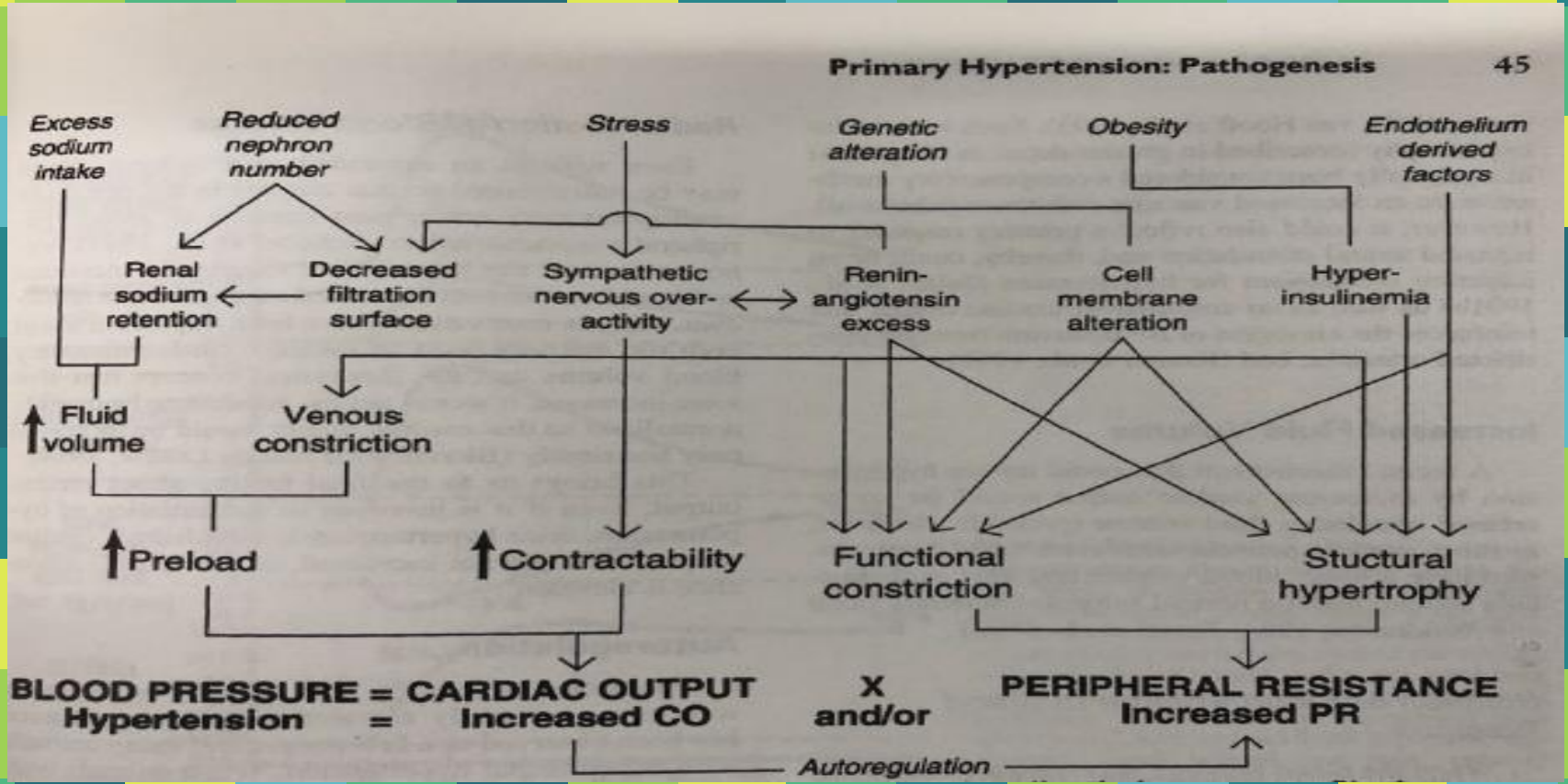
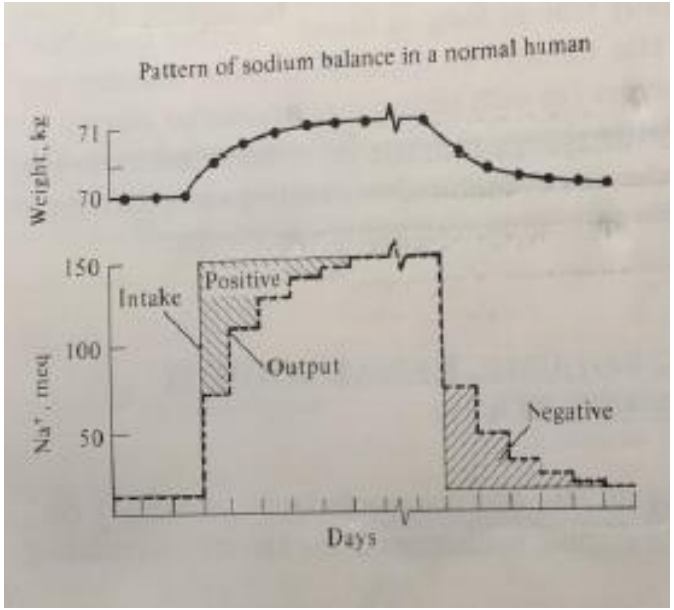
Ρόλος νατρίου και νεφρού

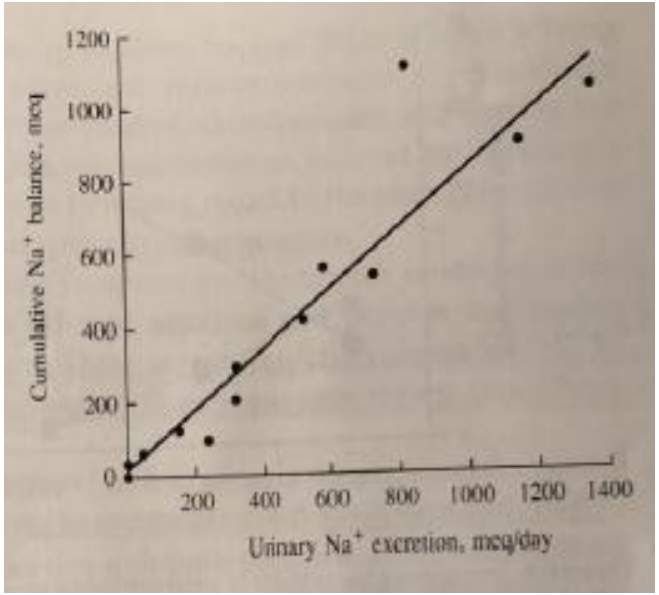
Ιωάννης Γριβέας, MD,PhD,
Νεφρολόγος

athens-NEPHROLOGY


Excess sodium intake
Reduced nephron number
Stress
Genetic alteration
Obesity
Endothelium derived factors
Renal sodium retention
Decreased filtration surface
Sympathetic nervous over-activity
Renin-angiotensin excess
Cell membrane alteration
Hyper-insulinemia
Fluid volume
Venous constriction
Preload
Contractability
Functional constriction
Stuctural hypertrophy
BLOOD PRESSURE = CARDIAC OUTPUT X PERIPHERAL RESISTANCE
Hypertension = Increased CO and/or Increased PR
Autoregulation

Effective circulating volume and Renal Na+ excretion





Effective circulating volume and Renal Na+ excretion

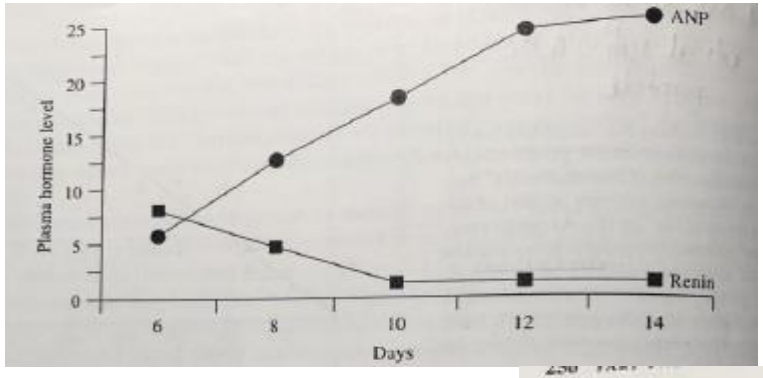
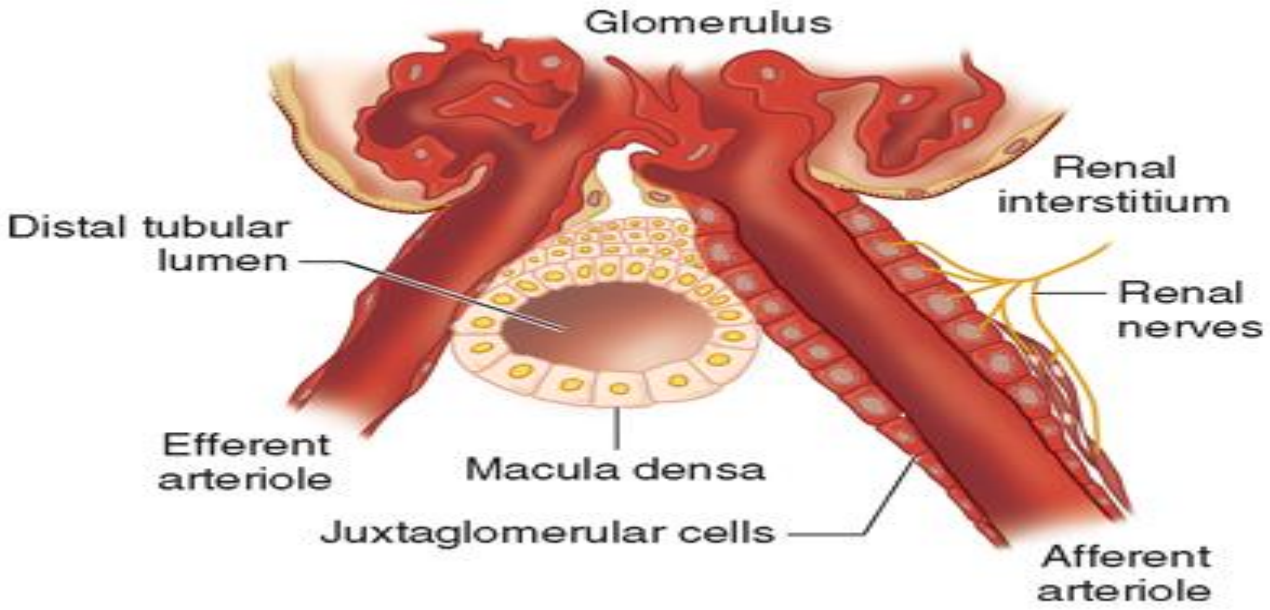


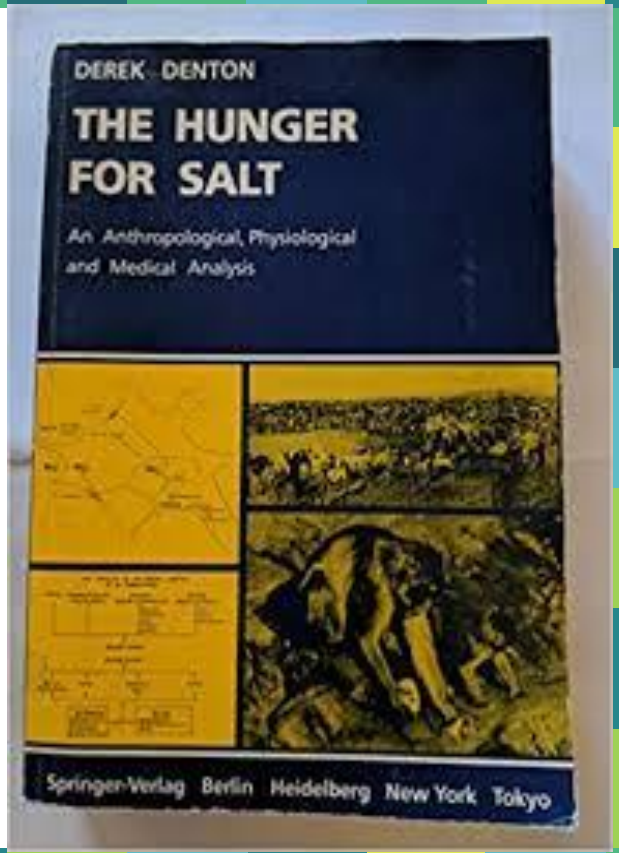
Table 8-4 Difference between osmoregulation and volume regulation

	Osmoregulation	Volume regulation
What is being sensed	Plasma osmolality	Effective circulating volume
Sensors	Hypothalamic osmoreceptors	Carotid sinus Afferent arteriole Atria
Effectors	Antidiuretic hormone Thirst	Renin-angiotensin-aldosterone system Sympathetic nervous system Atrial natriuretic peptide Pressure natriuresis Antidiuretic hormone
What is affected	Water excretion and via thirst, water intake	Urine sodium excretion



Source: Butterworth JF, Mackey DC, Wasnick JD: *Morgan & Mikhail's Clinical Anesthesiology*, 5th Edition: www.accessmedicine.com

"There are good grounds but by no means a proven case for suspecting excess salt intake, probably associated with reduced potassium intake , in the aetiology of hypetensionn in Western-Type communities "



The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

MECHANISMS OF DISEASE

Sodium and Potassium in the Pathogenesis of Hypertension

Horacio J. Adrogué, M.D., and Nicolaos E. Madias, M.D.

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potassium. Isolated populations that eat natural foods have an individual potassium intake that exceeds 150 mmol per day and a sodium intake of only 20 to 40 mmol per day (the ratio of dietary potassium to sodium is >3 and usually closer to 10).[6,8,10] By contrast, people in industrialized nations eat many processed foods and thereby ingest 30 to 70 mmol of potassium per day and as much as 100 to 400 mmol of sodium per day (the usual dietary potassium:sodium ratio is <0.4).[3,10]

Hypertension affects less than 1% of people in isolated societies but approximately one third of adults in industrialized countries.[3,10] Differ-

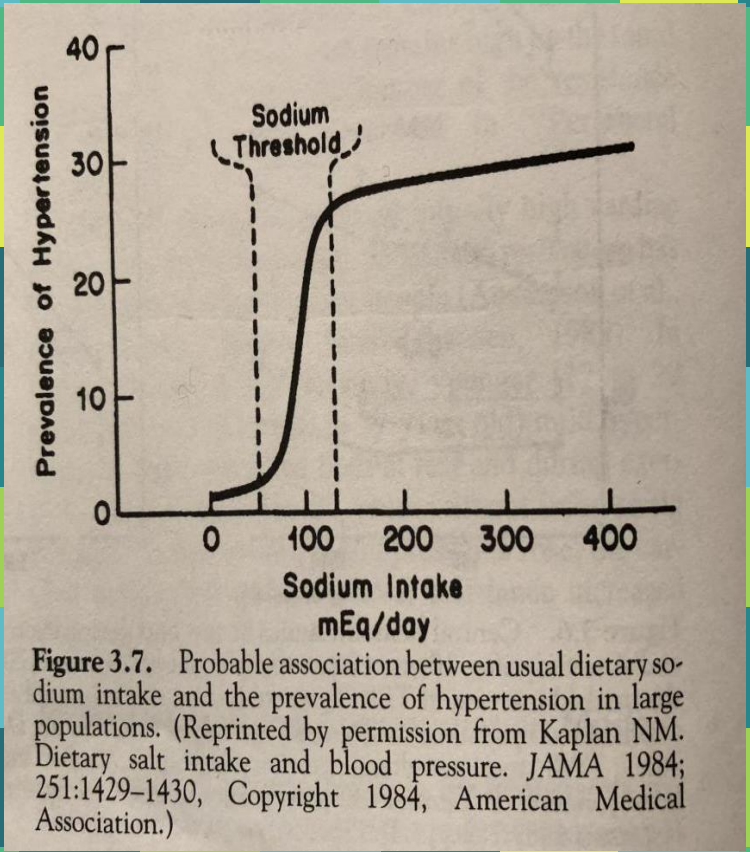
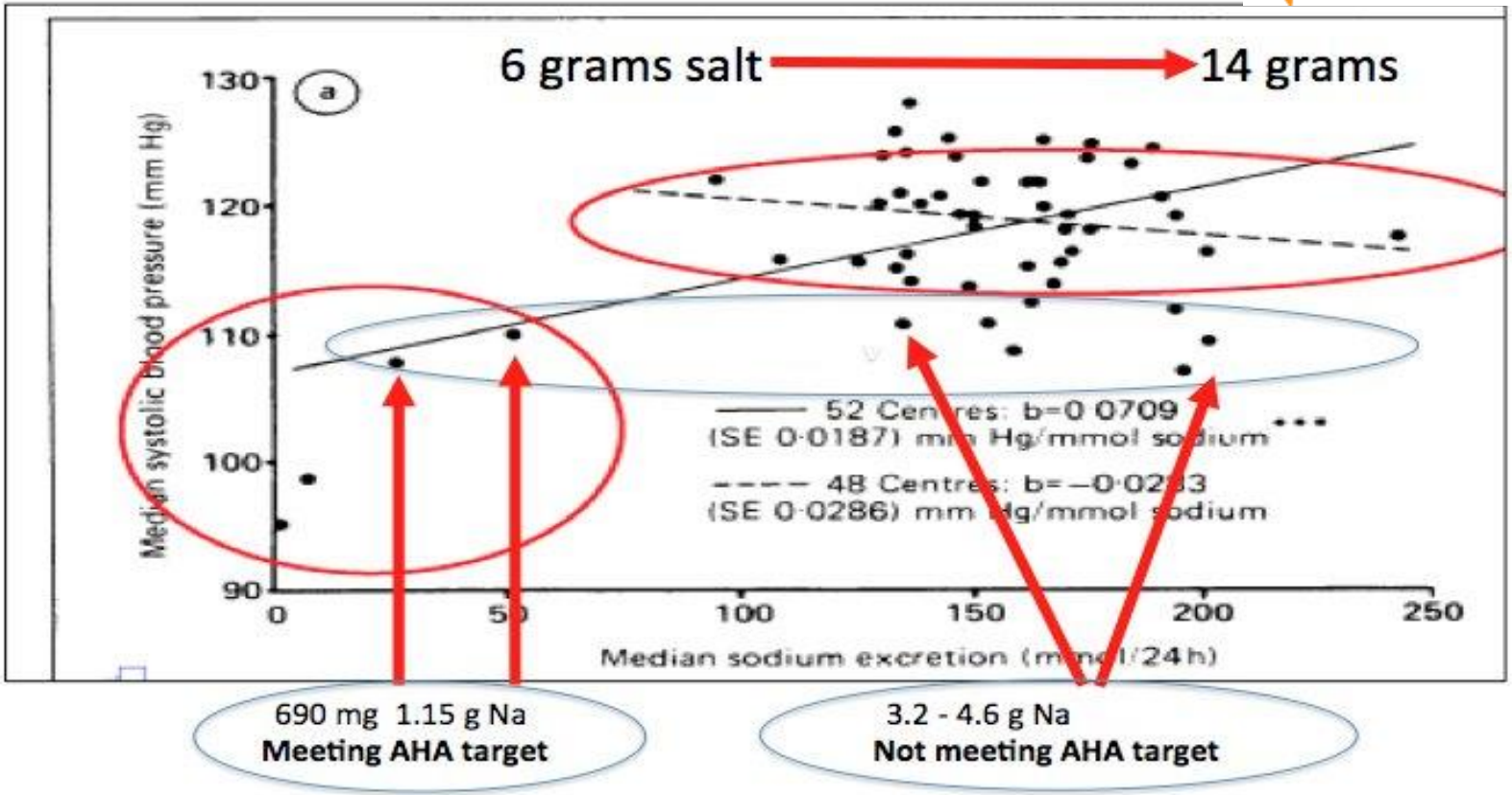
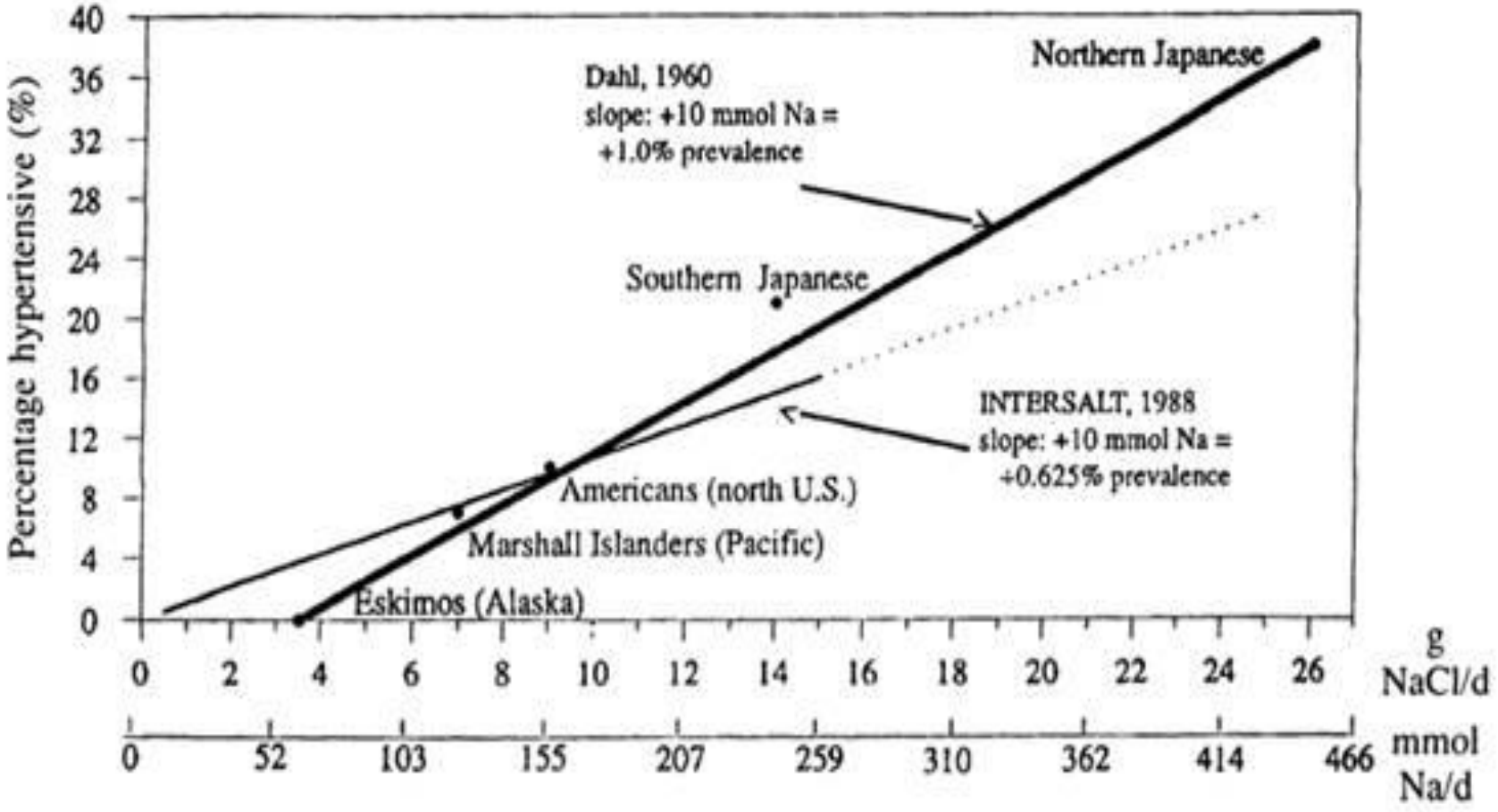


Figure 3.7. Probable association between usual dietary sodium intake and the prevalence of hypertension in large populations. (Reprinted by permission from Kaplan NM. Dietary salt intake and blood pressure. *JAMA* 1984; 251:1429–1430, Copyright 1984, American Medical Association.)

INTERSALT 1988 – 48 populations




Percentage hypertensive (%)
40
36
32
28
24
20
16
12
8
4
0
Dahl, 1960
slope: +10 mmol Na =
+1.0% prevalence
Northern Japanese
Southern Japanese
INTERSALT, 1988
slope: +10 mmol Na =
+0.625% prevalence
Americans (north U.S.)
Marshall Islanders (Pacific)
Eskimos (Alaska)
0 2 4 6 8 10 12 14 16 18 20 22 24 26
g NaCl/d
0 52 103 155 207 259 310 362 414 466
mmol Na/d

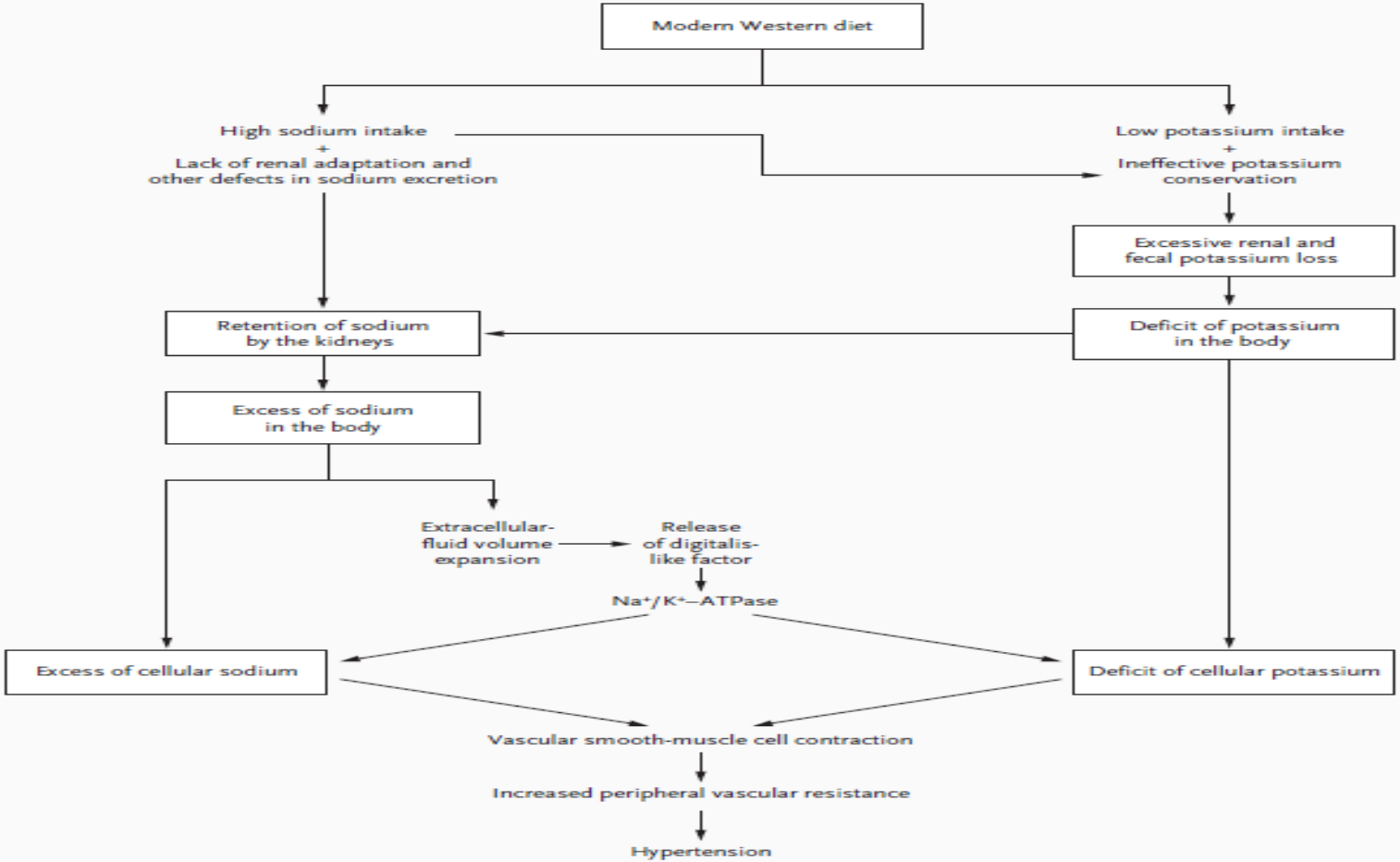


Figure 1. Interaction of the Modern Western Diet and the Kidneys in the Pathogenesis of Primary Hypertension.
The modern Western diet interacts with the kidneys to generate excess sodium and cause a deficit of potassium in the body; these changes increase peripheral vascular resistance and establish hypertension. An initial increase in the volume of extracellular fluid is countered by pressure natriuresis.

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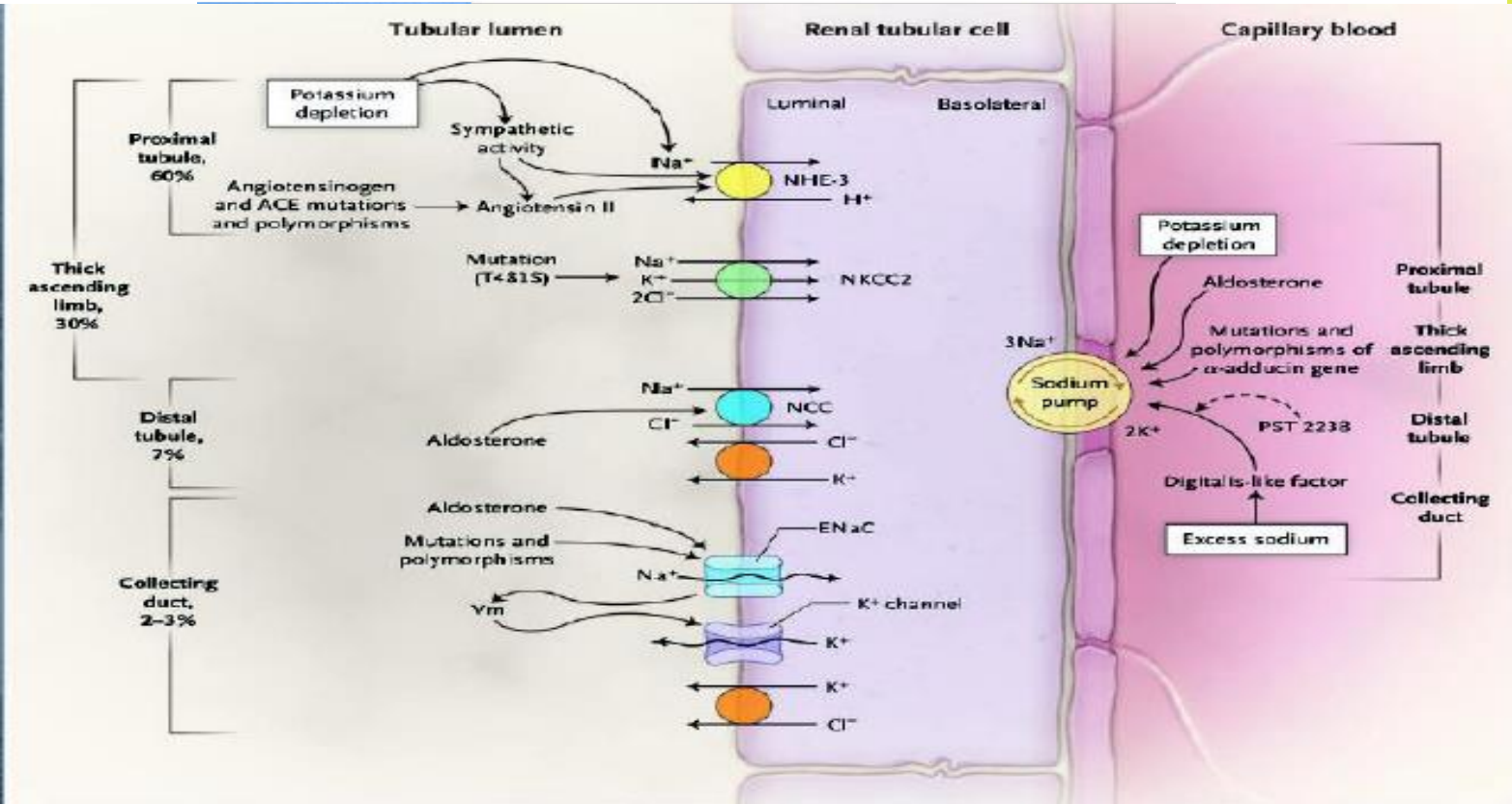

Ελληνική Νεφρολογία 2012; 24 (3): 167 - 173

Ανασκόπηση

Σηματοδοτικές οδοί της ενδογενούς ουαμπαΐνης και νατριούρηση

Ι. Γριβέας[1]
Π. Πασαδάκης[2]
Ν. Παπαγαλάνης[3]

Περίληψη

Η παρούσα ανασκόπηση αναφέρεται στην ενδογενή ουαμπαΐνη (ouabain), η οποία ανήκει στα ενδογενή καρδιοτονωτικά στεροειδή (endogenous cardiotonic steroids, CTS), ομάδα γνωστή και ως παράγοντες παρόμοιοι με δακτυλίτιδα (digitalis-like factors), ή αναστολέας της Na⁺/K⁺-ATPάσης. Τα CTS αποτελούν σύνδεσμο της διαφοφικής πρόσληψης NaCl και των καρδιαγγειακών και νεφρικών παθήσεων. Αν και η ύπαρξη και η σημασία των παραγόντων αυτών αποτέλεσε αντικείμενο διαμάχης, αξιοσημείωτη είναι η πρόοδος που έχει επιτευχθεί κατά τα τελευταία 15 χρόνια. Υπάρχουν σε υψηλά επίπεδα στο πλάσμα στο 40% περίπου ασθενών με ιδιοπαθή υπέρταση. Οι παράγοντες αυτοί προκαλούν κατακράτηση άλατος μέσω αύξησης της δραστηριότητας και της έκφρασης της νεφρικής αντλίας νατρίου. Μελέτες τα τελευταία 10 χρόνια έχουν διευκρινίσει πολλές και σημαντικές πρωτεϊνικές αλληλεπιδράσεις της Na⁺-K⁺-ATPάσης οι οποίες σηματοδοτούν την έναρξη μιας καινούργιας εποχής. Άς σημειωθεί ότι γνωρίζουμε μέχρι σήμερα λίγα για τη συσχέτιση μεταξύ της μεταφοράς ιόντων με βάση τη λειτουργία της Na⁺-K⁺-ATPάσης και των μηχανισμών της σηματοδότησης στη ρύθμιση των λειτουργιών των κυττάρων.

Λέξεις κλειδιά: *αντλία Na⁺, ουαμπαΐνη, υπέρταση.*

Εισαγωγή

Η παρούσα ανασκόπηση αναφέρεται στην ενδογενή ουαμπαΐνη (ouabain), η οποία ανήκει στα ενδογενή καρδιοτονωτικά στεροειδή (endogenous cardiotonic steroids, CTS), με ομάδα γνωστή και ως παράγοντες παρόμοιοι με δακτυλίτιδα (digitalis-like factors), ως αναστολέας της Na^+/K^+-ATασης[1]. Τα CTS αποτελούν σύνδεσμο μεταξύ της διαιτητικής πρόσληψης άλατος (NaCl) και καρδιαγγειακής και νεφρικής νόσου. Αν και η ύπαρξη και η σημασία, των παραγόντων αυτών αποτέλεσε αντικείμενο αντιπαράθεσης στην διεθνή επιστημονική κοινότητα, αξιοσημείωτη πρόοδος έχει επιτευχθεί κατά τα τελευταία 15 χρόνια. Υψηλά επίπεδα των CTS παρατηρούνται στο πλάσμα στο 40% περίπου των ασθενών με ιδιοπαθή υπέρταση, που δεν λαμβάνουν θεραπεία και συσχετίζονται άμεσα με την τιμή της αρτηριακής πίεσης. Οι παράγοντες αυτοί προκαλούν κατακράτηση νατρίου μέσω αύξησης

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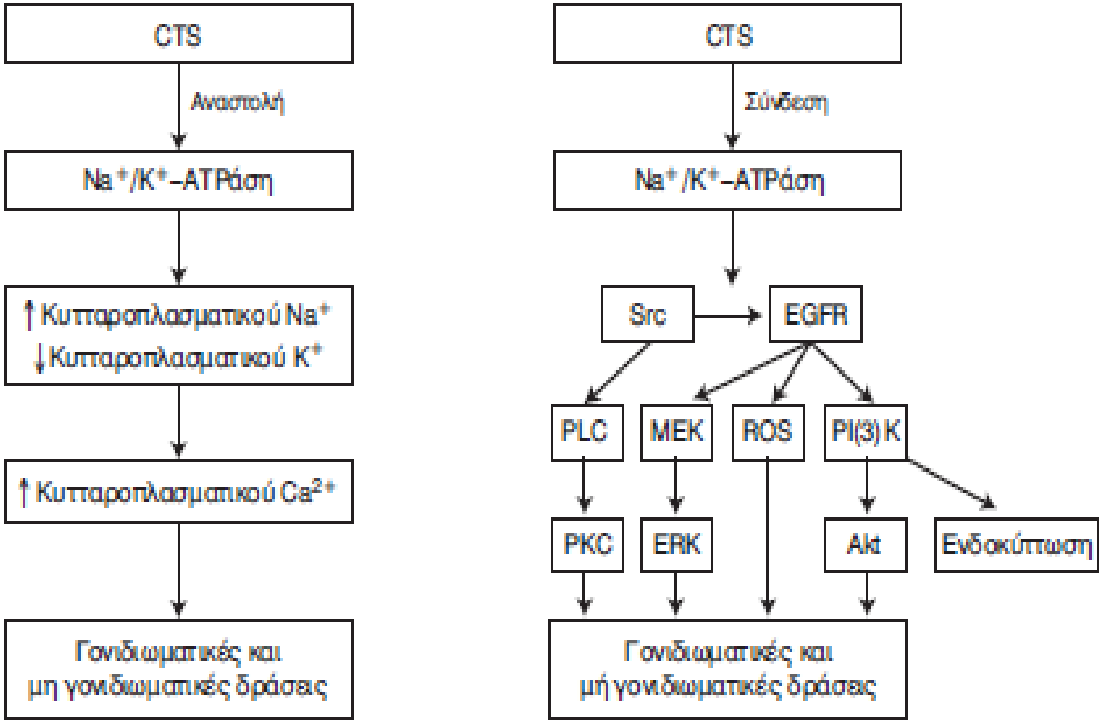
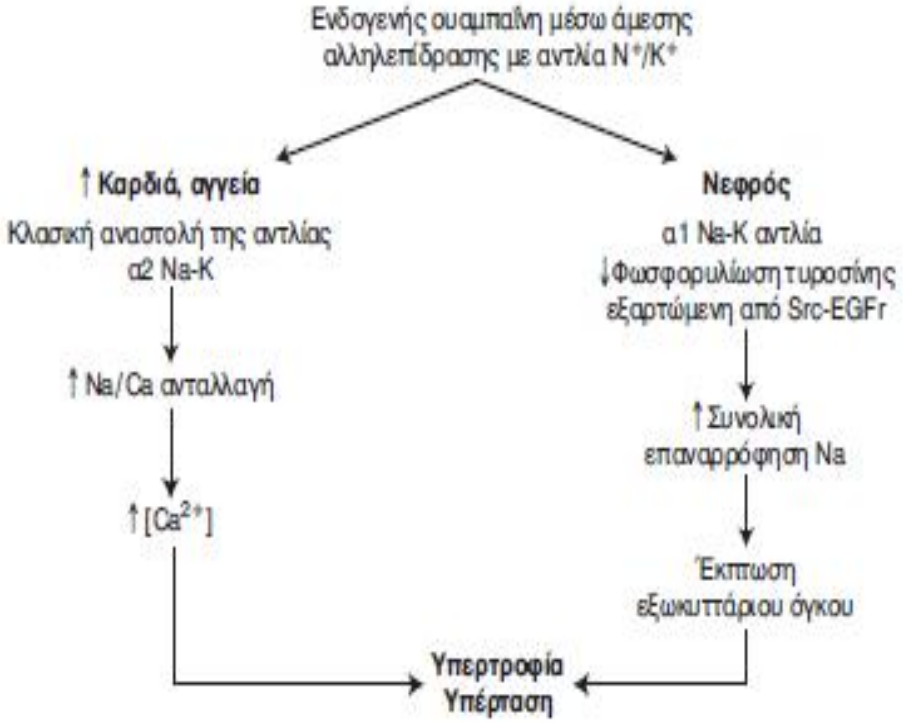
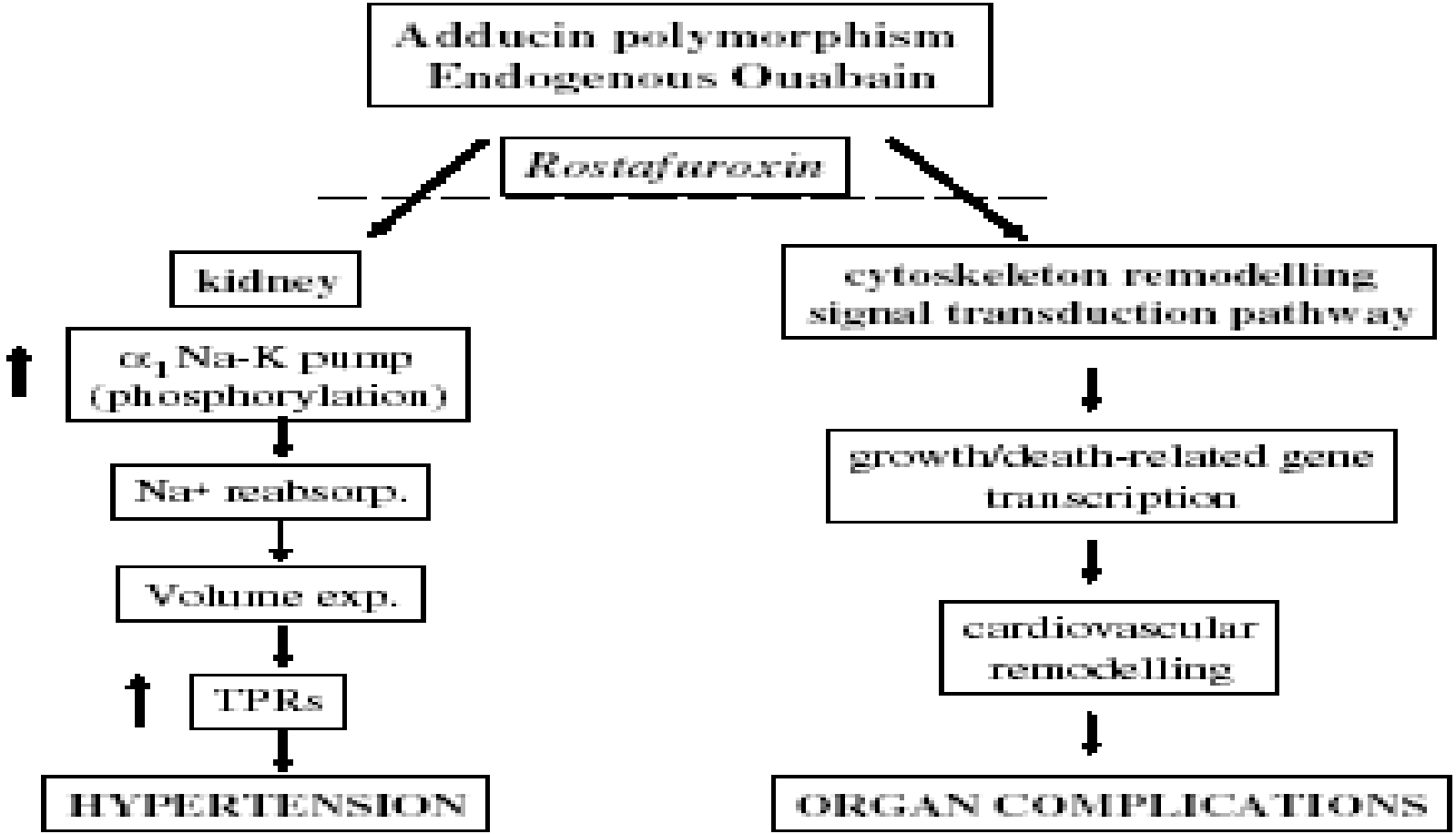
[2] **Ιατρική Σχολή Δημοκρίτειου Πανεπιστημίου Θράκης**
[3] **Νεφρολογικό Τμήμα, Γενικό Νοσοκομείο Αθηνών «Κοργιαλένειο-Μπενάκειο»**



Εικ. 2. Οι 2 οδοί μέσω των οποίων η σύνδεση των CTS με την Na^+/K^+-ATPάσης ασκεί γονιδιακή και μη γονιδιακή δράση.



Εικ. 4. Οι οδοί της ενδογενούς ουαμπαΐνης.


Adducin polymorphism
Endogenous Ouabain
Rostafuroxin
kidney
cytoskeleton remodelling
signal transduction pathway
α1 Na-K pump
(phosphorylation)
Na+ reabsorp.
Volume exp.
TPRs
growth/death-related gene
transcription
cardiovascular
remodelling
HYPERTENSION
ORGAN COMPLICATIONS

MOL PHARM

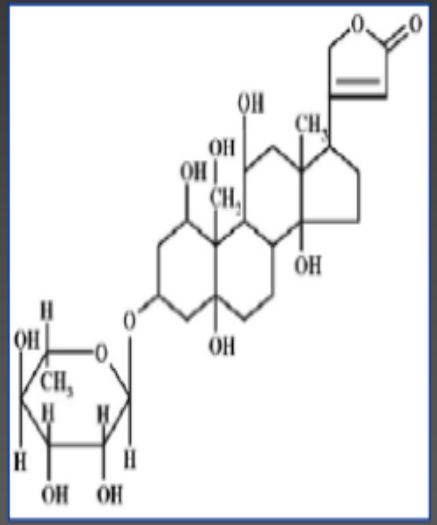
New Molecular Determinants Controlling the Accessibility of Ouabain to Its Binding Site in Human Na,K-ATPase α Isoforms

Gilles Crambert, Daniele Schaer, Sophie Roy, and Käthi Geering
Institute of Pharmacology and Toxicology of the University, Lausanne, Switzerland
Received August 26, 2004; accepted October 22, 2003 This article is available online at http://molpharm.aspetjournals.org

MOLECULAR PHARMACOLOGY

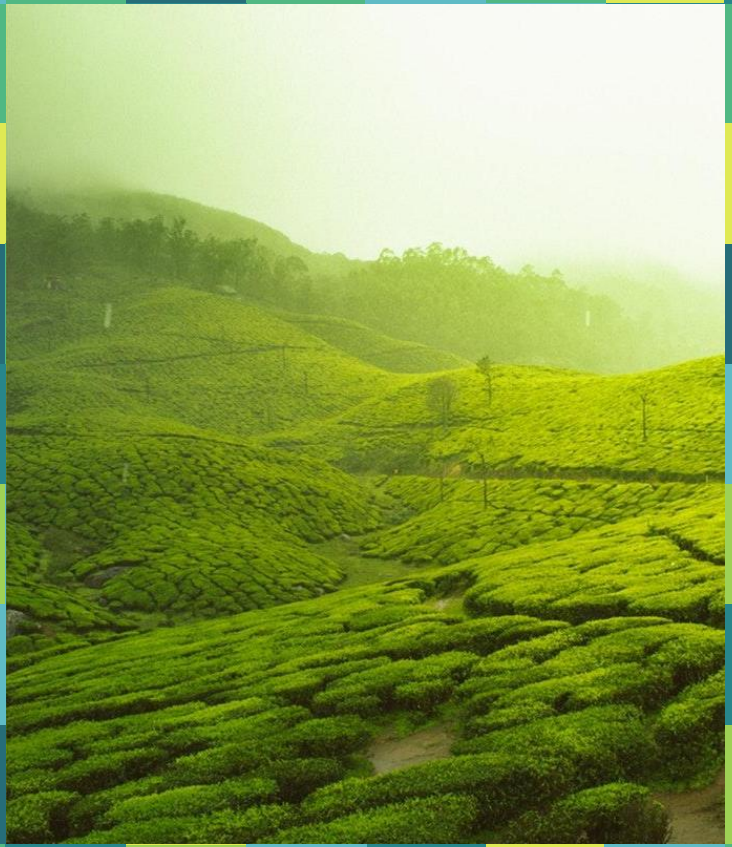
In conclusion, we have identified new amino acids in the Na,K-ATPase that differentially control discrete steps in the ouabain binding to α1 and α2 isoforms. These findings, which explain the isoform-specific differences in ouabain binding kinetics, may be of importance for the development of new drugs that are able to discriminate between the 'inotropic' α2 and the 'toxic' α1 isoform of Na,K-ATPase.

Therapeutic action of cardiotonic steroids like digitalis (ouabain derivatives)



ouabain

- Inhibition of Na,K-ATPase by ouabain-like cardiotonic steroids leads to decrease in Na^+ -gradient and decrease in the activity of Na^+/Ca^{2+} exchanger
- This in turn leads to increases in intracellular Ca^{2+} concentration and better cardiac muscle contraction



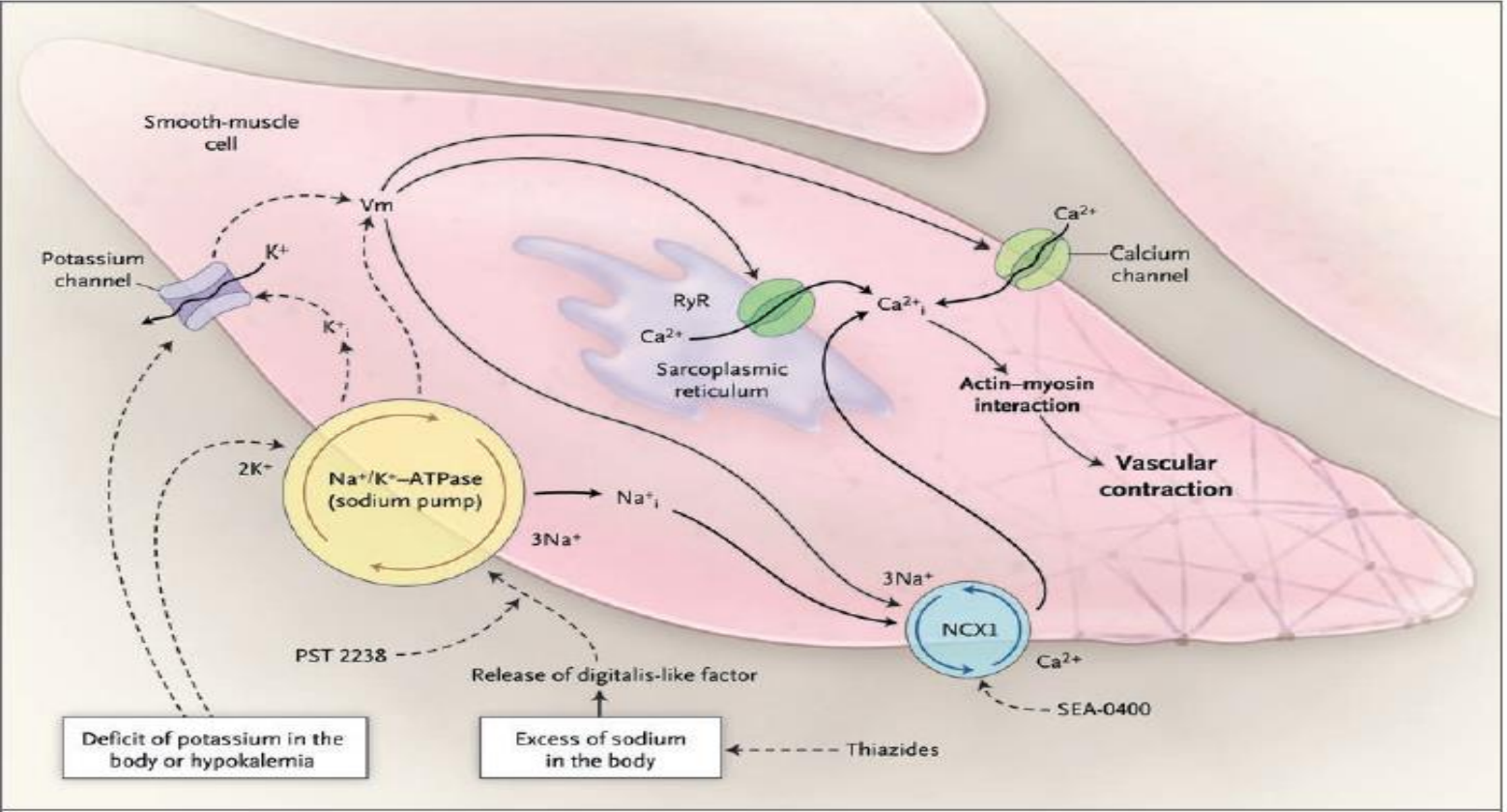
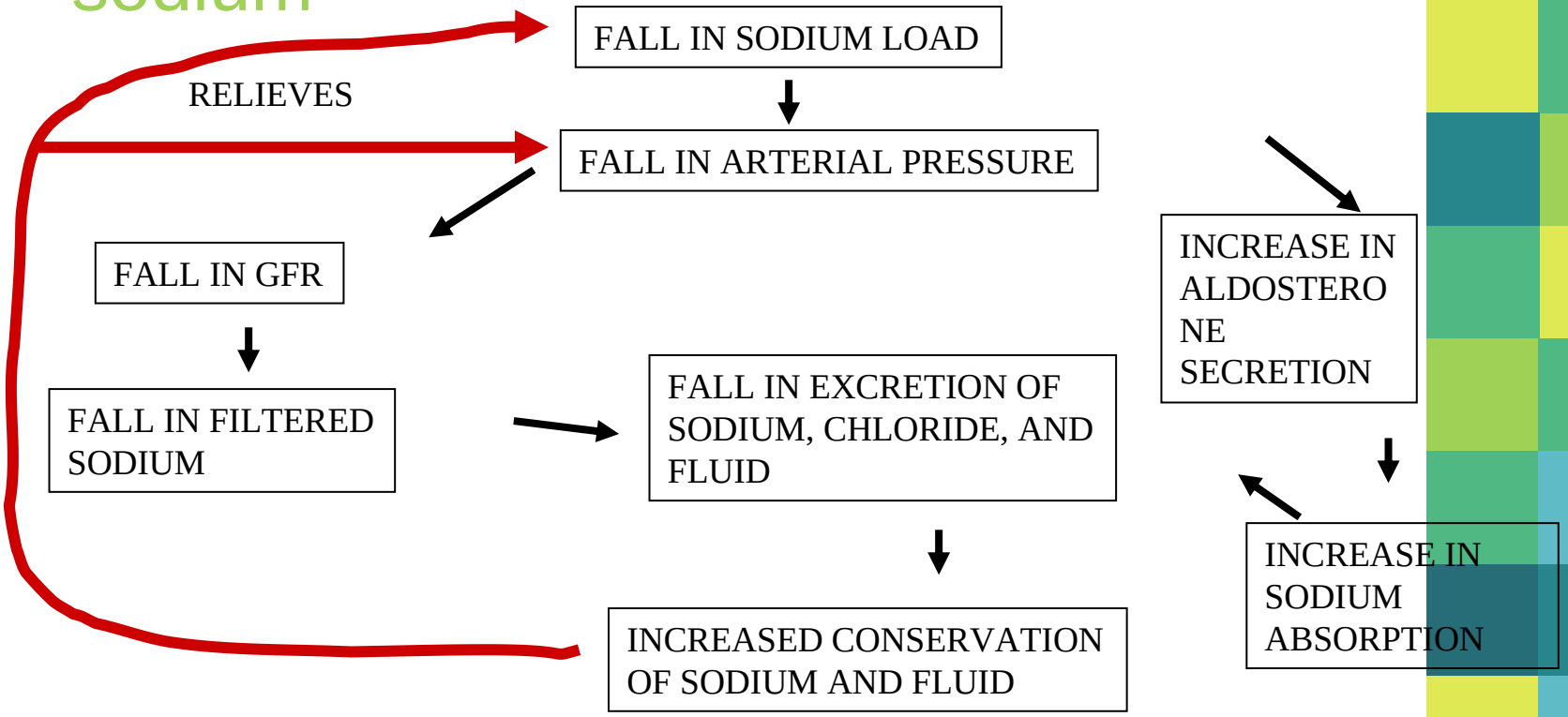


Figure 3. Molecular Pathways Implicated in the Generation of Increased Arterial and Arteriolar Smooth-Muscle Tone by an Excess of Sodium and a Deficit of Potassium in Primary Hypertension.

Solid arrows indicate an increase or stimulation, and broken arrows indicate a decrease or inhibition. The inhibition of the sodium pump and the resulting stimulation of the sodium–calcium exchanger type 1 (NCX1) increase the intracellular concentration of calcium that in turn triggers actin–myosin interaction and stimulation of vascular contraction. Na^+_i denotes intracellular sodium concentration, K^+_i intracellular potassium concentration, Ca^{2+}_i intracellular calcium concentration, Vm membrane potential, and RyR ryanodine-receptor calcium channel. PST 2238 (rostafuroxin) antagonizes the effect of digitalis-like factor on the sodium pump. SEA-0400 is a specific inhibitor of the bidirectional NCX1 preferentially blocking the calcium influx pathway.

Blood pressure and renal handling of sodium



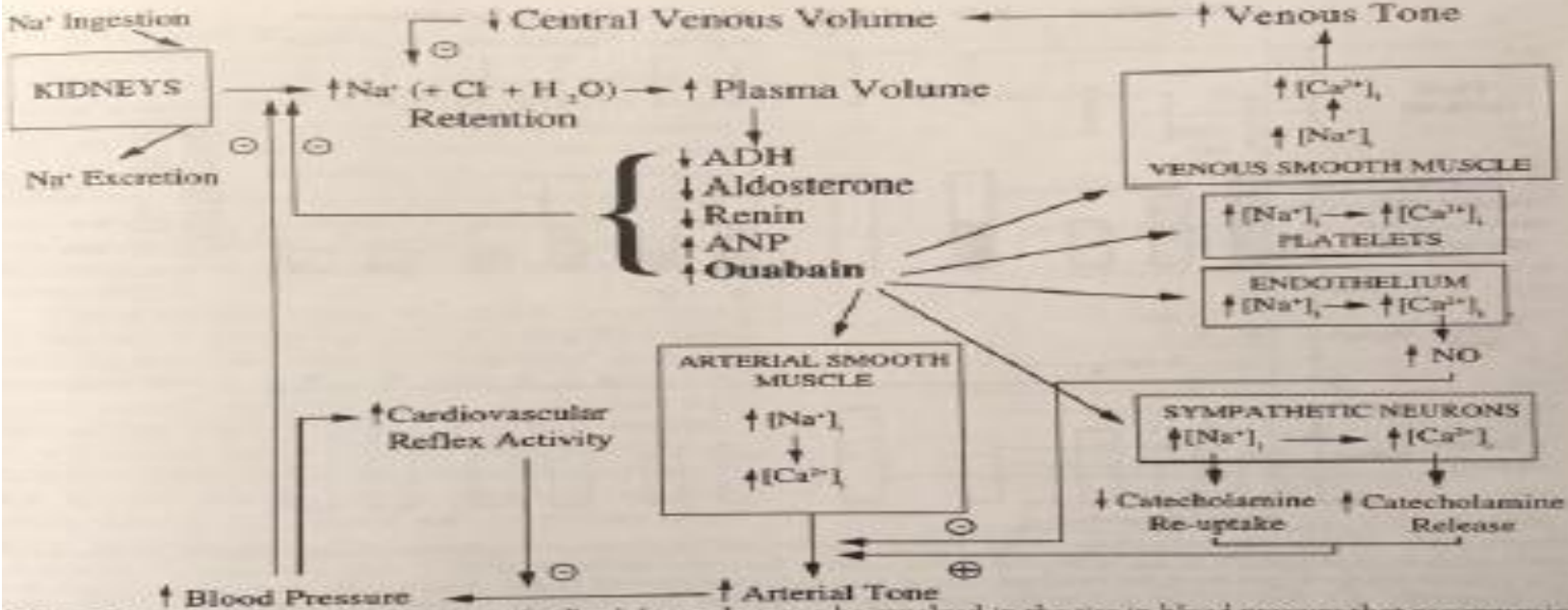


Figure 3.14. Diagram showing various feedback loops that may be involved in the rise in blood pressure that accompanies the attempt to prevent plasma volume expansion when excessive sodium is ingested relative to the innate ability of the kidneys to excrete a sodium load. The increase in intracellular sodium is the direct result of the inhibition of the Na^+ pump by ouabain; the increase in intracellular calcium is then mediated by the Na^+/Ca^{++} exchanger as a result of the rise in sodium. ⊕, positive-feedback loop; ⊖, negative-feedback loop. ADH, antidiuretic hormone; ANP, atrial natriuretic peptides. $[Na^+]_i$, intracellular sodium concentration; $[Ca^{++}]_i$, intracellular calcium concentration. (Reprinted with permission from Blaustein MP. Endogenous ouabain: role in the pathogenesis of hypertension. Kidney Int 1996;49:1748–1753.)

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NDT
Nephrology Dialysis Transplantation

Editorial Comment

Role of endogenous cardiotonic steroids in sodium homeostasis

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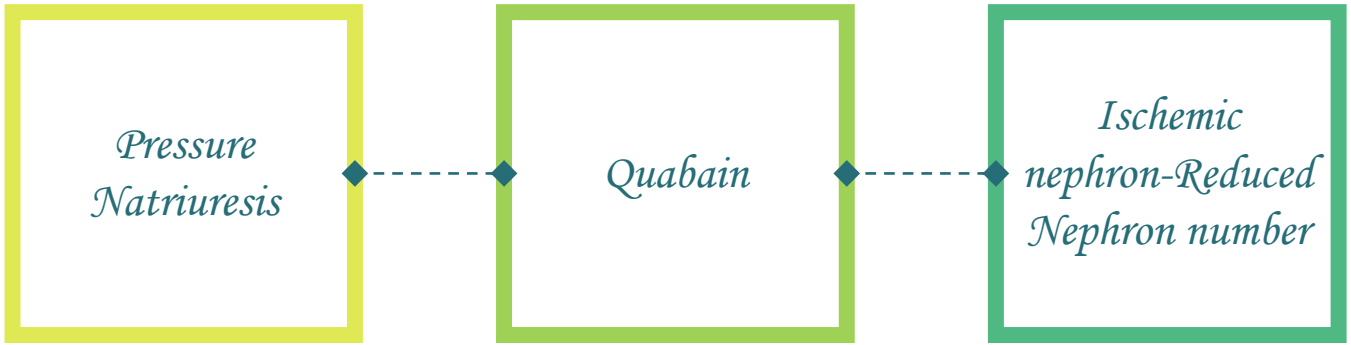
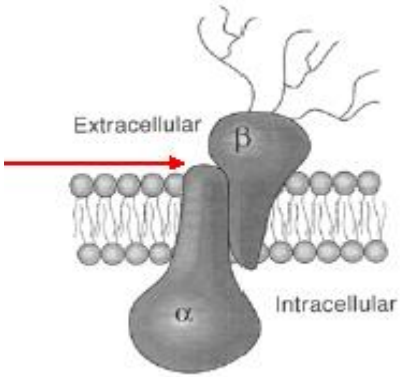
It is evident now that long-term excessive sodium consumption stimulates, in addition to other known mechanisms, the generation of arterial hypertension via the release of various endogenous cardiac glycosides. A long-lasting rise of

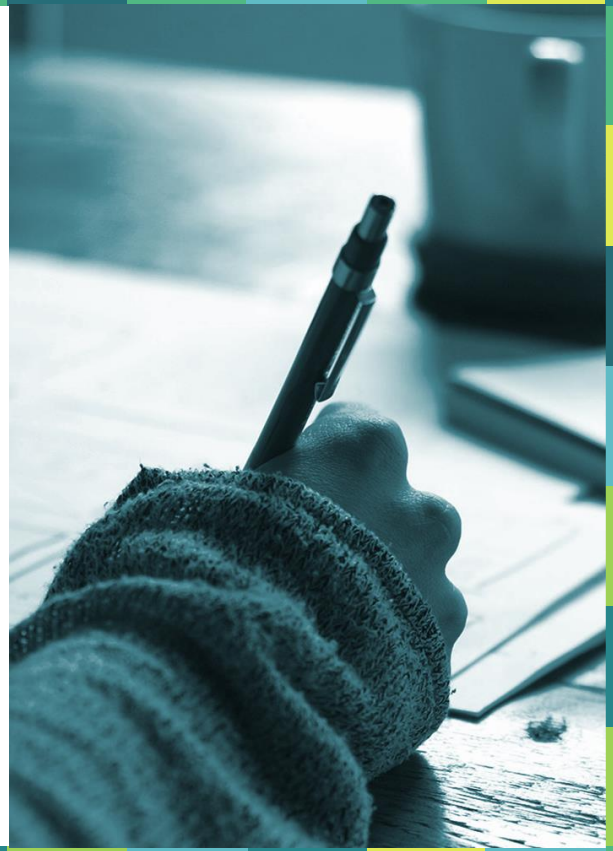
ous endogenous cardiac glycosides. A long-lasting rise of this new type of steroid hormone in blood plasma, and especially that of ouabain and marinobufagenin, leads to arterial hypertension, natriuresis and finally, via altered gene expression patterns, to remodelling of the heart, arterial wall and kidneys. In particular, a prolonged increased secretion

Renal Sodium Retention





And beyond the confines of nephrology: if such Na^+-K^+-ATPase inhibitors have been conserved during evolution so long—from foxglove to *Homo sapiens*—it is difficult to believe that the only reason why nature preserved them was to make life difficult for nephrologists. The substance must obviously have more basic physiologic regulatory functions that so far escape us. The future will hopefully give the answer to the question of what role it plays in normal physiology.



Thanks!

Any questions?

You can find me at

www.athens-nephrology.gr