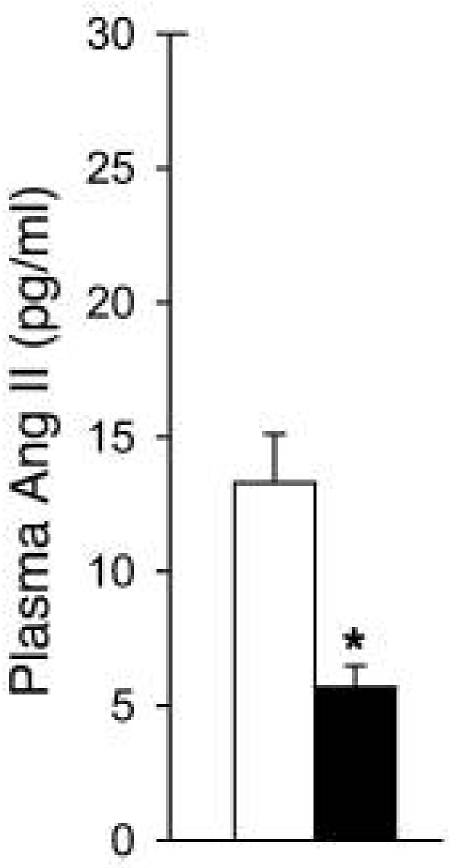
8 weeks *20 weeks*

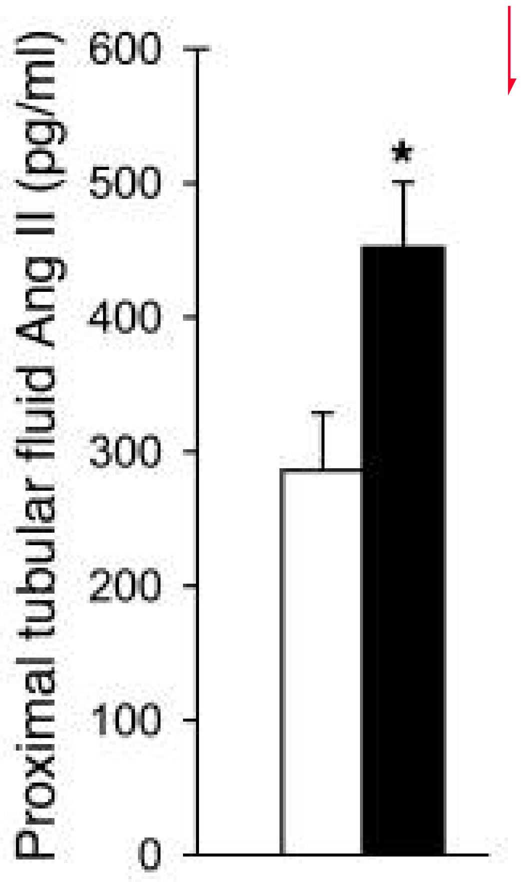
Woods, Hypertension (2001) 38: 337

Discrepancy between plasma ANG II and renal interstitial ANG II



Paradoxical increase of tubular fluid ANGII on high salt



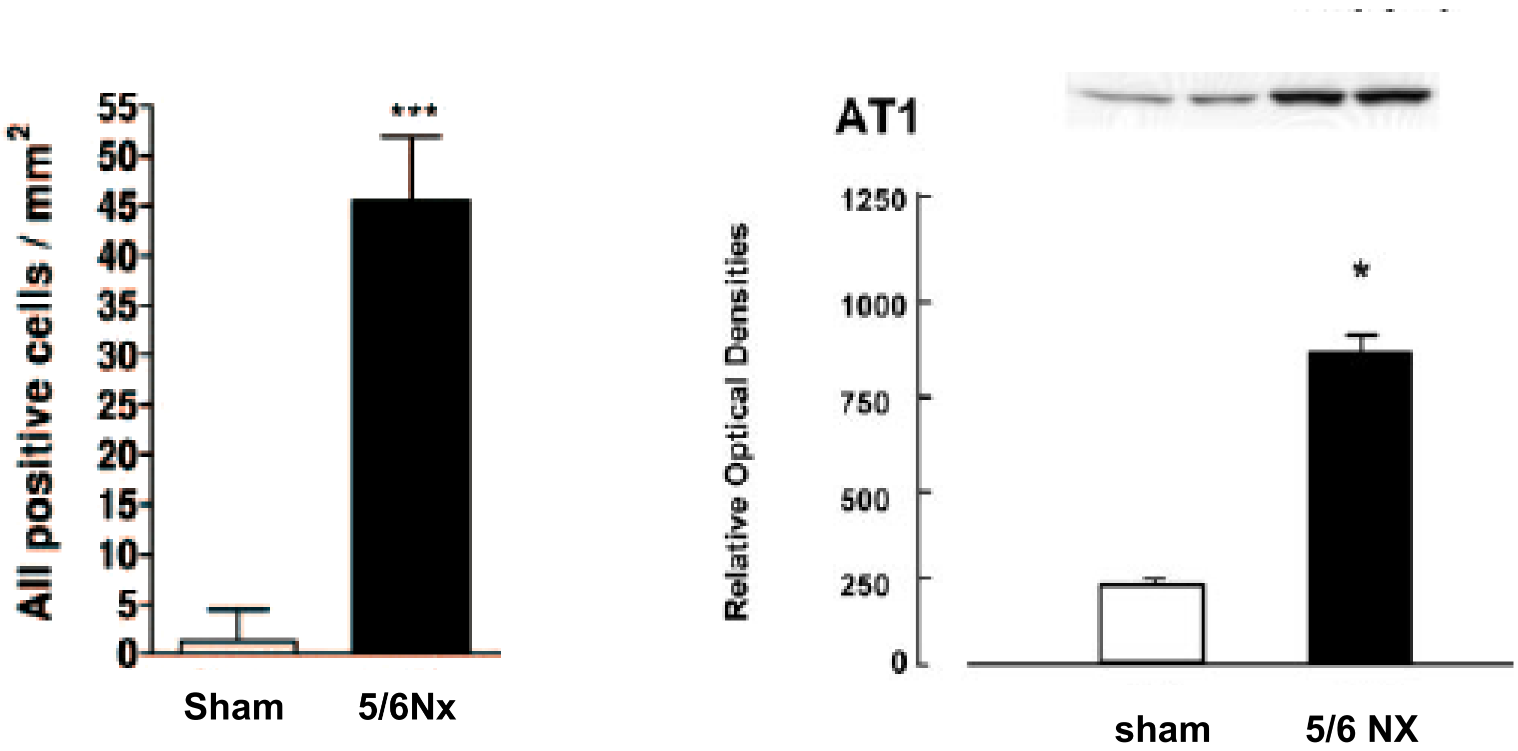


□ *low salt*

■ *high salt*

Thomson, J Clin Invest (2006) 116:1110

ANG II positive cells and upregulation of AT1 receptor in kidney after subtotal nephrectomy – *local intrarenal RAS*

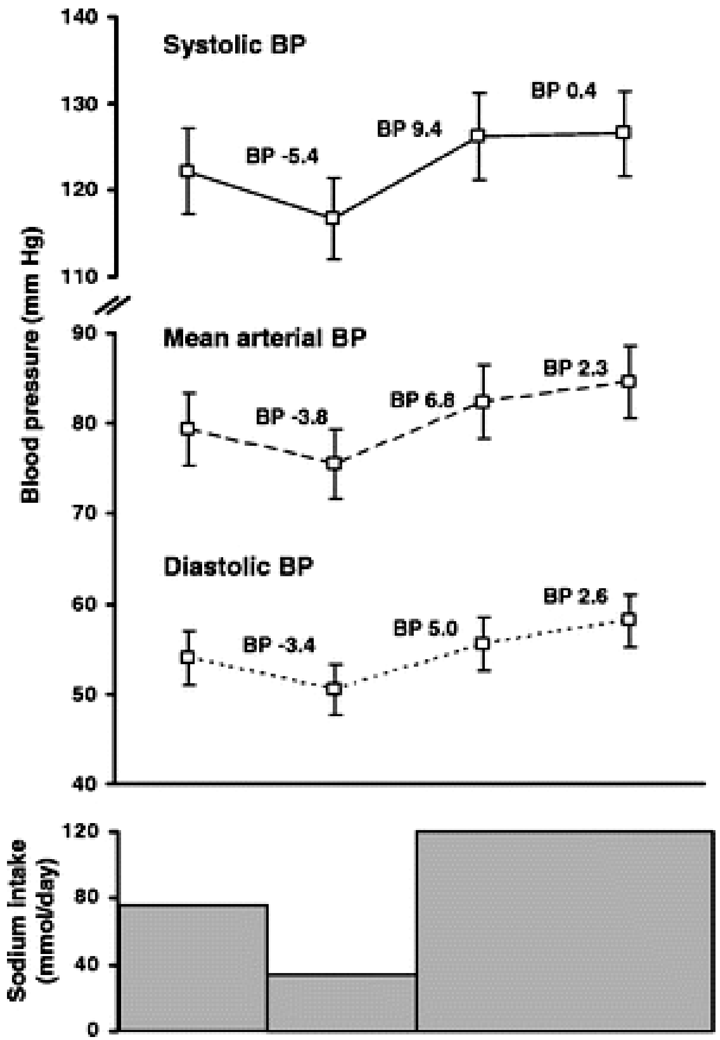


Vaziri, J.Pharmacol.Exp.Ther.(2007) 323:85

Variation of blood pressure in Chimpanzees with changes in salt intake corresponding to human intakes

blood presure reaction

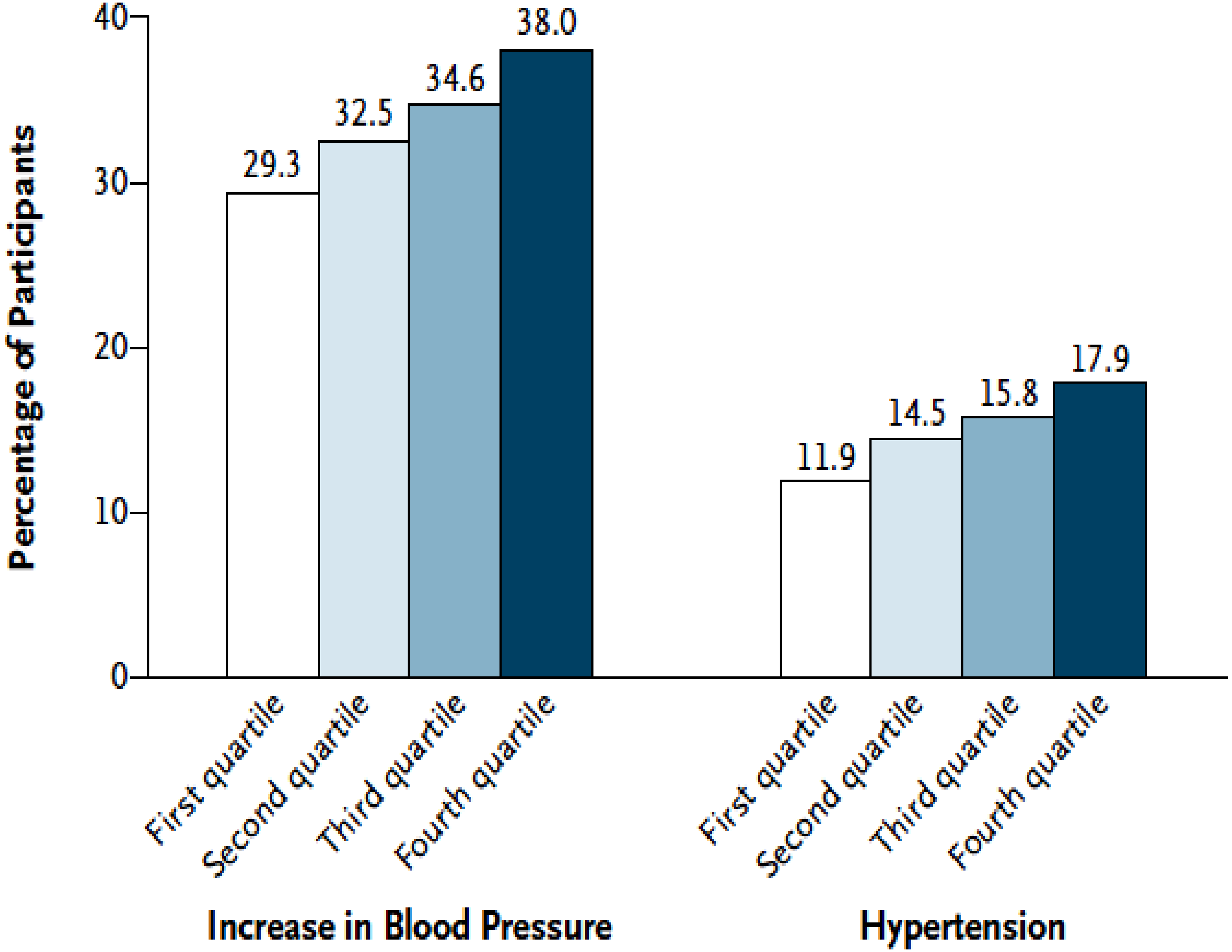
sodium intake



Elliott, Circulation (2007) 116:1563

Blood pressure and prevalence of hypertension increase stepwise with S-aldosterone concentration

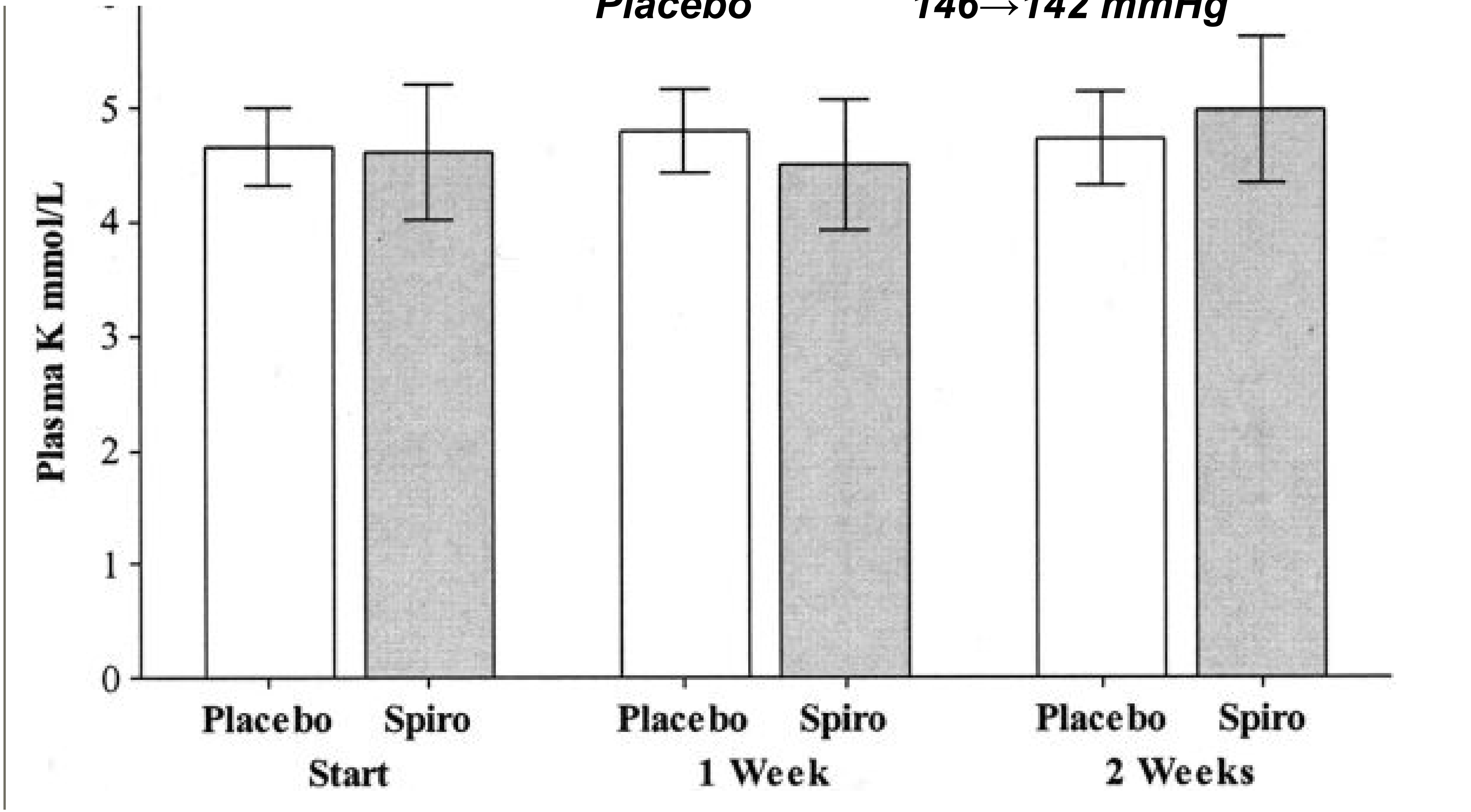
Framingham study



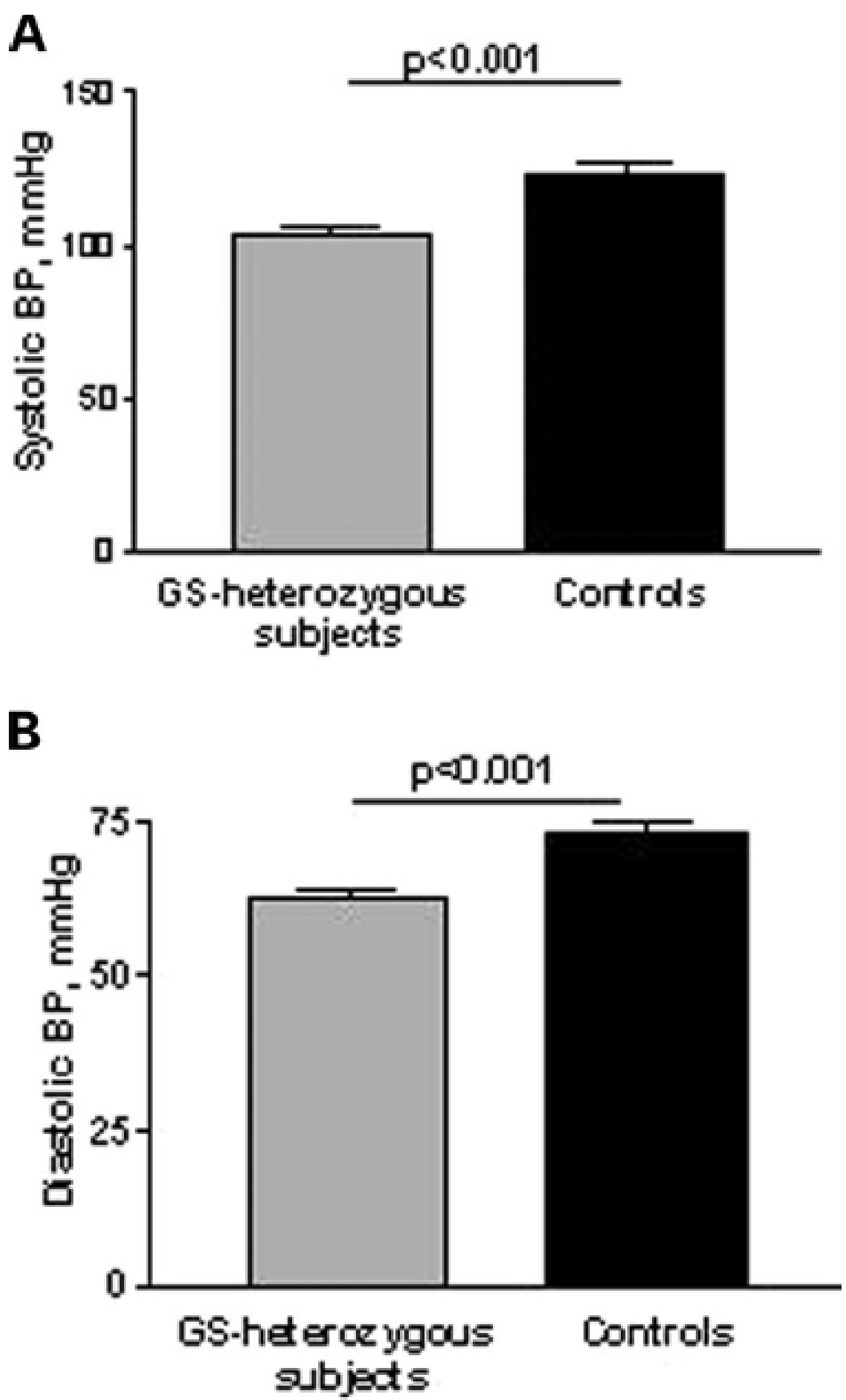
Vasan, New Engl.J.Med.(2004) 350:655

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

Blood pressure : Spironolactone 142→131 mmHg
Placebo 146→142 mmHg



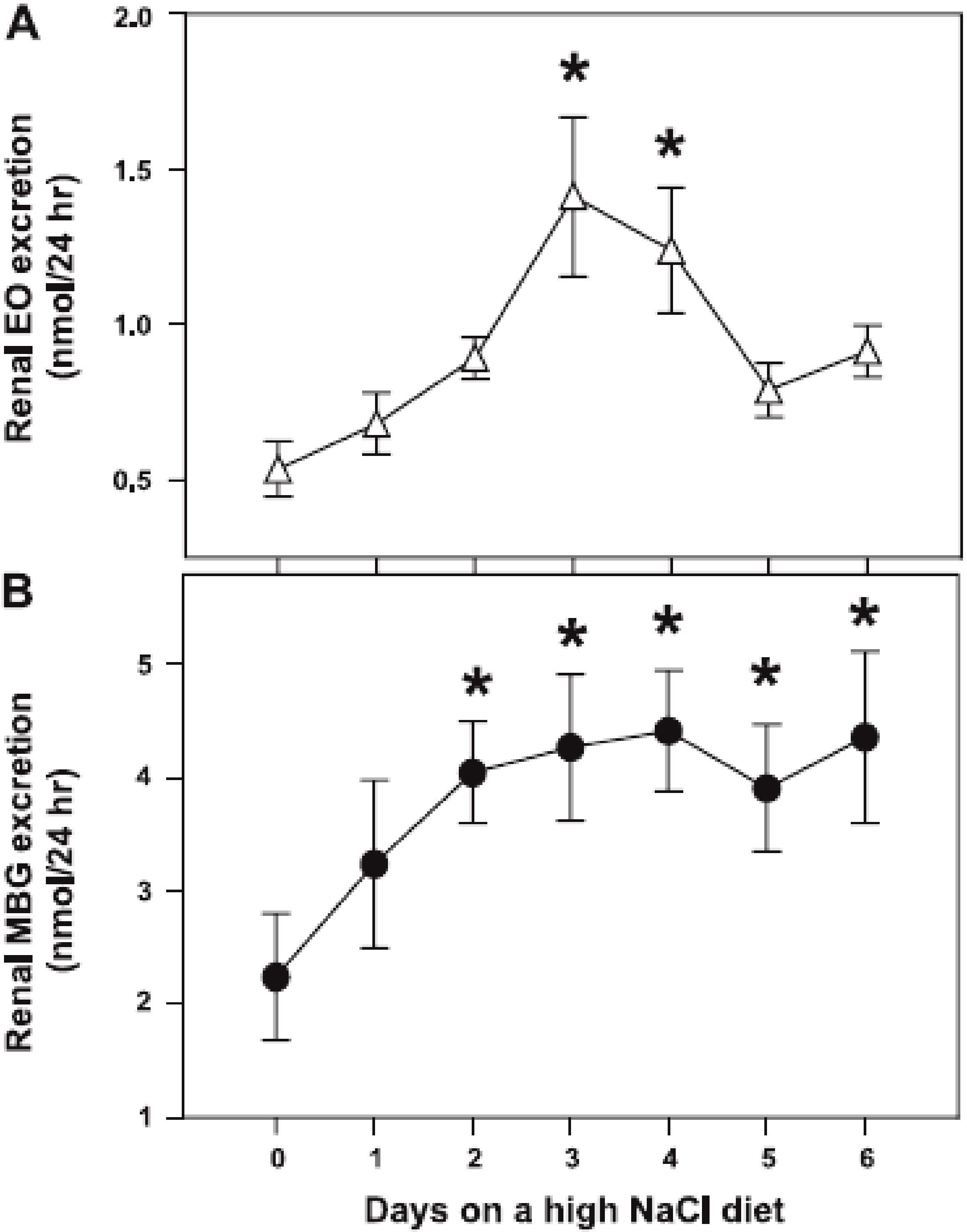
Gross, Am.J.Kidn.Dis (2005) 46:94



Lower blood pressure in heterozygote carriers of the Gitelman mutation

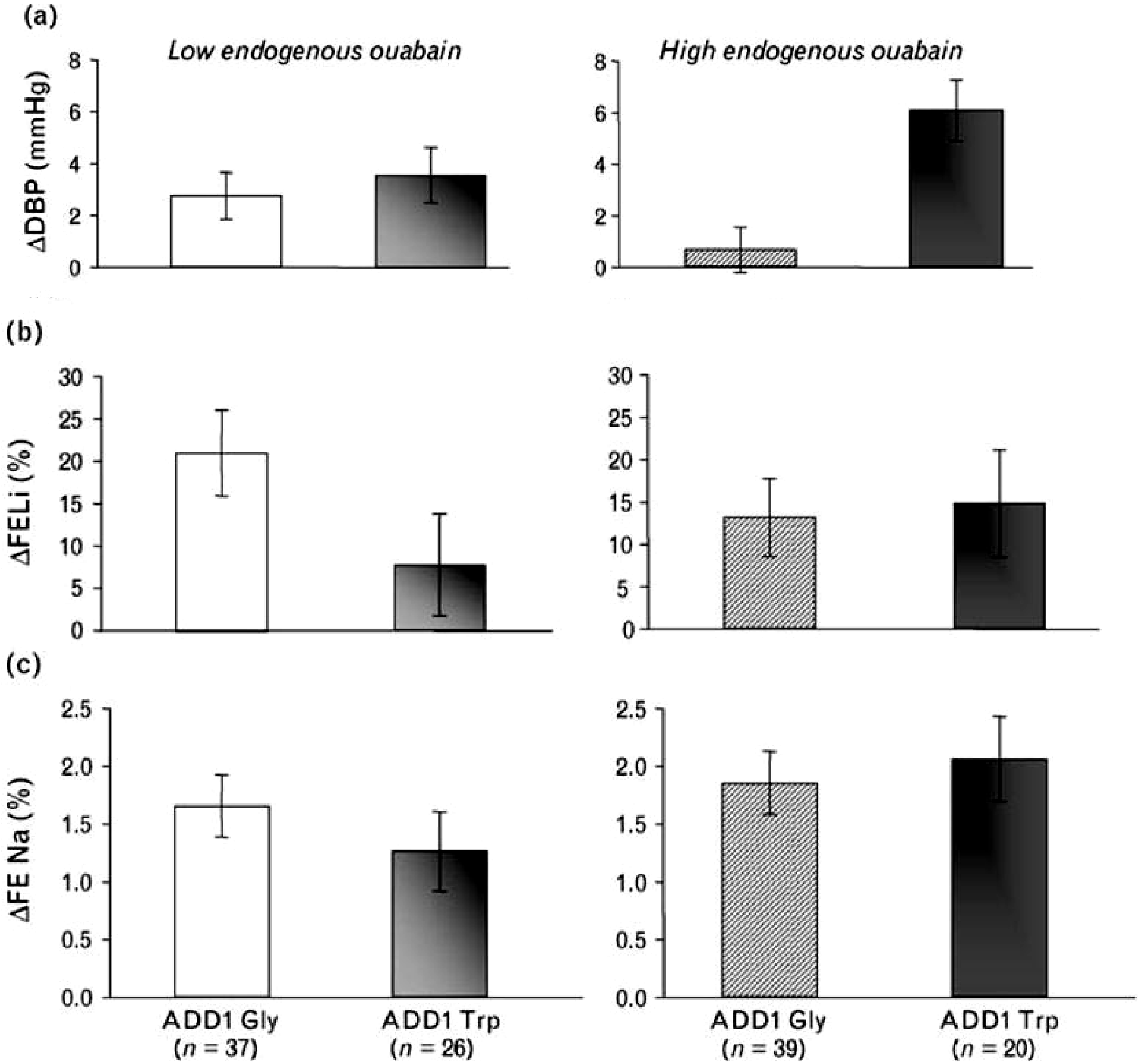
(NaCl cotransporter)
~ thiazides

Fava, Hum.Mol.Gen. (2008) 17:413



Increase of endogenous cardiotonic steroids with salt load

David, Am.J.Physiol.Regul.Comp. (2008) 294:1248



Acute Na^+ load –

amplified blood pressure response to Na^+ load if:

- **high plasma ouabain**
- **high tubular Na+ reabsorption**

(Trp adducin mutant)

Manunta, J.Hypertens. (2008) 26:914

The kidney and hypertension

1. The kidney – cause of hypertension

2. Prenatal programming and adult hypertension

3. The renal mechanisms leading to hypertension

4. Salt sensitivity in renal hypertension

5. Hormonal mediation of salt effects

- **triggering signal**
  - ***plasma (cerebrospinal) sodium concentration***
    de Wardener, Kidn.Intern.(2004) 66:2454
    Lichtstein,Neurochem.Res.(2001)26:971
  - ***sodium balance or extracellular volume***
    Hamlyn, Am.J.Physiol.(1986) 252:F563
    Titze, Am.J.Physiol.(2004) 287:H203
- **potassium – modulating sodium effect**
  Adrogué, New Engl J.med.(2007) 356: 1966
- **mediator(s)**
  - ***sodium per se (via ADMA and other mechanisms)***
    Fujiwara, Circulation (2000)101:856
  - ***hormonal signals (RAS,aldosteron)***

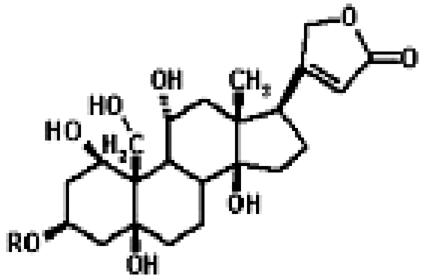
    cardiotonic steroids
    Siani, Ann.Int.Med. (1991)115:753
    Ferrari,Am.J.Physiol.(RICP)(2006)290:R529

Sir William Withering
1741 – 1790

An account of the foxglove
and some of its medical uses
1785

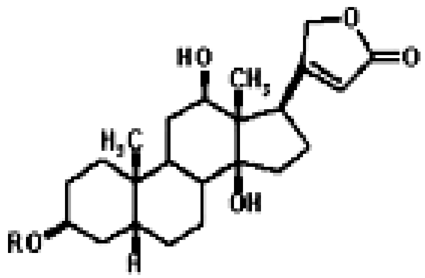
Cardiotonic steroids in mammalian tissues

Cardenoloids



OUABAIN
R = Rhamnose

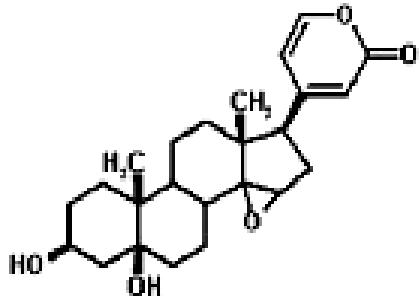
blood pressure raising



DIGOXIN
R = 3 Digitoxosen

blood presssure lowering

Bufadenoloids



MARINOBUFAGENIN

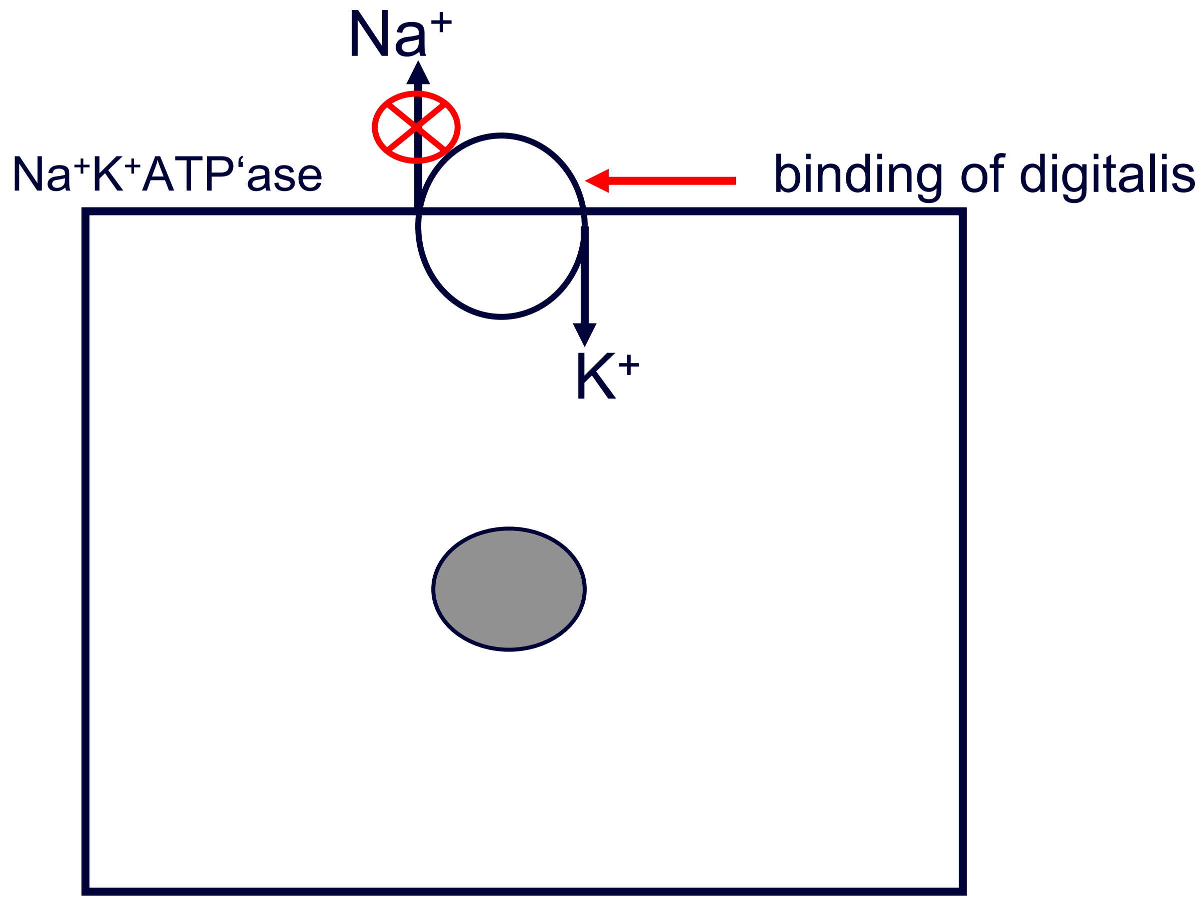
natriuretic

blood pressure raising

Classical view :

inhibition of enzymatic activity of Na^+K^+ATP'ase

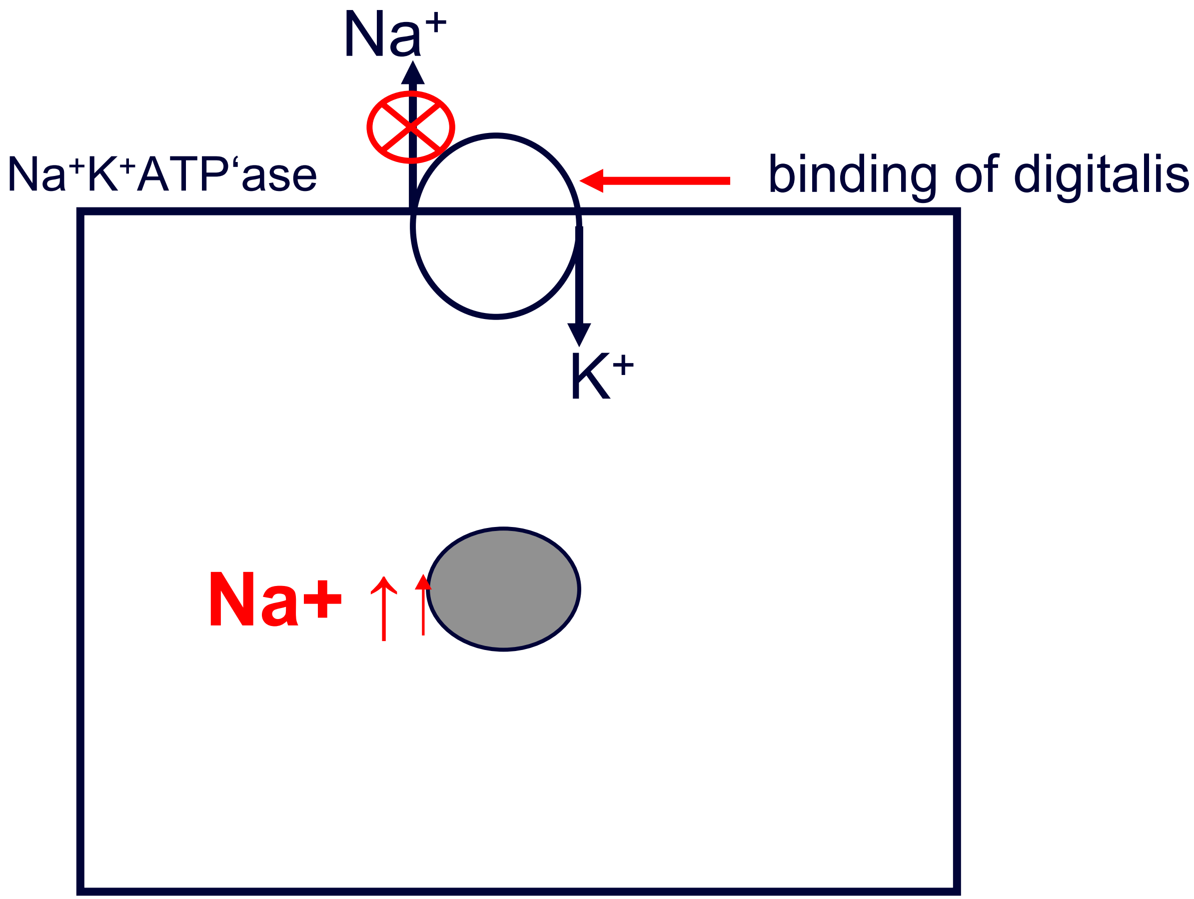
reduced Na^+ extrusion →



Classical view :

inhibition of enzymatic activity of Na^+K^+ATP‘ase

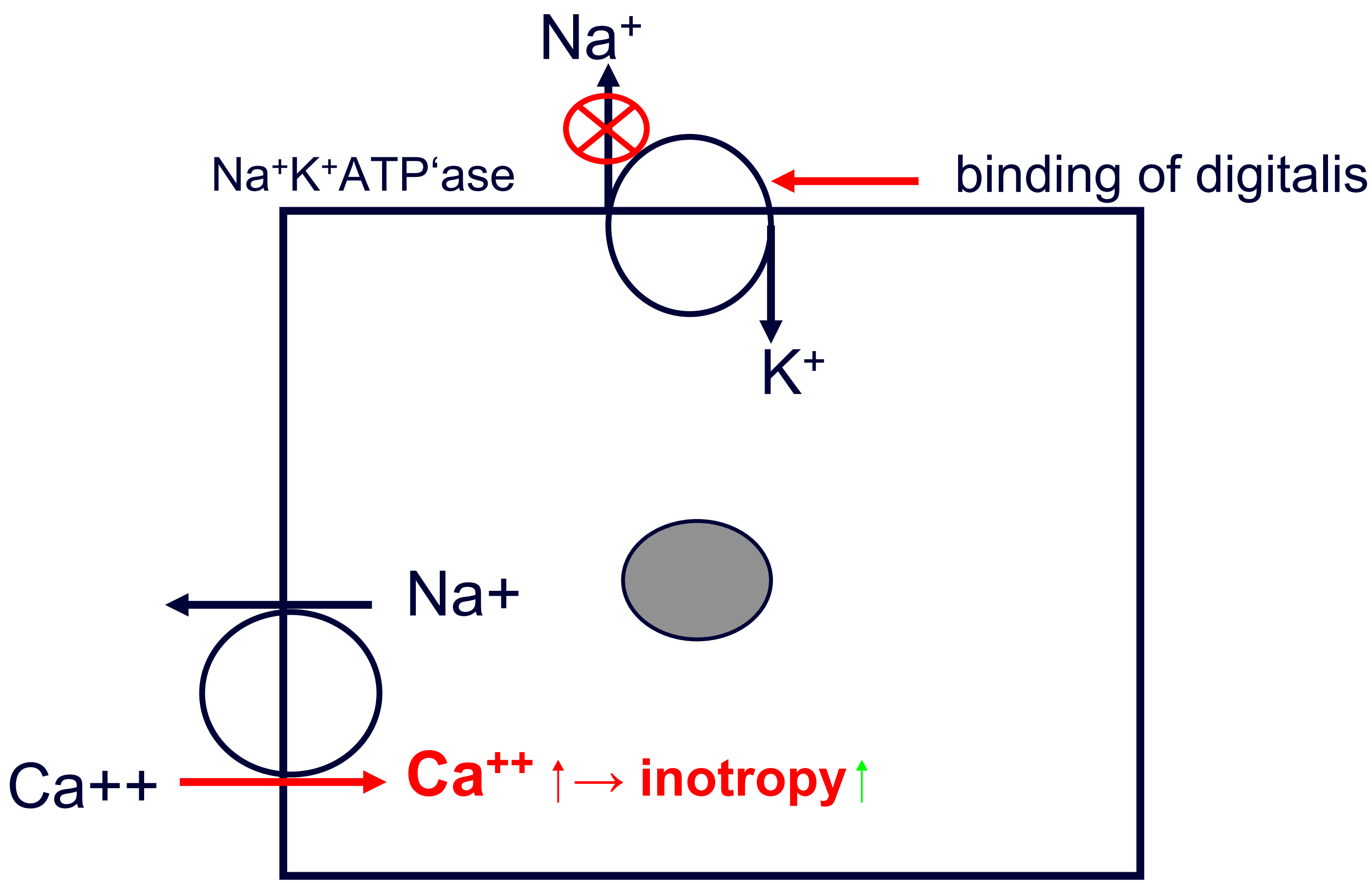
reduced Na^+ extrusion → ICC Na^+ cumulation →



Classical view :

inhibition of enzymatic activity of Na^+K^+ATP'ase

reduced Na^+ extrusion → ICC Na^+ cumulation → **Na^+ Ca^{++} exchanger running backward → increased inracellular Ca^{++}**



Cardiotonic steroids –
signal transducers

endoplasmic reticulum

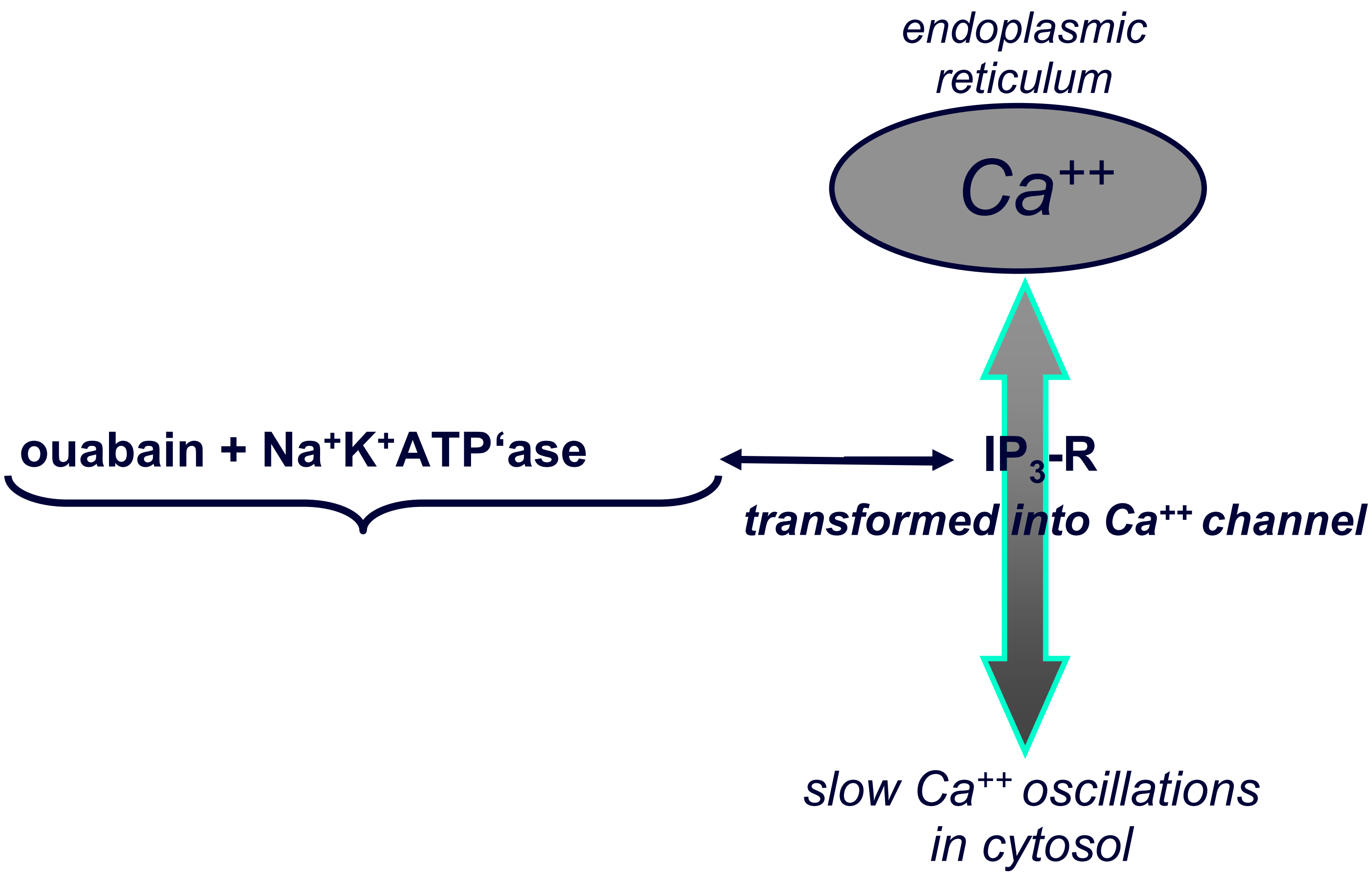
Ca^{++}

ouabain + $Na^{+}K^{+}$ATP'ase → **inosin-triphosphate receptor (IP_3-R)**

protein/protein interaction

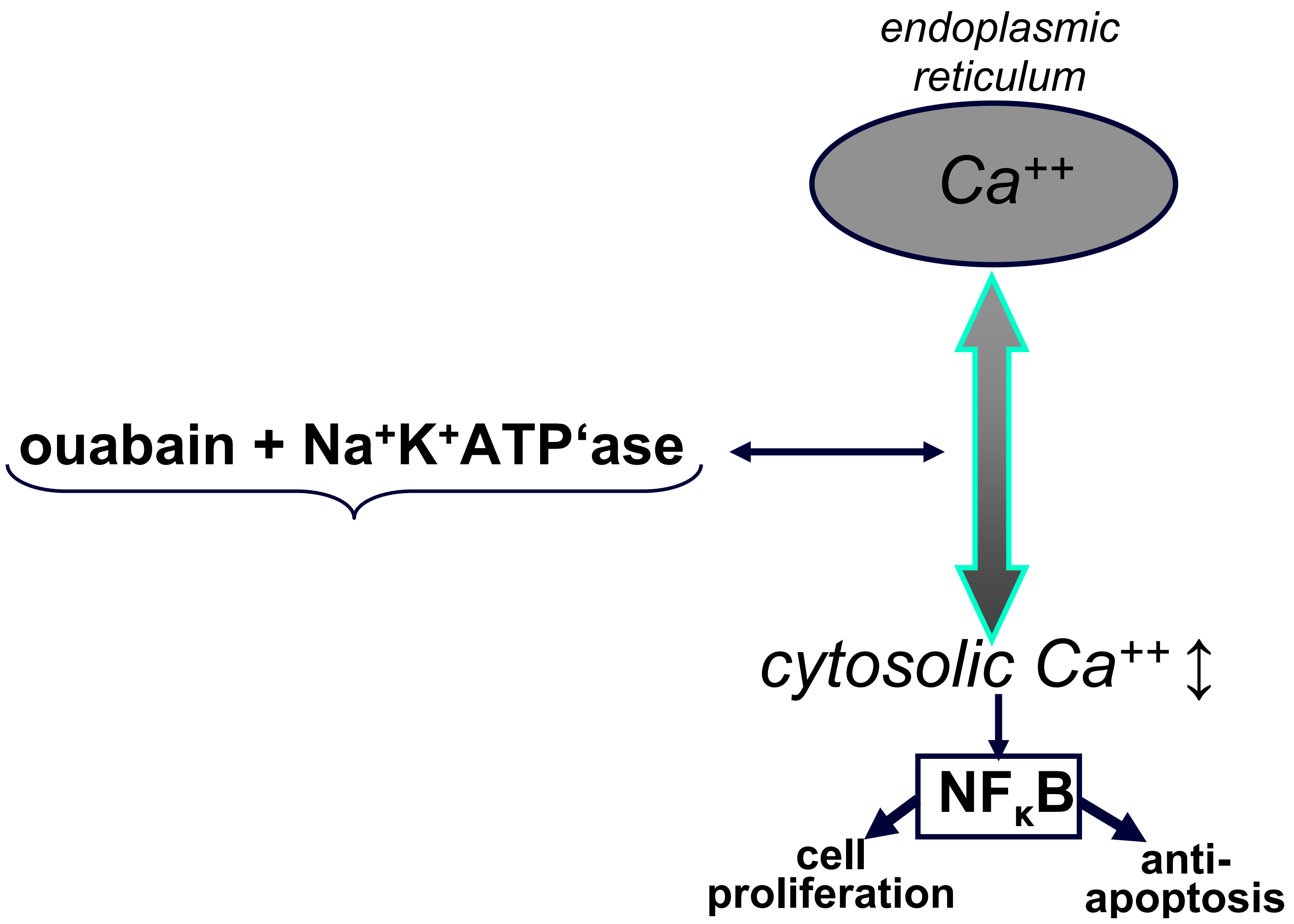
Schoner, Am.J.Physiol.(2007) 293:C509
Aperia, J.Intern.Med.(2007) 261:44

Cardiotonic steroids –
signalling pathways

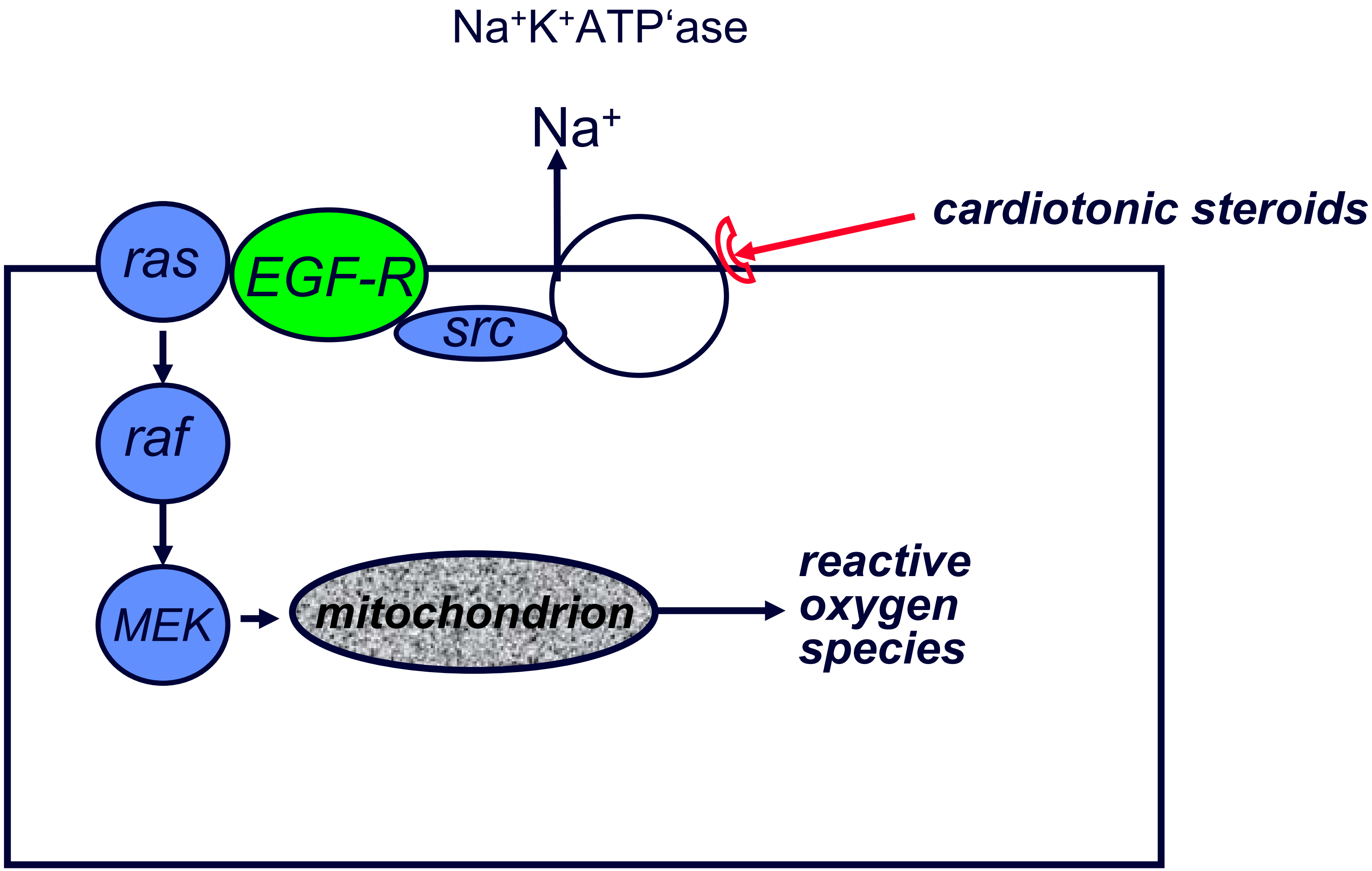


Schoner, Am.J.Physiol.(2007) 293:C509

Cardiotonic steroids –
signalling pathways

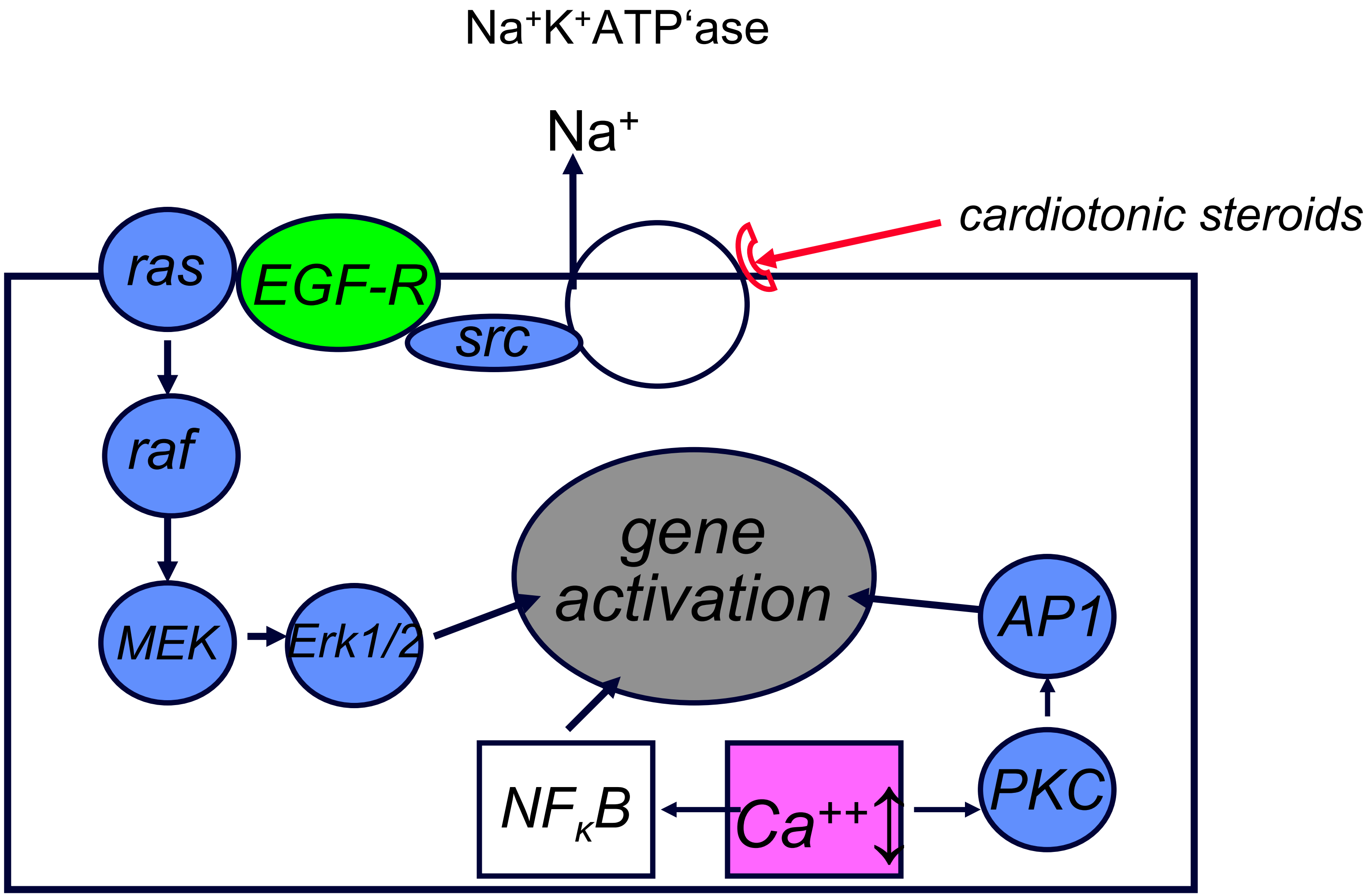


Activation via src and EGF-R → mitochondrial ROS + nuclear gene programmes

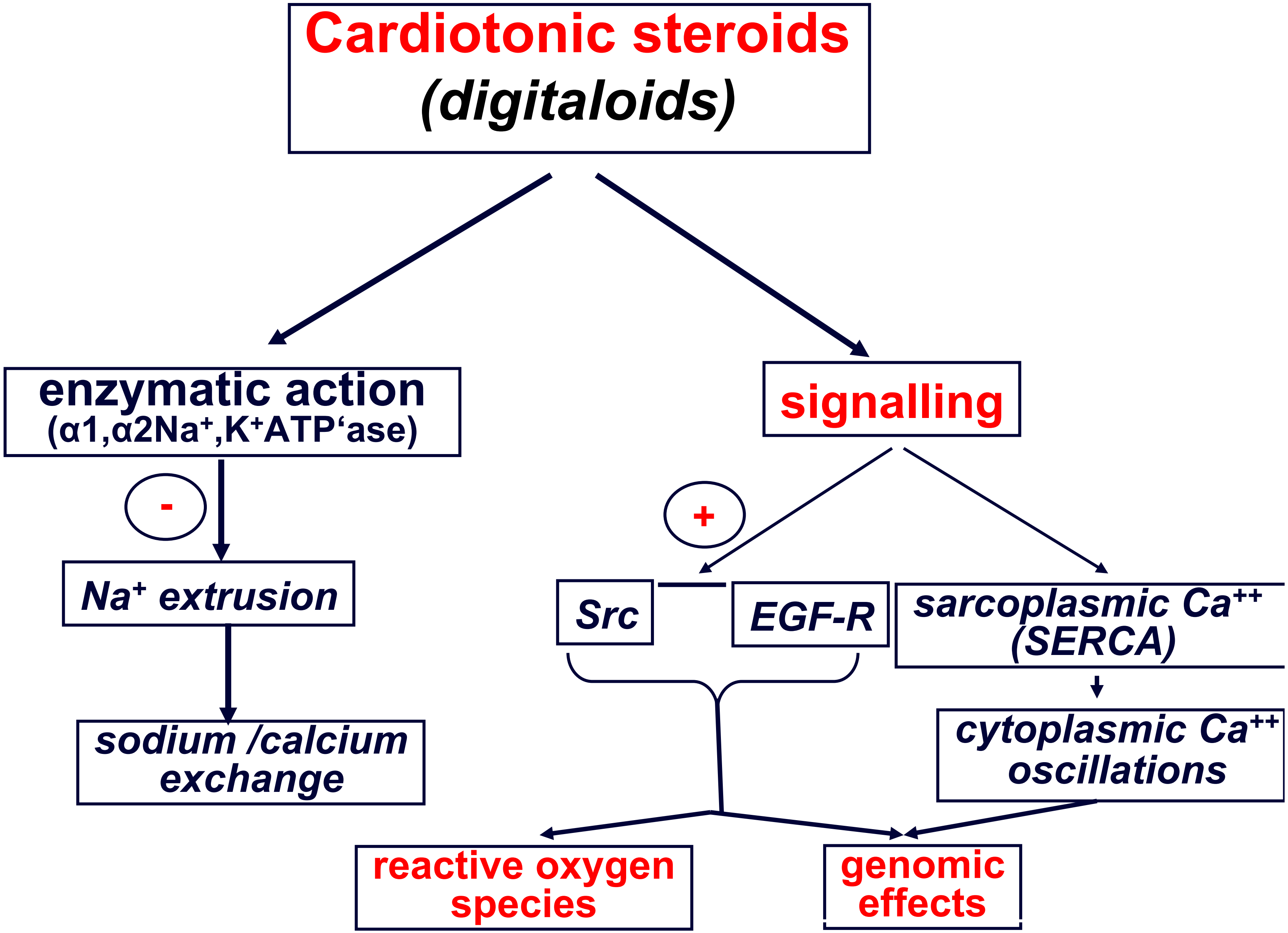


Schoner, Am.J.Physiol.(2007) 293:C509
Aperia, J.Intern.Med.(2007) 261:44

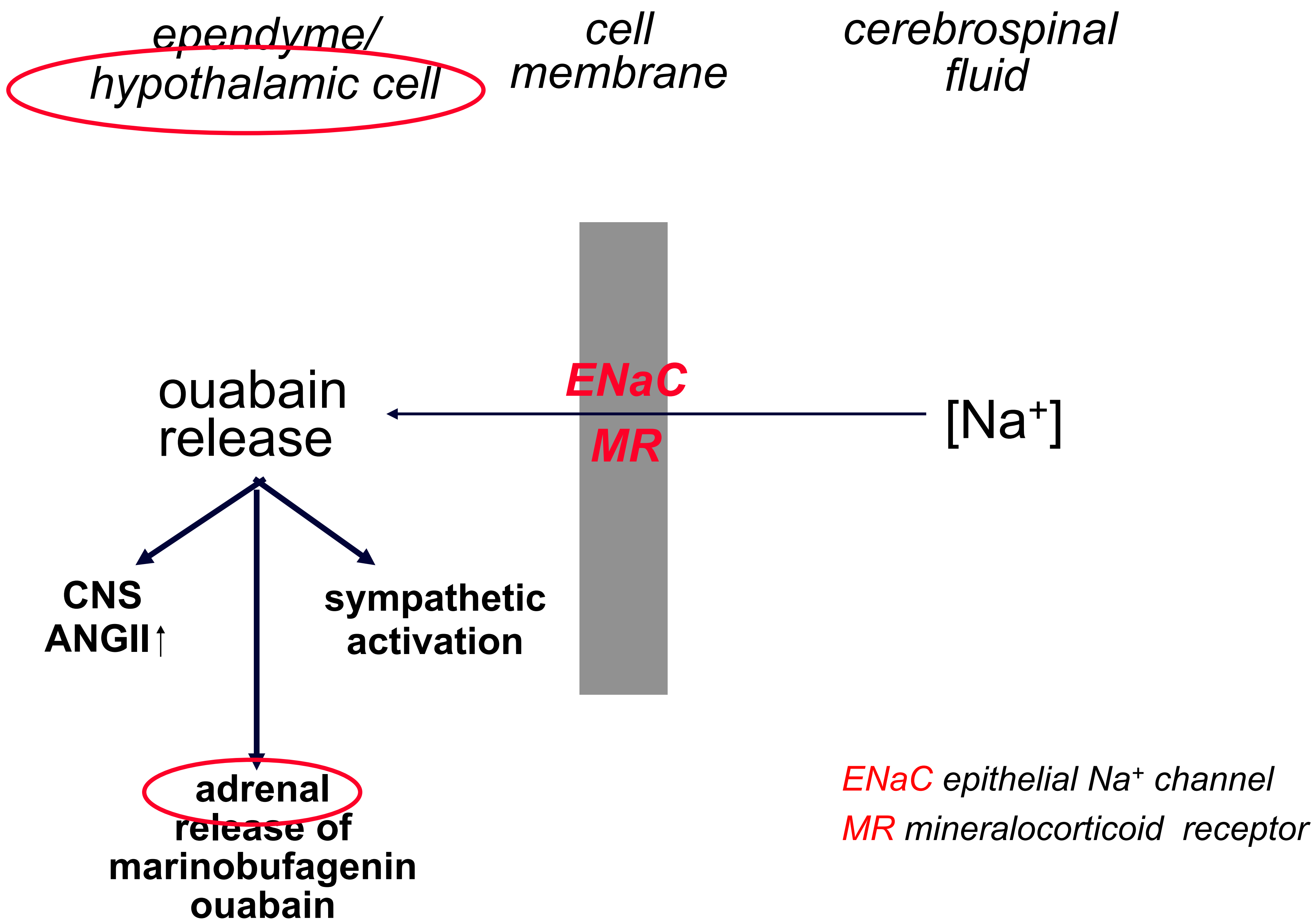
Activation via src and EGF-R → mitochondrial ROS + nuclear gene programmes



Schoner, Am.J.Physiol.(2007) 293:C509
Aperia, J.Intern.Med.(2007) 261:44



Schoner, Am.J.Physiol.(2007) 293:C509
Aperia, J.Intern.Med.(2007) 261:44


ependyme/
hypothalamic cell
cell
membrane
cerebrospinal
fluid
ouabain
release
ENaC
MR
[Na+]
CNS
ANGII↑
sympathetic
activation
adrenal
release of
marinobufagenin
ouabain
ENaC epithelial Na+ channel
MR mineralocorticoid receptor

Marinobufagenin

- *vasoconstriction*

  Lopatin, J.Hypertens.(1999) 117:1179

- *affinity α1 > α3 isoform Na^+K^+ATP'ase*

  Fedorova, Circulation (2000) 102:3009

- *excretion via urine*

  Fedorova, Hypertension (2001) 37:462

- *increased after volume expansion*

  Bagrov, Cardiovasc.Res. (1996) 31:296

- *increased in pathological states of volume expansion, e.g. uremia and preeclampsia*

  Gonick, Clin.Exp.Hypertens.(1998) 20:617
  Lopatin, J.Hypertens.(1999) 17:1179


Thank you for your attention