



Brigham and Women's Hospital
Founding Member, Mass General Brigham

Potassium Disorders

David Bruce Mount MD, FRCPC
Associate/Clinical Chief,
Renal Division BWH
Assistant Professor HMS



David B. Mount, MD, FRCPC



University of Toronto Medical School
Medicine Residency @Toronto General
Hospital, Toronto, Canada

Renal Fellowship @ Brigham and
Women's Hospital (BWH)

Associate/Clinical Chief, Renal BWH

Co-Director, Glomerular Diseases Clinic BWH

Director of Dialysis Services, BWH

Physician, Renal Division VABHS

Research Focus: Urate transport

Clinical Focus: Glomerulonephritis,

Electrolyte disorders, Gout,

Consultative Nephrology



Financial Disclosures

Author, peer reviewer – UpToDate, McGraw Hill
Consultant/advisory boards
– Gout: Shanton Pharma
– ANCA-associated vasculitis: Amgen



A Physiological Approach to Potassium Disorders

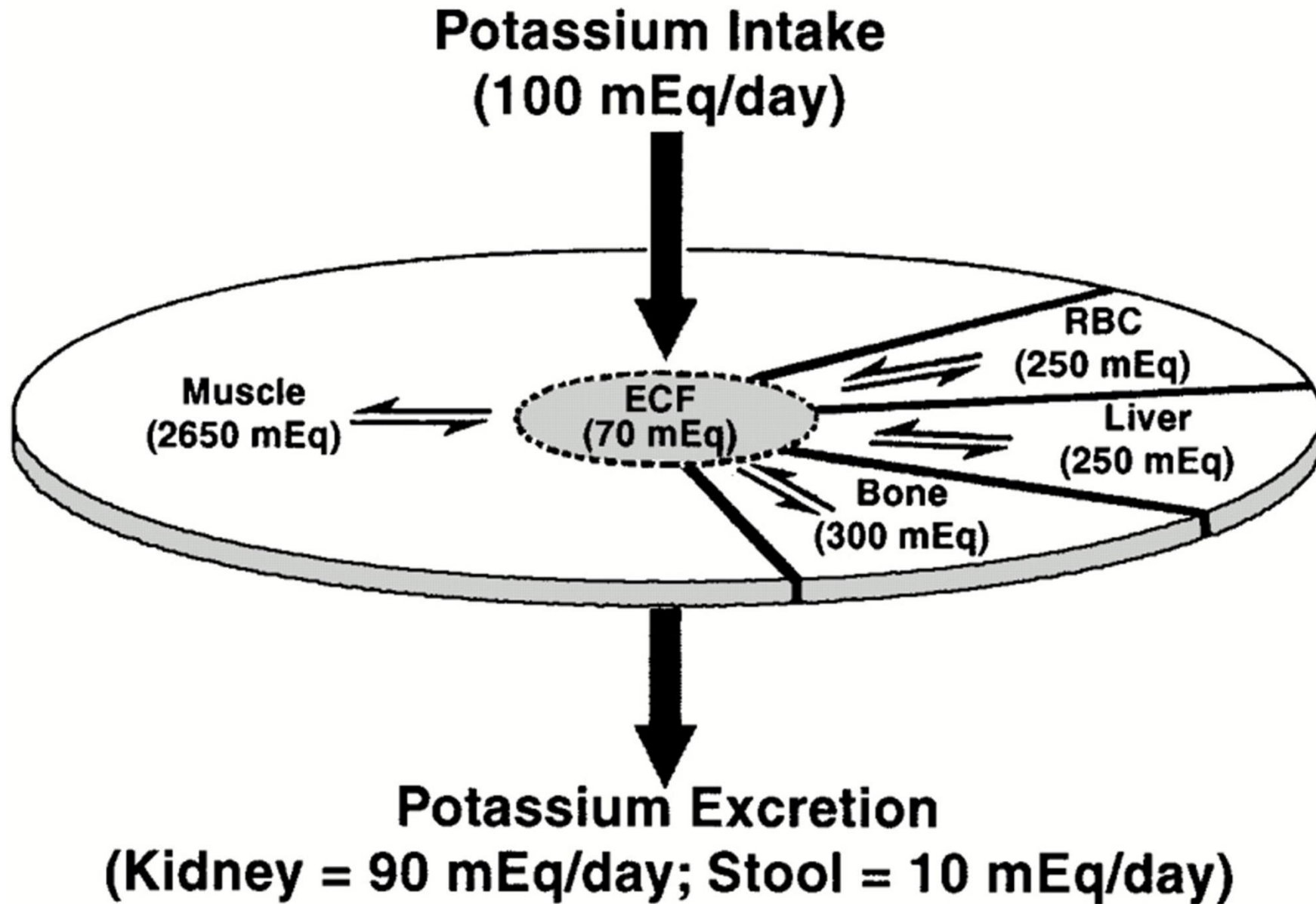
Overview of the relevant physiology

- Regulated K^+ secretion by the distal nephron
- Renal and adrenal RAS and K^+ homeostasis

Hyper/hypokalemia

- Urinary indices and other diagnostic tests
- Clinical consequences
- Treatment of both disorders
- DD_x of both disorders

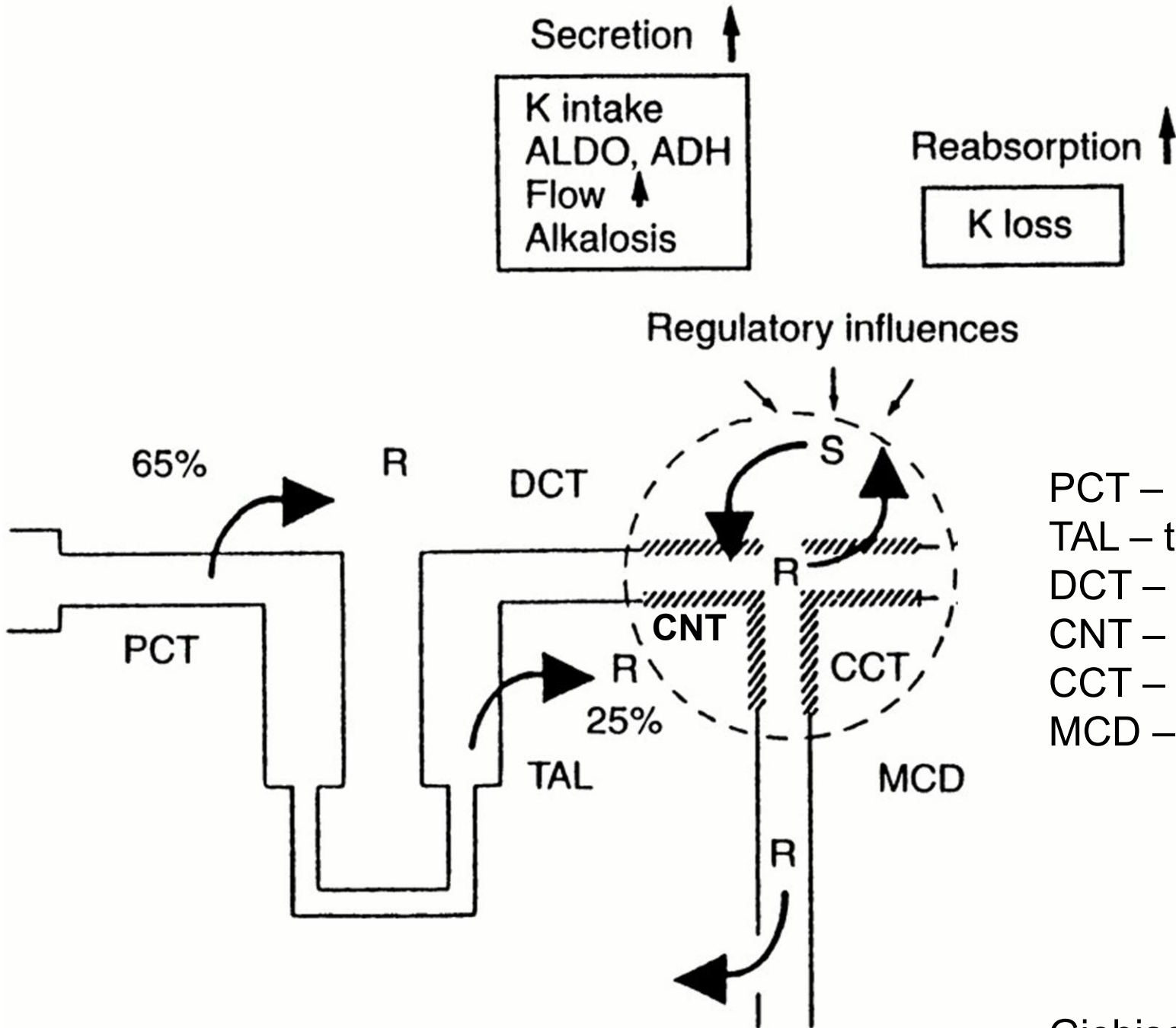




Factors Affecting K^+ Shift

<i>Factor</i>	<i>Transmembrane K^+ Shift</i>
<i>Insulin</i>	↑ uptake
<i>β</i> catecholamine	↑ uptake
<i>α</i> catecholamine	↓ uptake
<i>Acidosis</i>	↓ uptake
<i>Alkalosis</i>	↑ uptake
<i>Hyperosmolarity</i>	↑ efflux



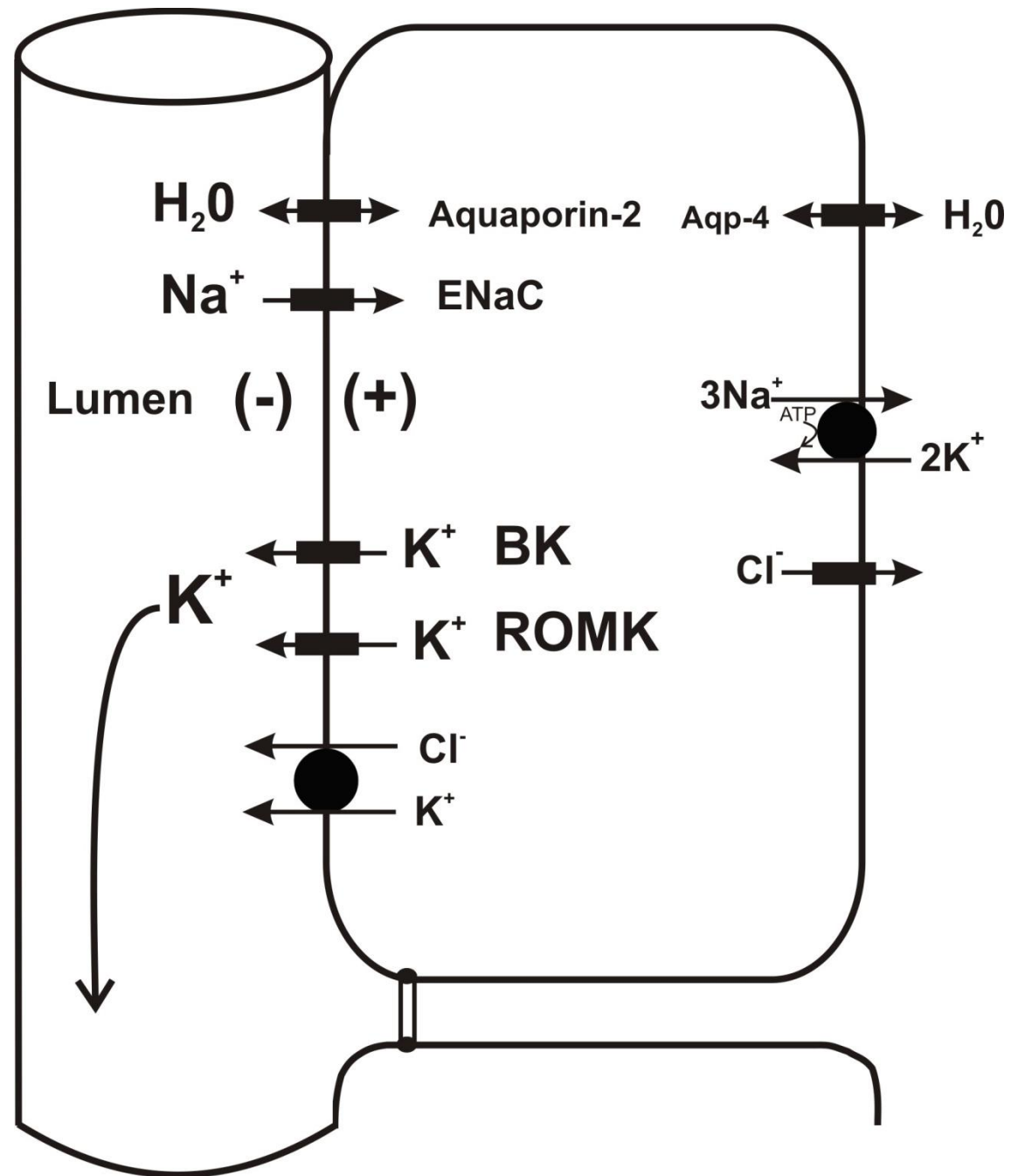


PCT – proximal convoluted tubule
 TAL – thick ascending limb
 DCT – distal convoluted tubule
 CNT – connecting tubule
 CCT – cortical collecting tubule
 MCD – medullary collecting duct



Na^+ , K^+ and H_2O Transport in Principal Cells

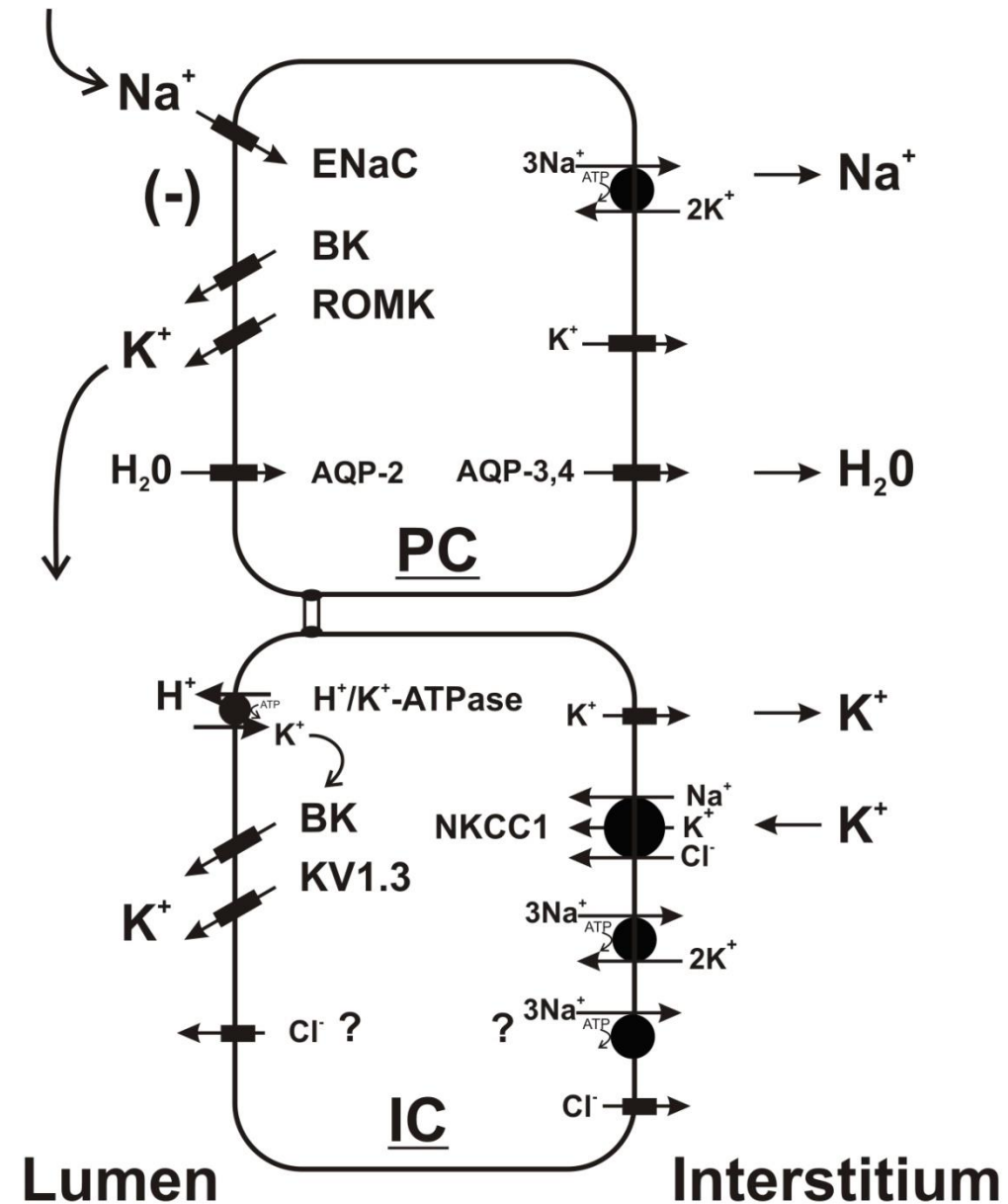
ENaC – epithelial Na^+ channel
ROMK – secretory K^+ channel
Maxi-K/BK – flow-activated K^+ channel



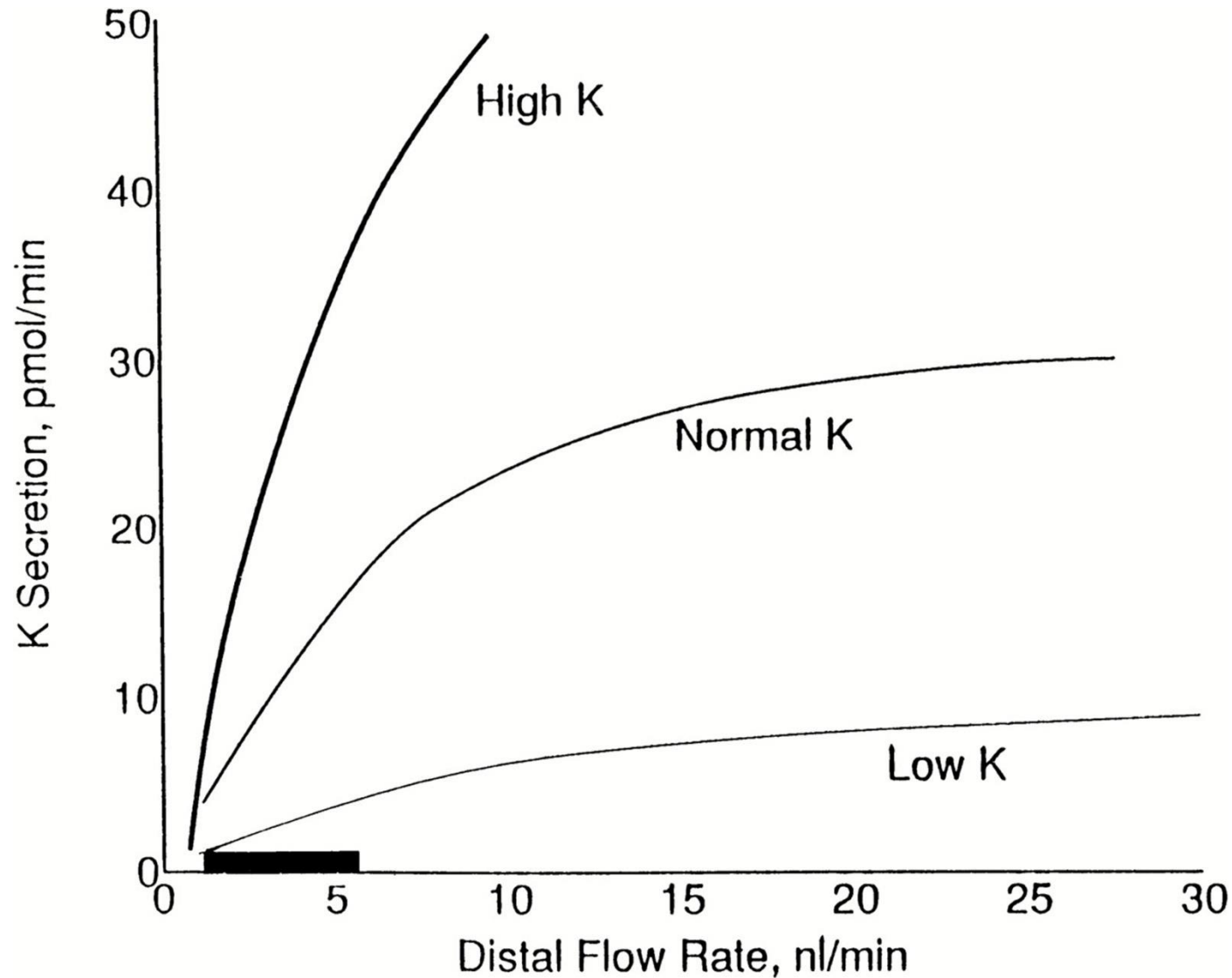
K^+ in Intercalated Cells (IC) and Principal Cells (PC)

TAKE-HOME
MESSAGE:

K^+ excretion also
involves ?
electroneutral
secretion by
intercalated cells.



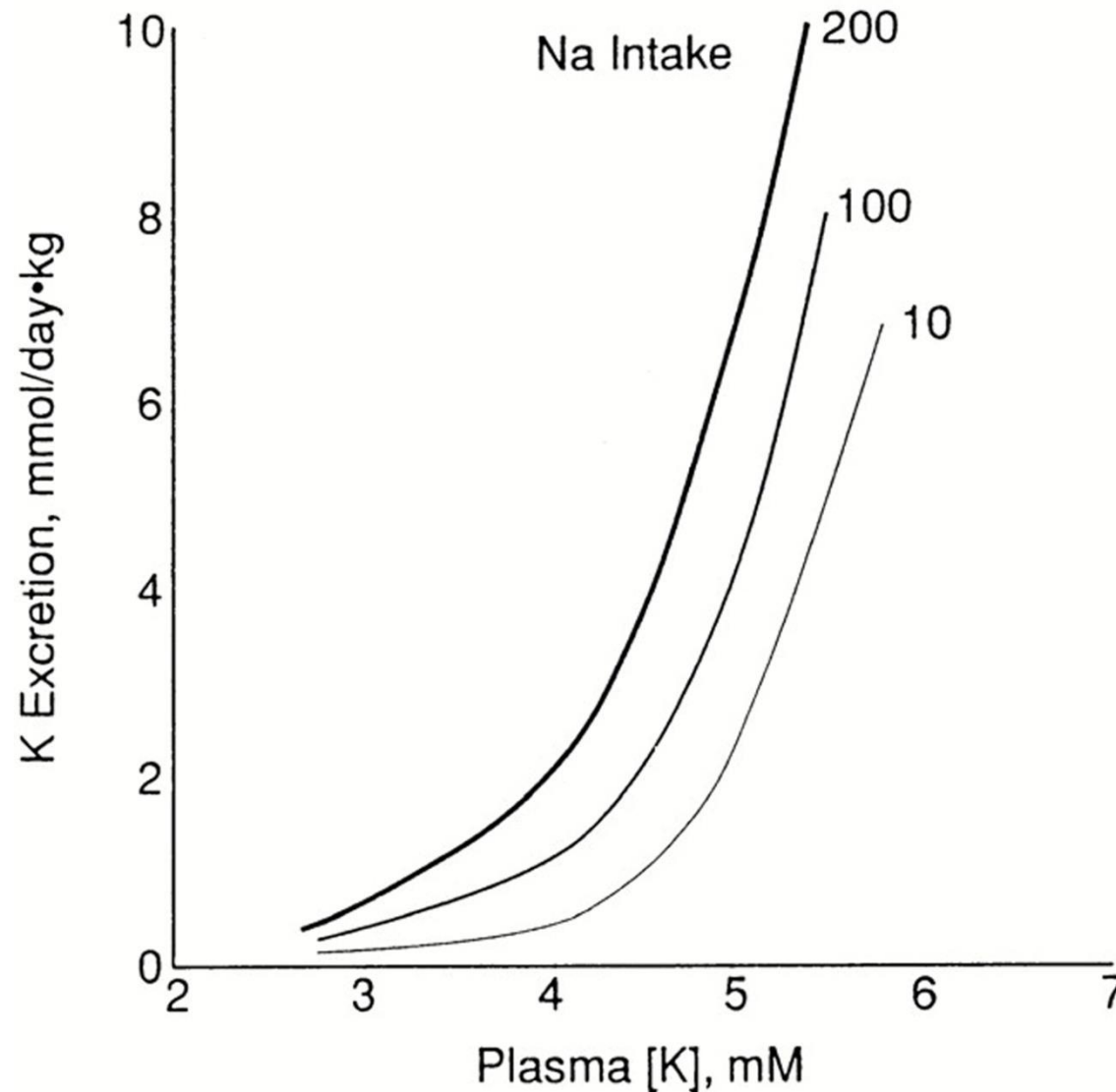
K^+ Secretion is Proportional to Distal Flow



Animals
on
different
 K^+ diets



K^+ Excretion is Dependent on Na^+ Intake



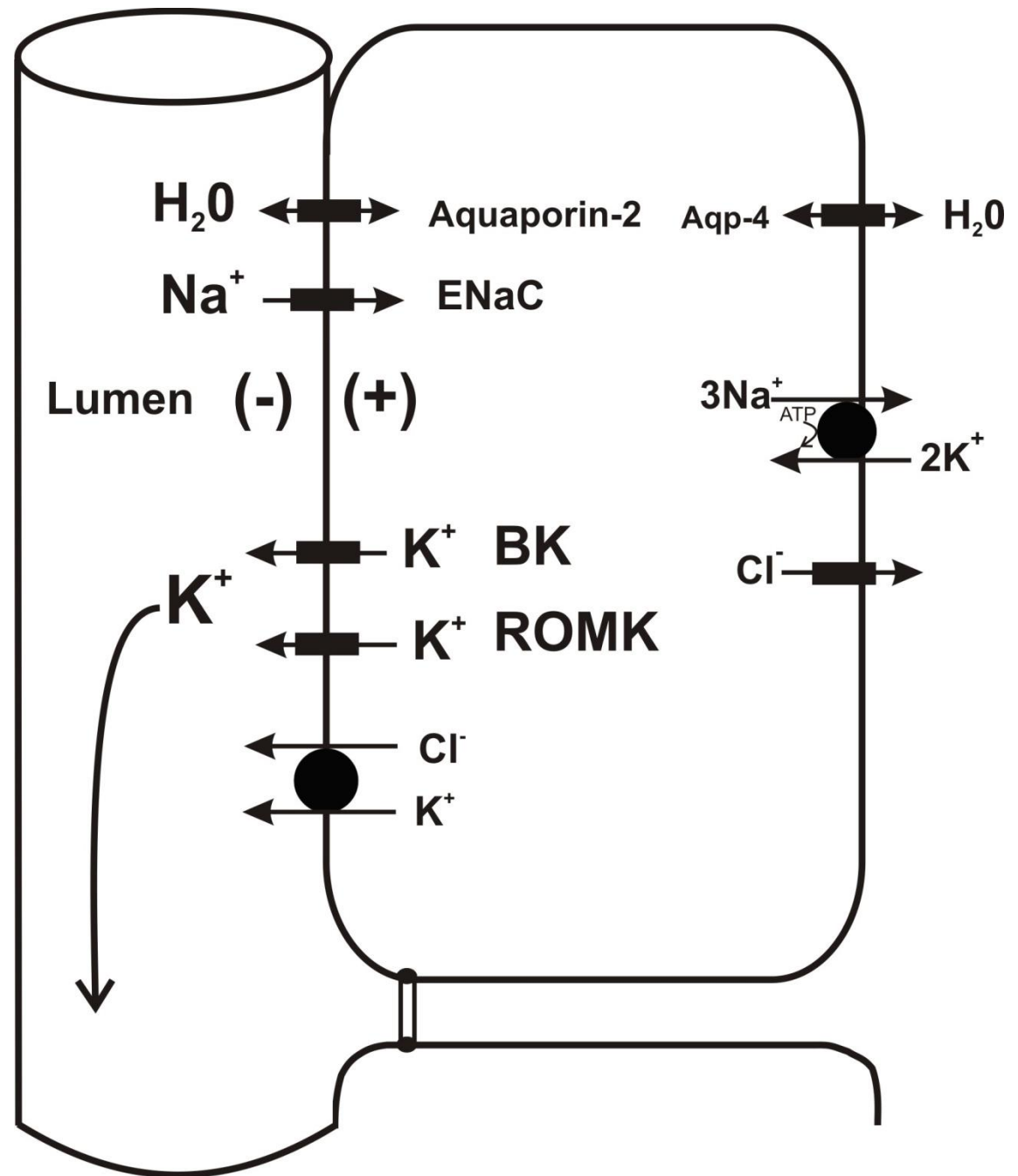
Young et al, *AJP-Renal*, 246, 1984



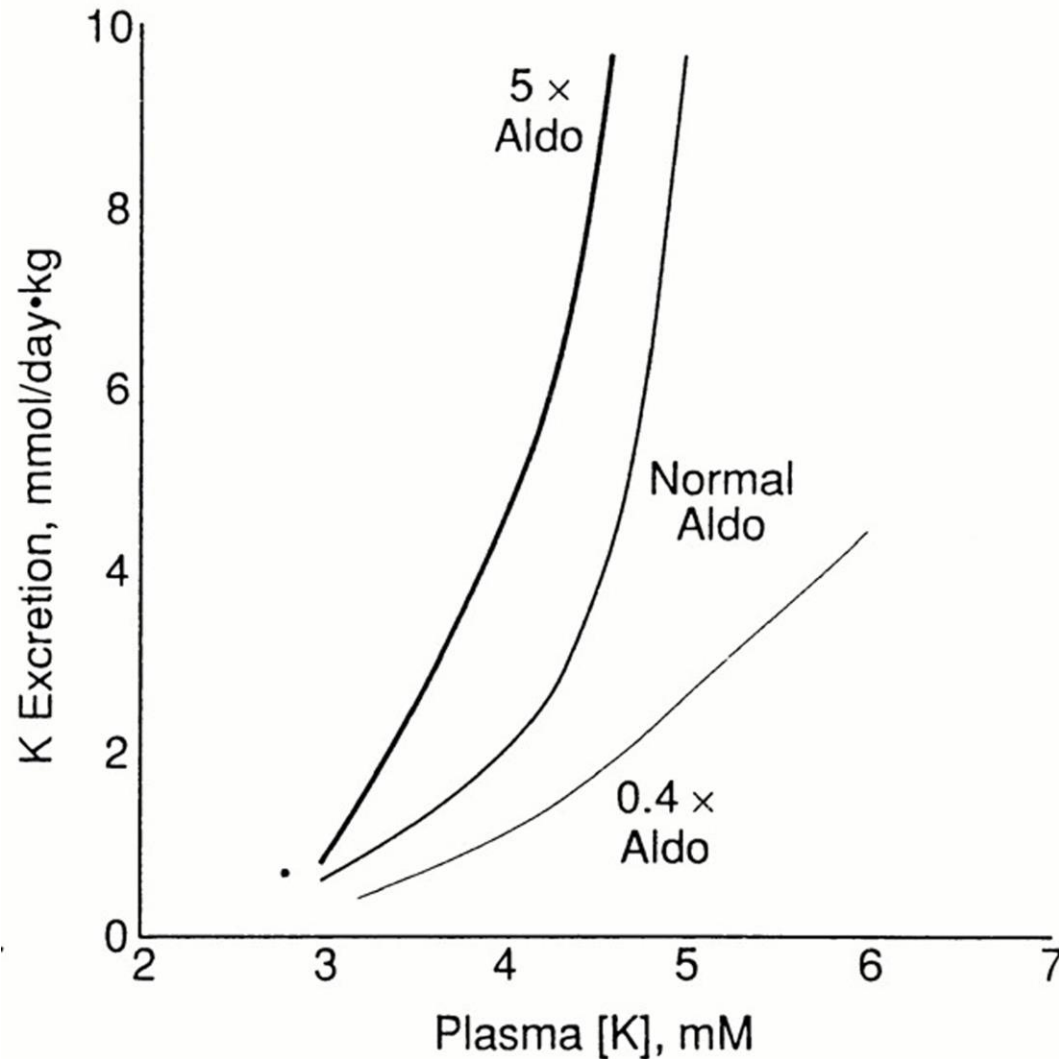
Na^+ , K^+ and H_2O Transport in Principal Cells

TAKE-HOME MESSAGE:

K^+ excretion requires delivery of Na^+ to the distal nephron, to generate a lumen-negative potential difference



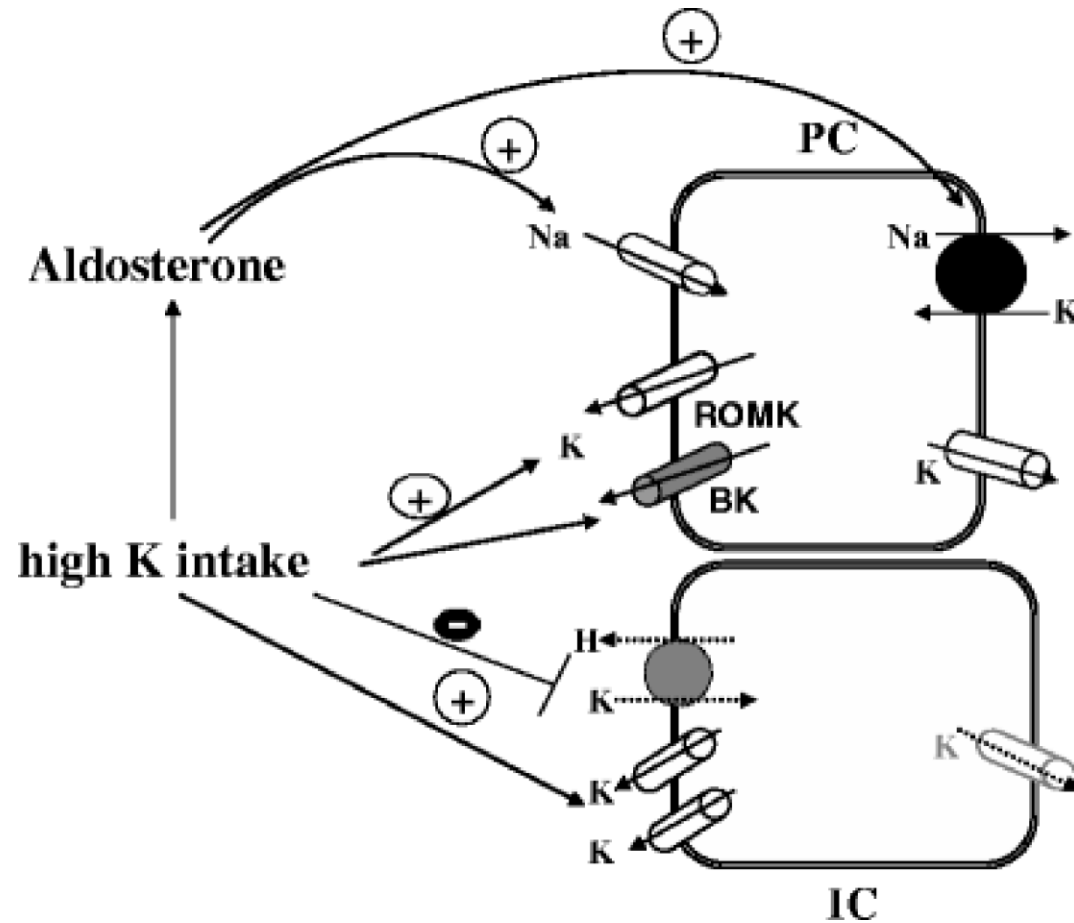
K^+ Excretion as a Function of Plasma K^+ and Circulating Aldosterone



Adrenalectomized
with different levels
of aldo replacement



Aldo-Dependent and Aldo-Independent Regulation of K^+ Excretion



TAKE-HOME:

K^+ channels are mostly regulated by K^+ intake, whereas aldosterone mostly regulates ENaC, and thus the “driving force” for K^+ excretion.

Causes of Hyperkalemia

Increased intake

- K^+ supplements, diet, transfusions, iatrogenic

Decreased renal excretion

- Renal disease, particularly with type IV RTA
- DRUGS
- Adrenal insufficiency – hyperkalemia is not universal

Intra → extracellular shifts

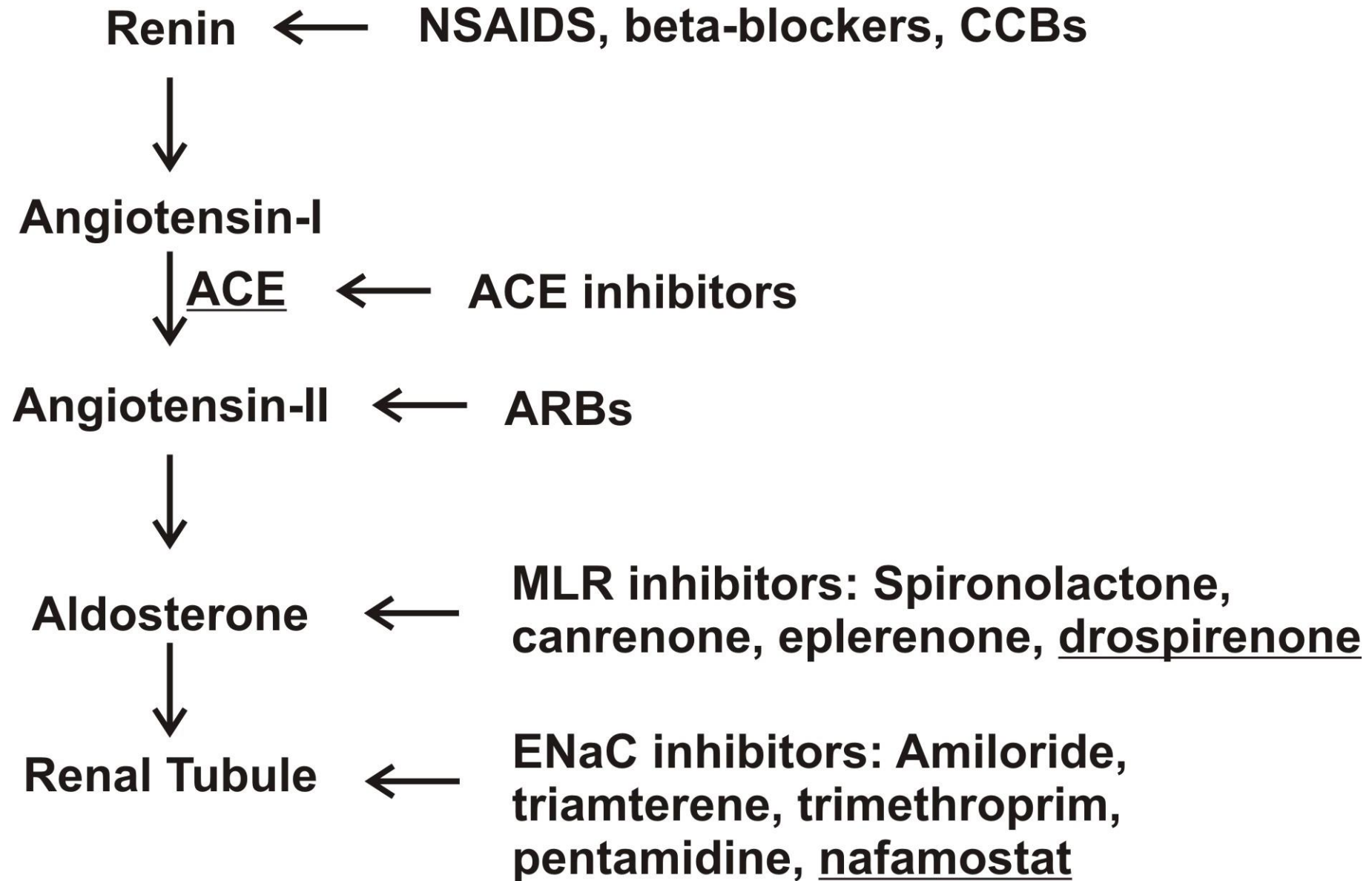
- Hyperosmolarity
- Insulinopenia
- Metabolic acidemia – but NOT with AG acidosis
- DRUGS – Amicar, lysine, K^+ channel blockers

Artifactual

- *in vitro* hemolysis, leukocytosis, thrombocytosis
- “pseudohyperkalemia”



Drugs and the RAS



Take A Dietary History!

Consider both **quantity** and potassium content:

Highest content (>25 mmol/100 g)

- Dried figs, molasses, seaweed

Very high (>12.5 mmol/100 g)

- Dried fruits, nuts, avocados, bran cereals, wheat germ, lima beans

High content (>6.2 mmol/100 g)

- Vegetables: spinach, tomatoes, broccoli, beets, carrots, potatoes
- Fruits: bananas, kiwis, oranges, mangos, kiwis
- Meats: ground beef, steak, pork, veal, lamb



Hyporeninemic Hypoaldosteronism

Hyperchloremic acidosis in ~50%, with urine pH classically < 5.5

Hyperkalemia

↓ Plasma renin activity (PRA) and ↓ aldosterone

↓ Response of PRA to stimuli such as furosemide and captopril

Commonly with ↑ age and ↓ GFR, classically in diabetics

Often hypertensive, with clinical ↑ ECFV



Causes of Hyporeninemic Hypoaldosteronism

Diabetic nephropathy

Acute GN, i.e. nephritic syndrome

[Tubulointerstitial nephropathies, eg. Sickle cell disease] – mostly tubular damage

Drugs, e.g. NSAIDs, COX-2 inhibitors, cyclosporin, tacrolimus

Hereditary causes, e.g.

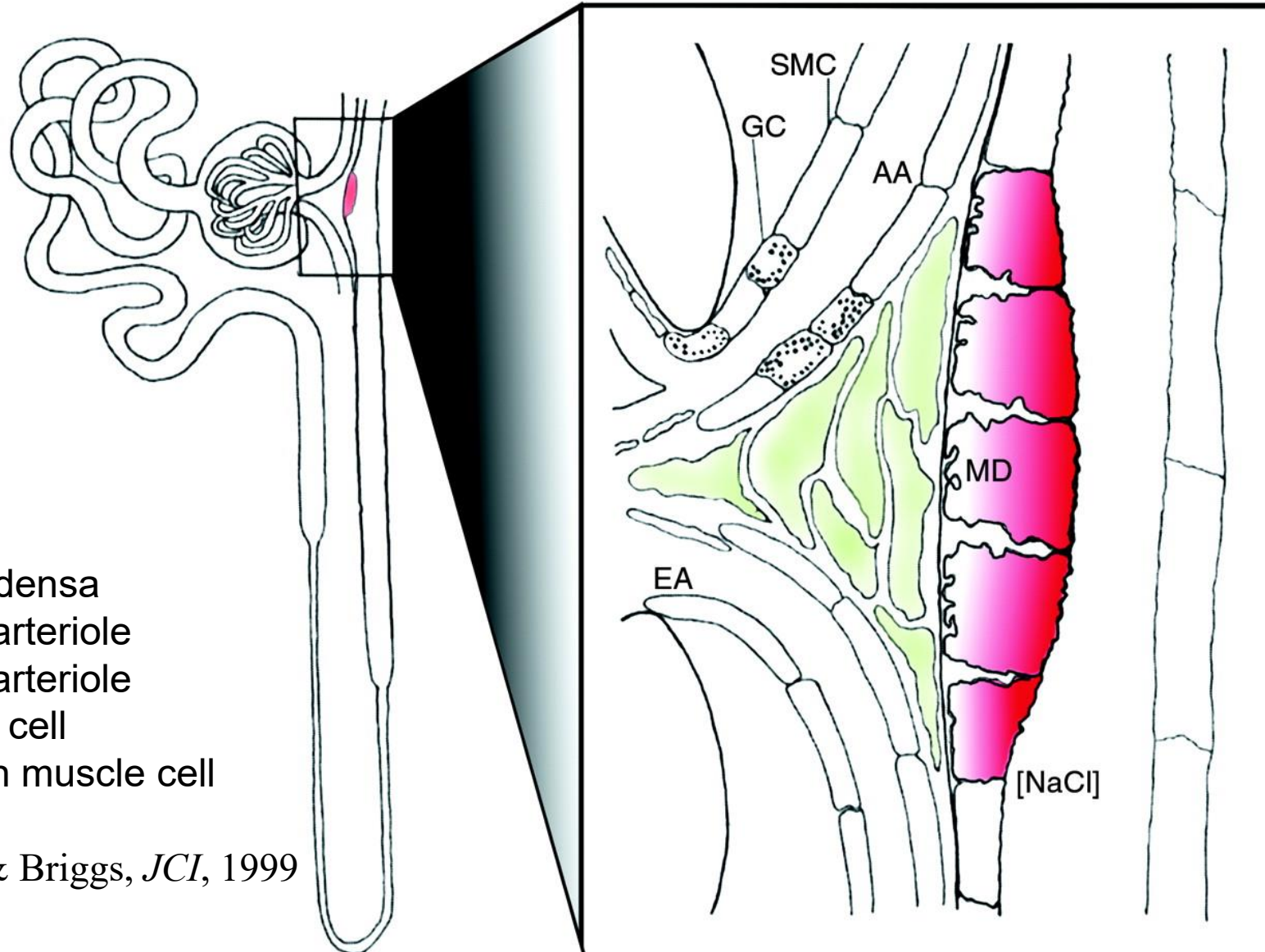
pseudohypoaldosteronism type II



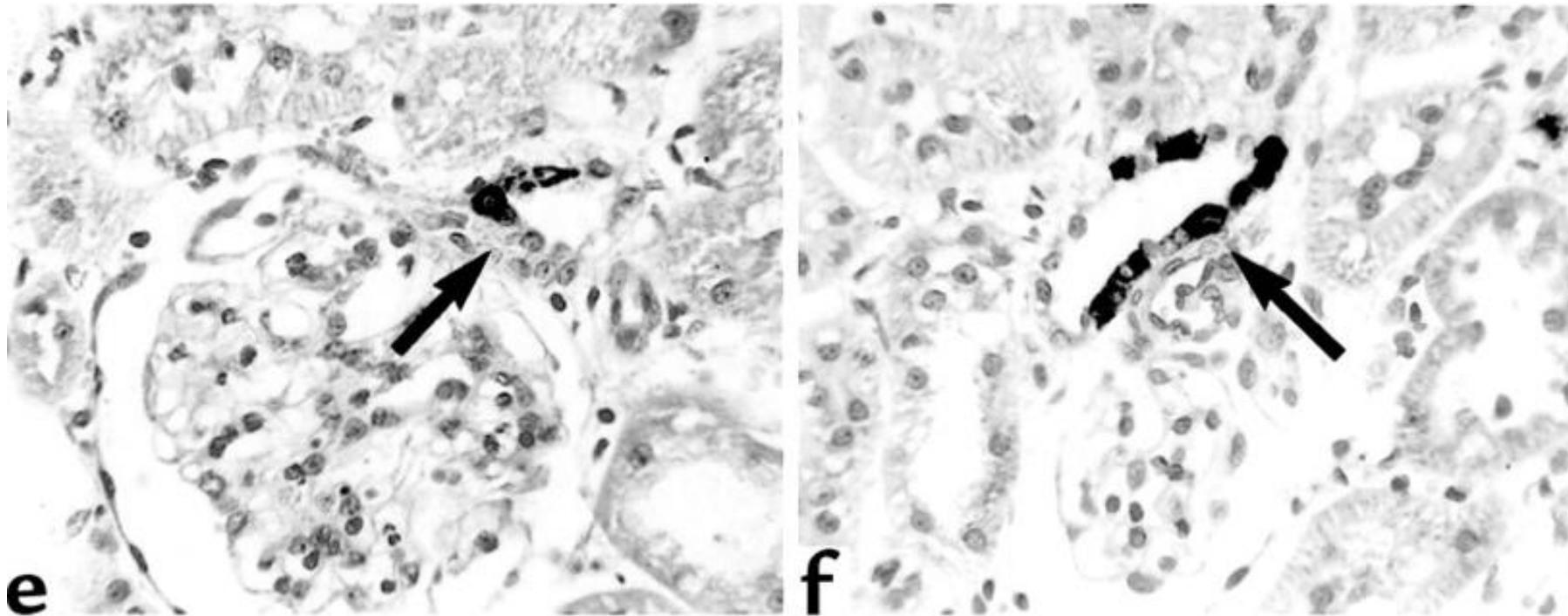
The Juxtaglomerular Apparatus, Intra-Renal Source of Renin

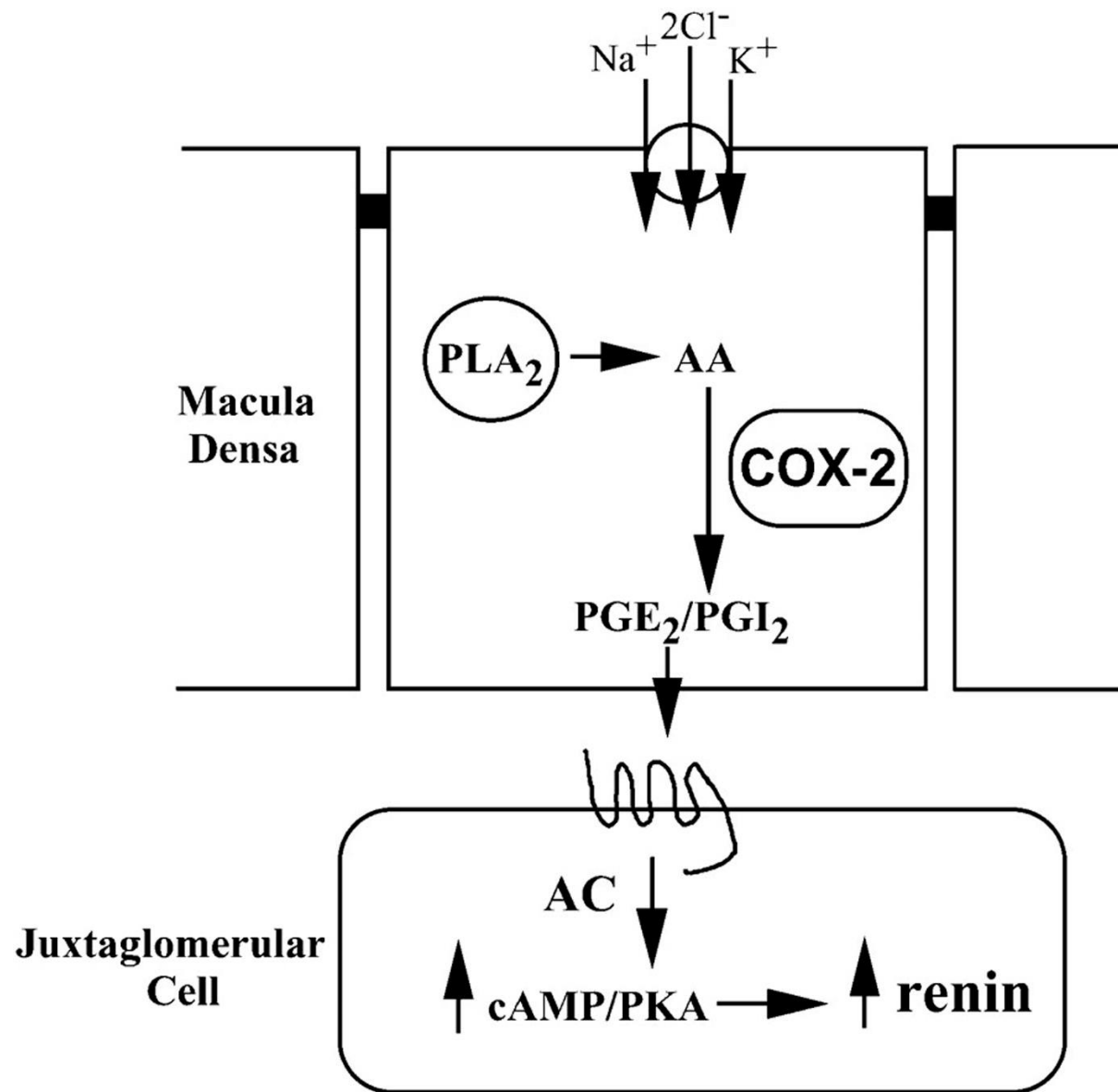
MD, macula densa
AA, afferent arteriole
EA, efferent arteriole
GC: granular cell
SMC: smooth muscle cell

Schnermann & Briggs, *JCI*, 1999



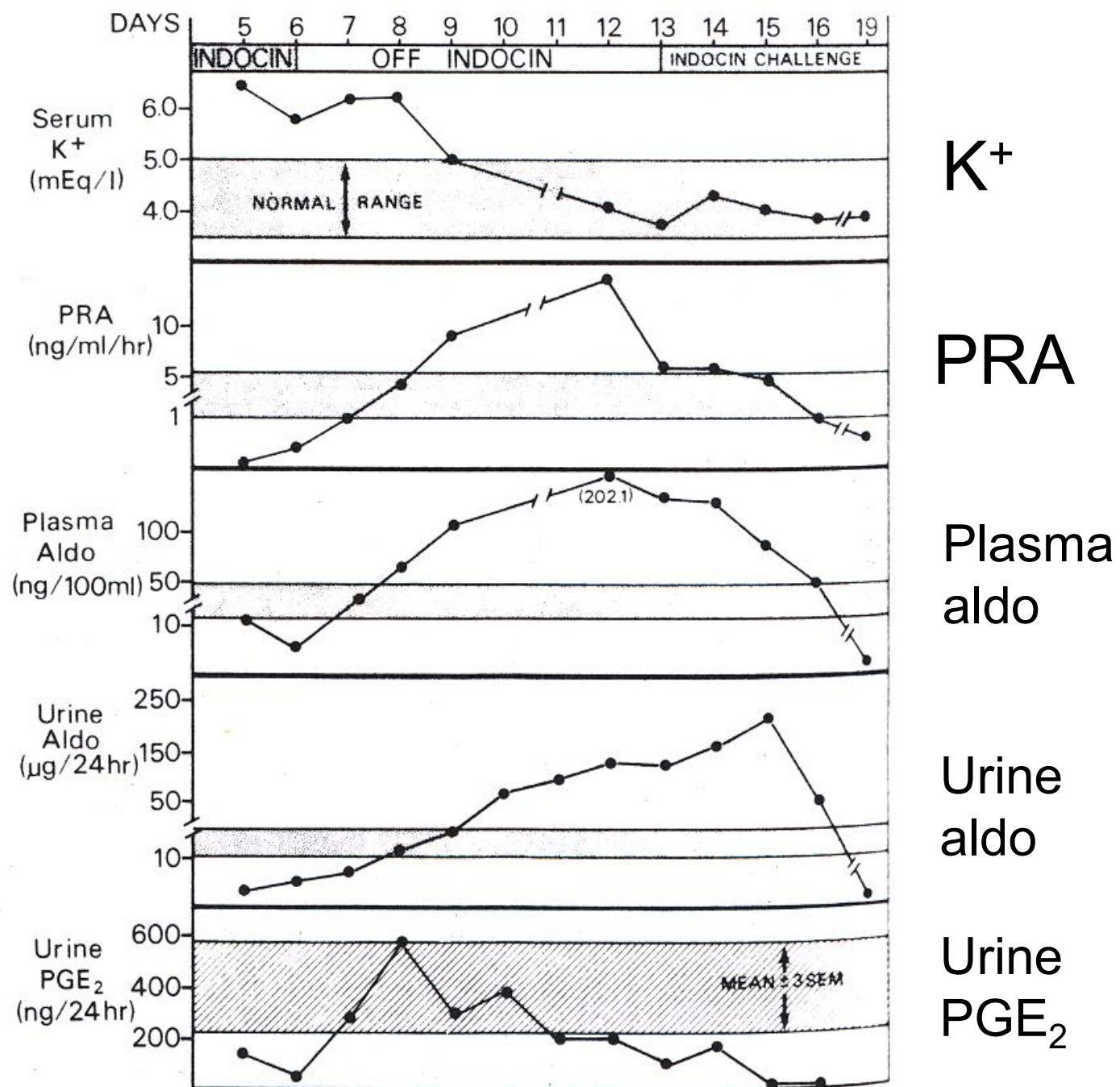
COX-2 is Expressed in the Macula Densa





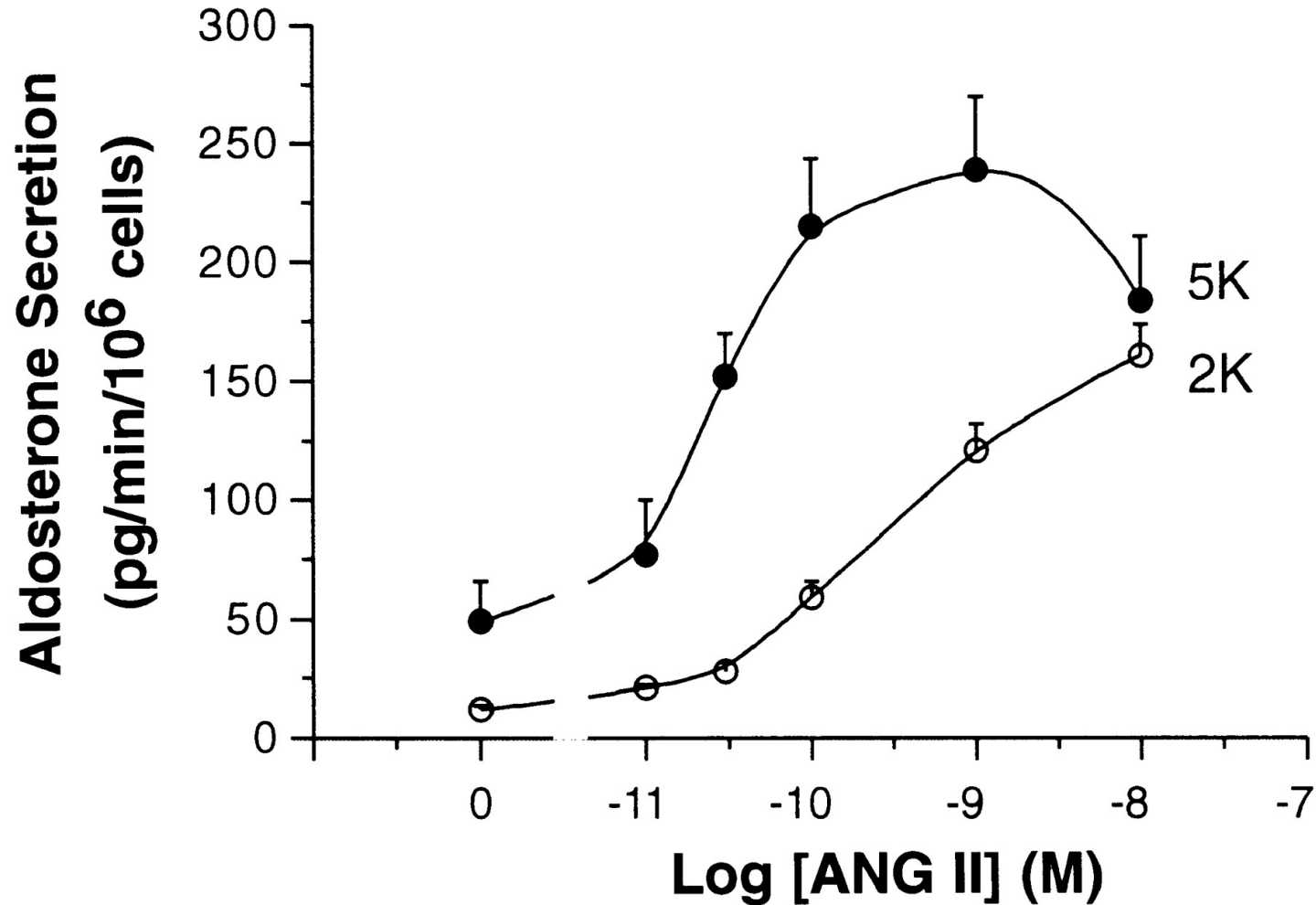
COX-2 and Paracrine Regulation of Renin Release by the JGA

NSAIDs and Type IV RTA



Tan et al, *Ann Int Med*, 90, 1979

Adrenal Aldosterone Release due to $\uparrow[K^+]$ is Modulated by ANG-II



Aldo release by adrenal cells, in response to K of 5 vs. 2 mM

Chen et al, *AJP-Renal*, 276, 1999

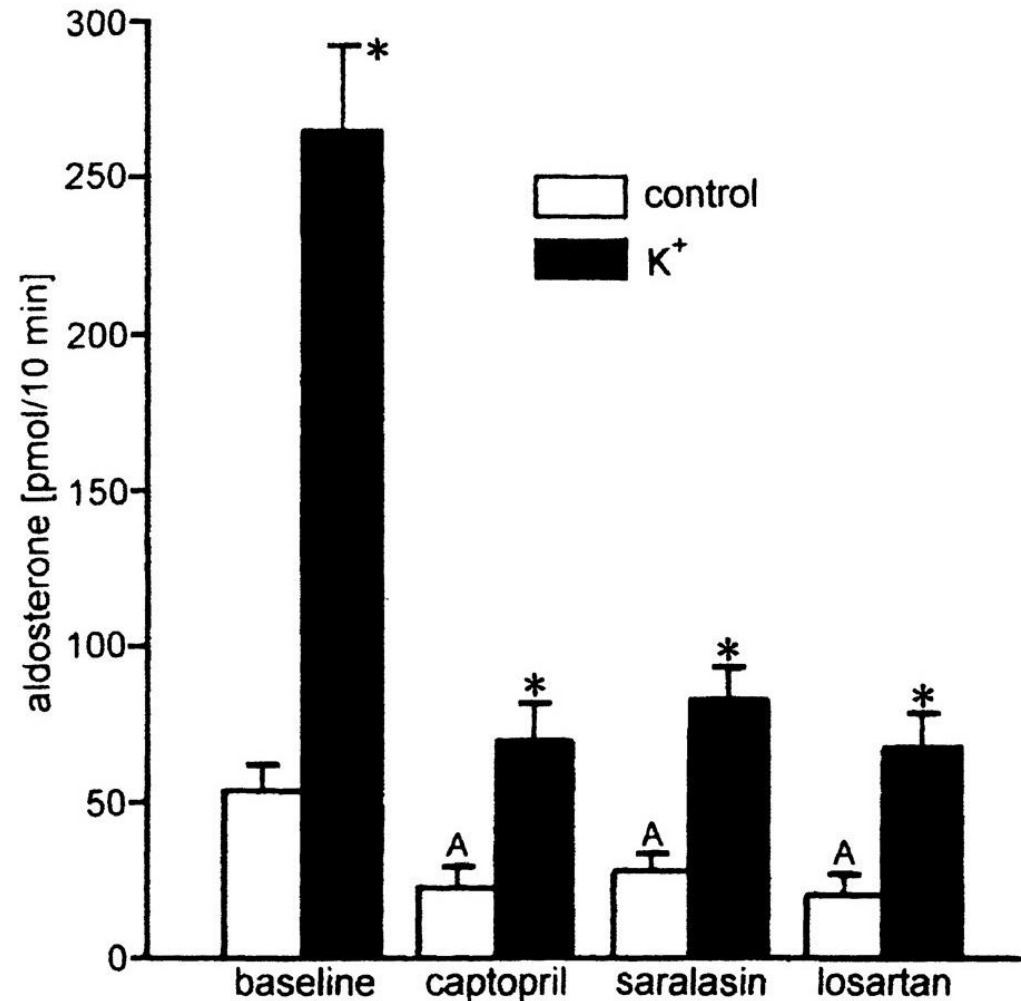


An Intact Adrenal RAS is Required For the Response to Hyperkalemia

Aldo release
from perfused
adrenals,
NaCl-restricted
animals

TAKE-HOME MESSAGE:

RAS inhibition
blunts adrenal
response to hyperK



Mazzocchi et al, AJP-Renal, 278, 2000

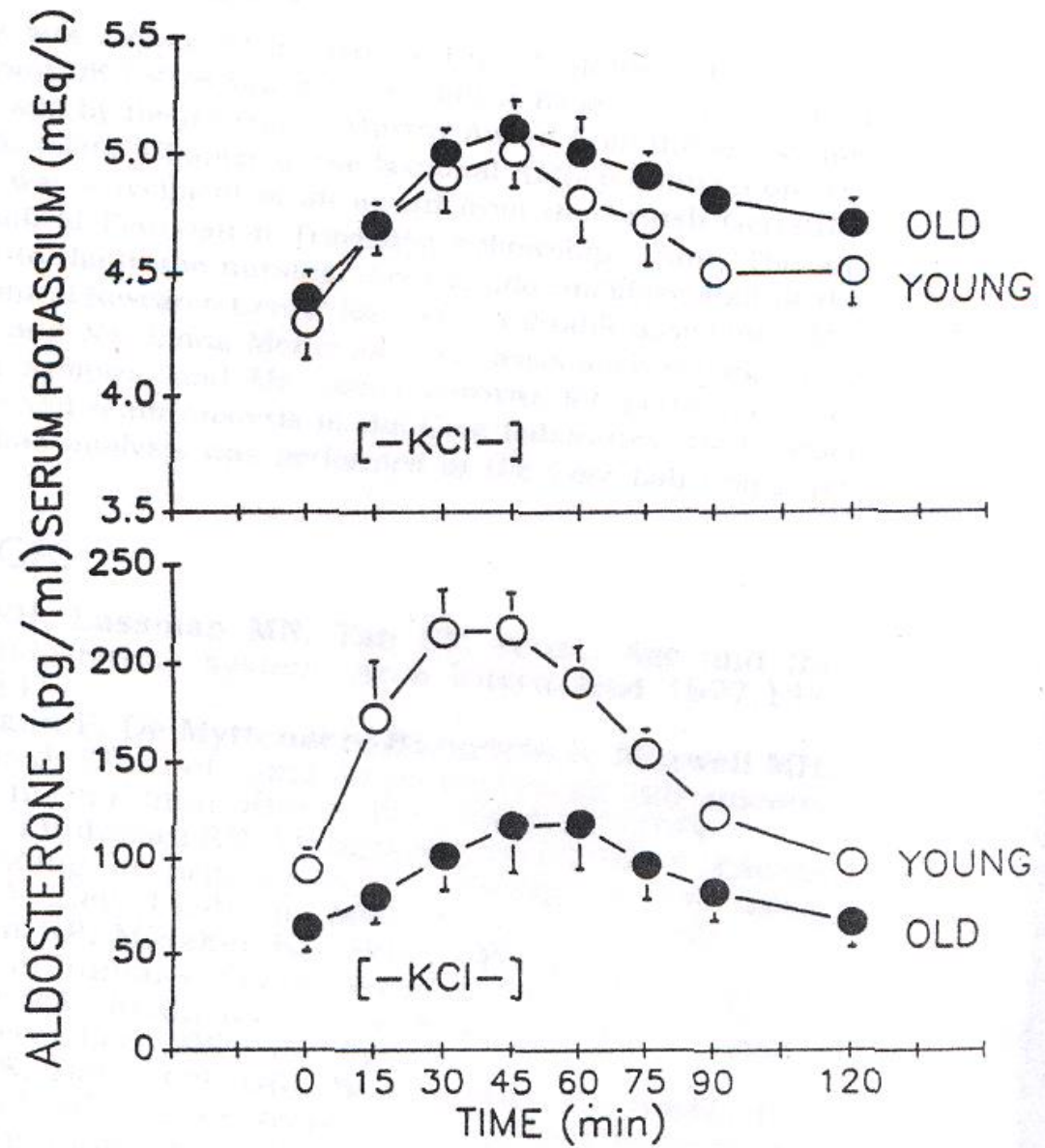


Hyporeninemic Hypoaldo in the Elderly: Correlation with Increased ANP

<i>Age</i>	<i>K⁺</i>	<i>Creat</i> (μ M)	<i>Aldo</i> (pM)	<i>PRA</i> (ng/L/s)	<i>ANP</i> (pM)
<i>Patients:</i>					
<i>81</i>	5.7	265	<65	0.14	3000
<i>94</i>	4.9	88	302	0.06	321
<i>83</i>	5.3	71	202	0.58	1107
<i>84</i>	5.1	115	83	0.06	387
<i>Mean :83</i>	5.3	147	216	0.34	1186
<i>Healthy:</i>					
<i>Mean: 75</i>	4.1	106	211	0.17	91

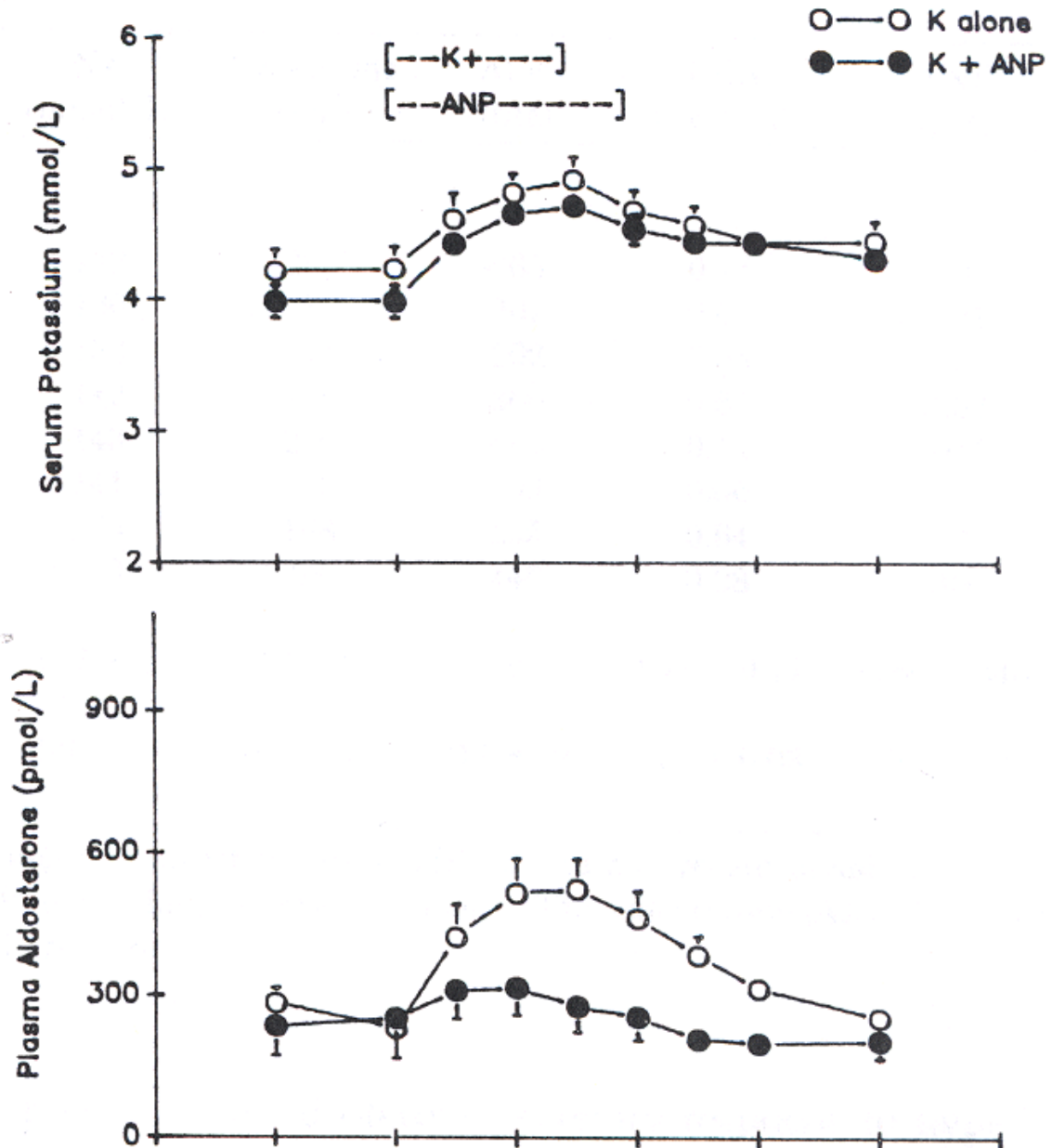


Aldo Response to K-Cl Infusion



ANP Blunts the $\uparrow$ Aldo from $\uparrow K^+$

Healthy young
subjects, infused
With K +/- ANP



Clark et al, *J Am Soc Nephrol*. 1995 Nov;6(5):1459-62



TAKE HOME MESSAGES:

The Renin-Angiotensin-Aldosterone Axis and Hyperkalemia

ANP, systemic and local RAS, and prostaglandins all affect renal renin release **AND** adrenal aldosterone release, i.e. remember the *adrenal* effect

The role in hyporeninemic hypoaldosteronism of volume expansion and $\uparrow$ ANP/BNP

→ $\downarrow$ renal renin and $\downarrow$ adrenal aldosterone release



Question #1

You are referred a 17 year-old high school student for management of high blood pressure. He has not seen a physician since childhood, is on no medications.

He denies drug abuse, including cocaine.

FH: His 50 year-old father is also hypertensive, with a history of renal stones.

Since you have access to a clinical research center, you admit the father and son for biochemical profiling while ingesting a diet with rigorously controlled salt content.



Parameter	Son		Father	
Dietary Na ⁺ (mmol/day)	200	10	200	10
BP	150/90	110/64	142/90	110/70
K ⁺	6.0	4.5	5.6	4.6
Cl ⁻	119	102	114	102
HCO ₃ ⁻	18	25	21	27
pH	7.33	7.41	7.36	7.38
PRA	0.2	6.3	0.4	2.6
Aldo	15	61	13	41
ANP	48	9	32	14
FE _K (%) basal	7.8	10.3	8.5	7.8
FE _K (%) saline	8.1	33.8	8.2	15.0



Which of the following is the most appropriate therapy for this patient?

- A. Aggressive K restriction
- B. NaCl restriction to 10 mEqu/day
- C. Nifedipine
- D. Amiloride
- E. Hydrochlorothiazide



Pseudohypoaldosteronism Type II (PHA-II)

Also known as Gordon's syndrome or the "chloride-shunt" disorder, familial hypertension with hyperK

The "mirror image" of Gitelman's syndrome due to loss of function in the thiazide-sensitive NaCl cotransporter:

- hypertension
- hyperkalemic acidosis
- suppression of plasma renin, aldosterone
- **hypercalciuria**, nephrolithiasis

Responsive to thiazides

Autosomal dominant transmission, rarely recessive;
five different genes, four characterized



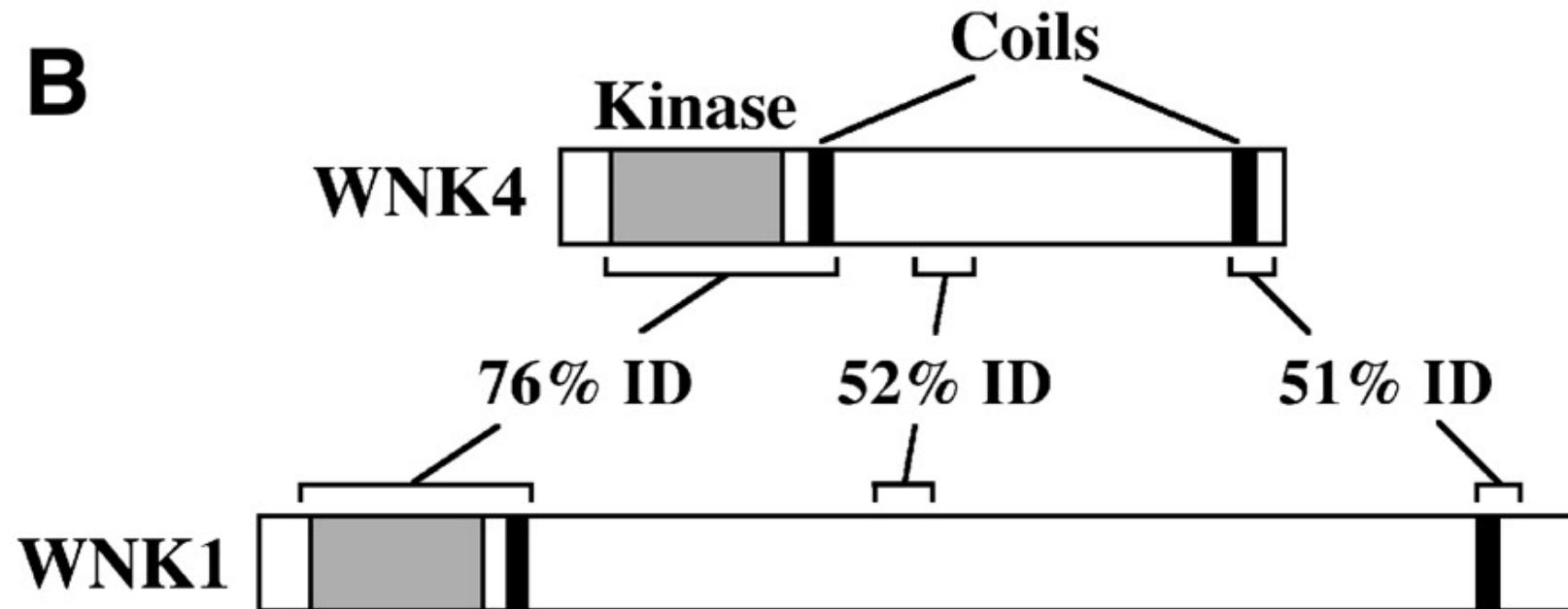
Human Hypertension Caused by Mutations in WNK Kinases

**Frederick H. Wilson,¹ Sandra Disse-Nicodème,^{2*}
Keith A. Choate,^{1*} Kazuhiko Ishikawa,^{1*} Carol Nelson-Williams,¹
Isabelle Desitter,² Murat Gunel,¹ David V. Milford,³
Graham W. Lipkin,⁴ Jean-Michel Achard,⁵ Morgan P. Feely,⁶
Bertrand Dussol,⁷ Yvon Berland,⁷ Robert J. Unwin,⁸
Haim Mayan,⁹ David B. Simon,¹ Zvi Farfel,⁹ Xavier Jeunemaitre,²
Richard P. Lifton^{1†}**

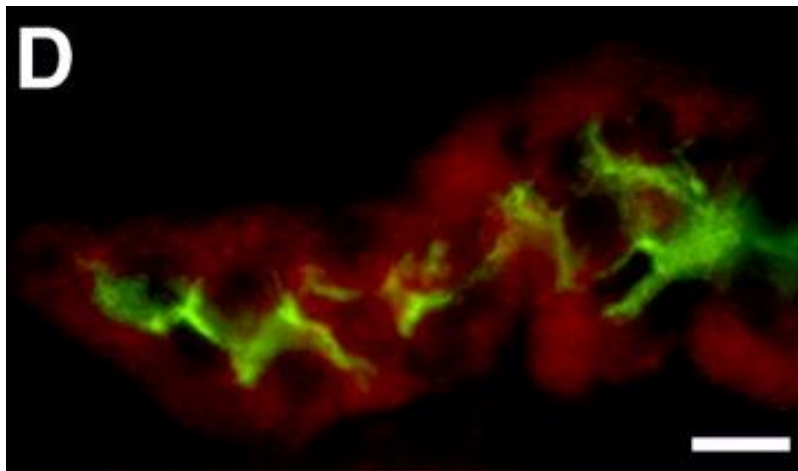
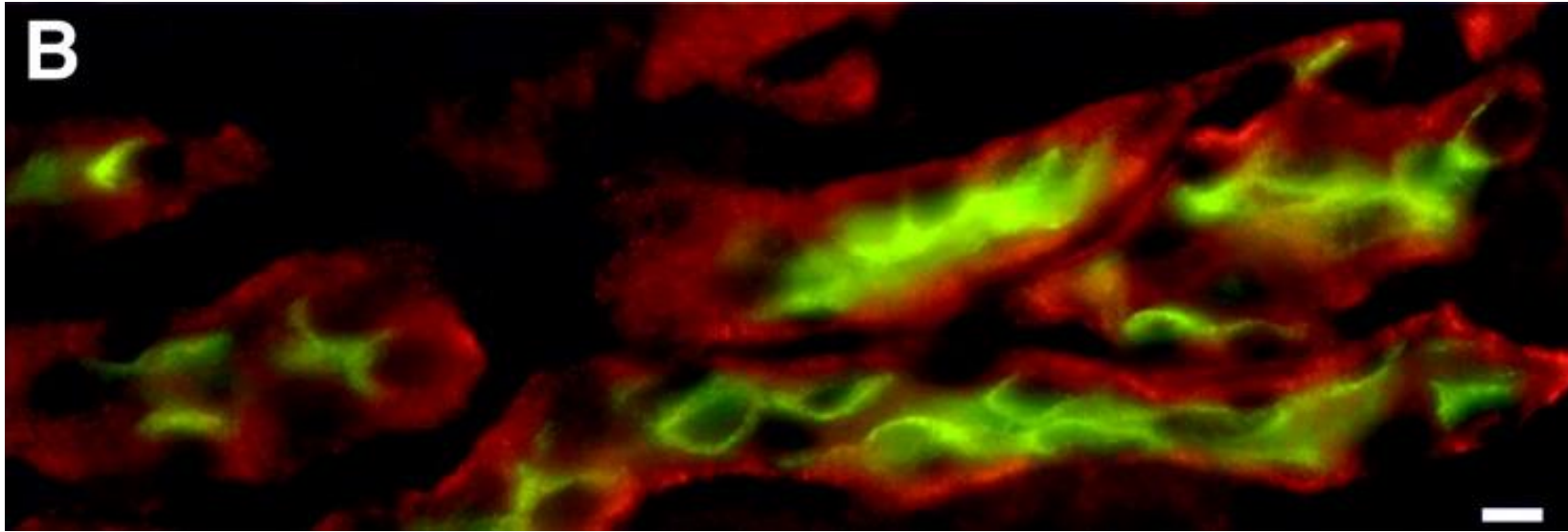
SCIENCE VOL 293 10 AUGUST 2001



WNK1 and WNK4 are Homologous Serine/Threonine Kinases

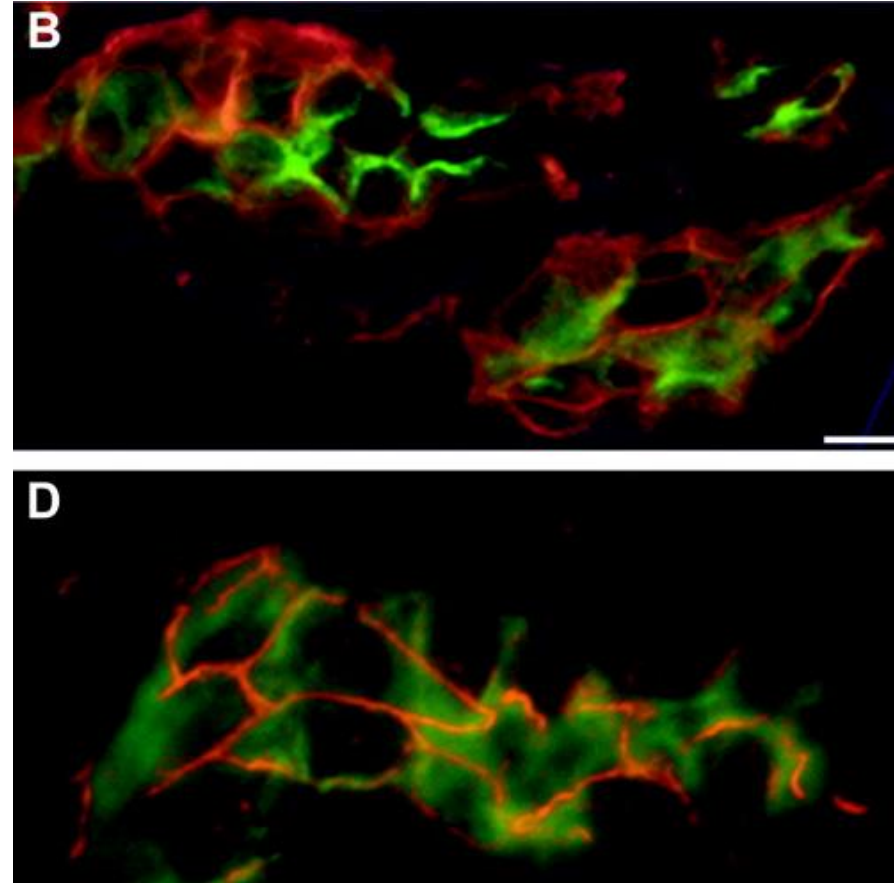


WNK1 is Expressed in the DCT and CCD



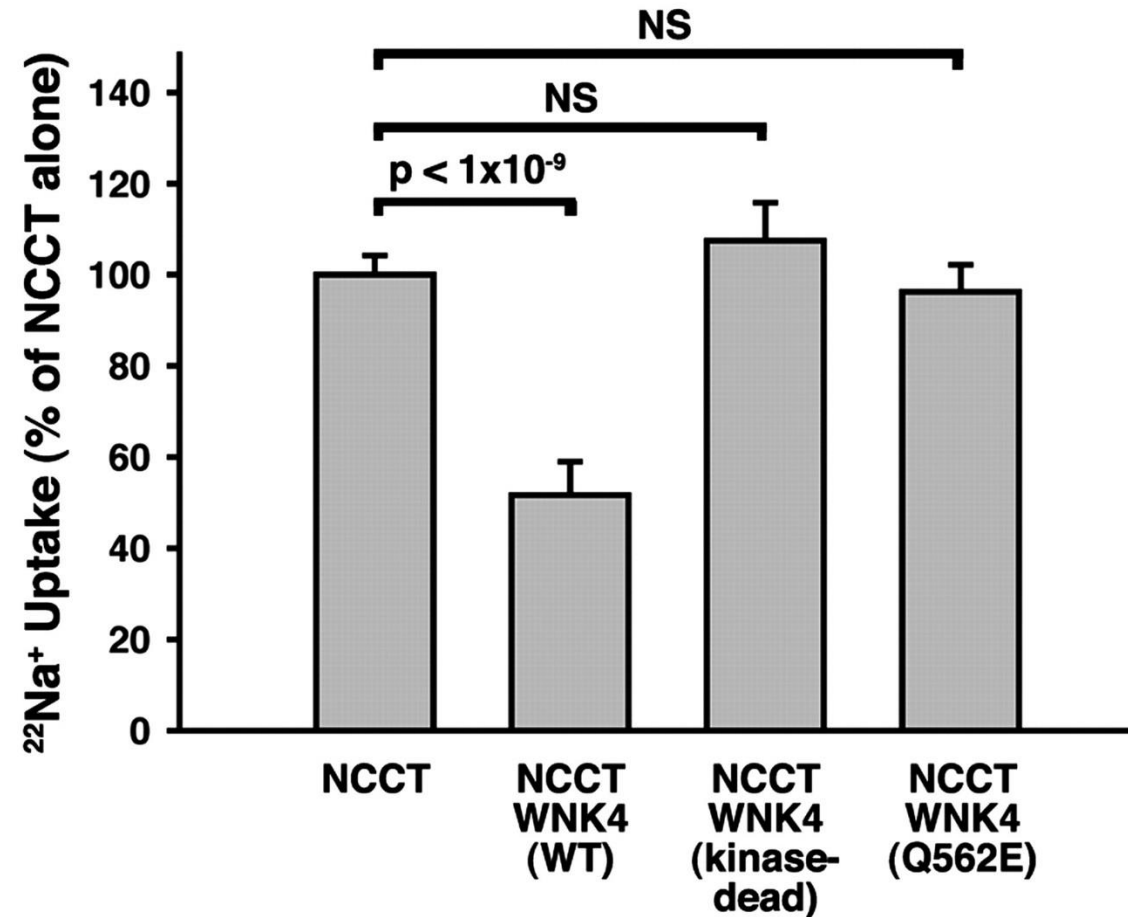
B) WNK1 (red) and Aqp-2 (green)
D) WNK1 (red) and NCC (green)

WNK4 is Expressed in the DCT and CCD



- B) Co-expression of WNK4 (red) and Aqp-2 (green)
D) Co-expression of WNK1 (red) and NCC (green)

PHA-II Mutations in the WNK4 Kinase Abrogate Its Inhibition of the Thiazide-Sensitive Na-Cl Cotransporter



NCCT – Na-Cl cotransporter

Choate et al, *PNAS*, 100, 2003

The Aldosterone Paradox: Integrated Distal Na^+ and K^+ Transport

↑ in Ang-II by hypokalemia/ K^+ restriction → inhibition of apical secretory K^+ channels (ROMK)

K^+ -dependent regulation of the NCC Na^+ - Cl^- cotransporter in DCT → Na^+ delivery to principal cells.

- suppression of NCC by hyperkalemia/ K^+ loading
- Ang-II-dependent ↑ of NCC in hypokalemia/ K^+ restriction.

K^+ -dependent modulation of WNK kinases.

Aldo-dependent induction of *electroneutral* Na^+ - Cl^- transport (coupled Na^+ -anion exchangers) in the CCD → no effect on electrogenic K^+ secretion.

Electroneutral, ENaC-independent K^+ secretion, ? primarily in intercalated cells.



Hypokalemia - Causes

Pseudohypokalemia – leukocytosis, with uptake of K^+ by WBCs, e.g. in AML

Redistribution

- Insulinopenia → DKA
- Sympathomimetics
- β_2 -agonists, dopamine, theophylline
- Hypokalemic periodic paralysis, incl. thyrotoxic
- Acute anabolic state → pernicious anemia

Non-renal loss → skin, stomach (suctioning), intestine (diarrhea, laxatives, K^+ secretion)



Question #2

You are asked to evaluate a female patient with intestinal pseudo-obstruction (Ogilvie's syndrome), with diarrhea and profound hypokalemia.

Meds include metoprolol, risperidone, insulin

Exam and imaging notable for signs of colonic distension.

Laboratory Studies:

Na ⁺	151	BUN	30
K ⁺	2.5	creatinine	1.5
Cl ⁻	115	TTKG	3
HCO ₃ ⁻	15	stool K ⁺	100 mEqu/kg
		stool Na ⁺	10 mEqu/kg



Which of the following is the most likely cause of this patient's hypokalemia?

- A. Ischemic bowel
- B. C diff colitis
- C. Activation of colonic K^+ secretion
- D. Osmotic diarrhea
- E. Sympathetic activation with redistributive hypokalemia



Ogilvie's Syndrome and Hypokalemia

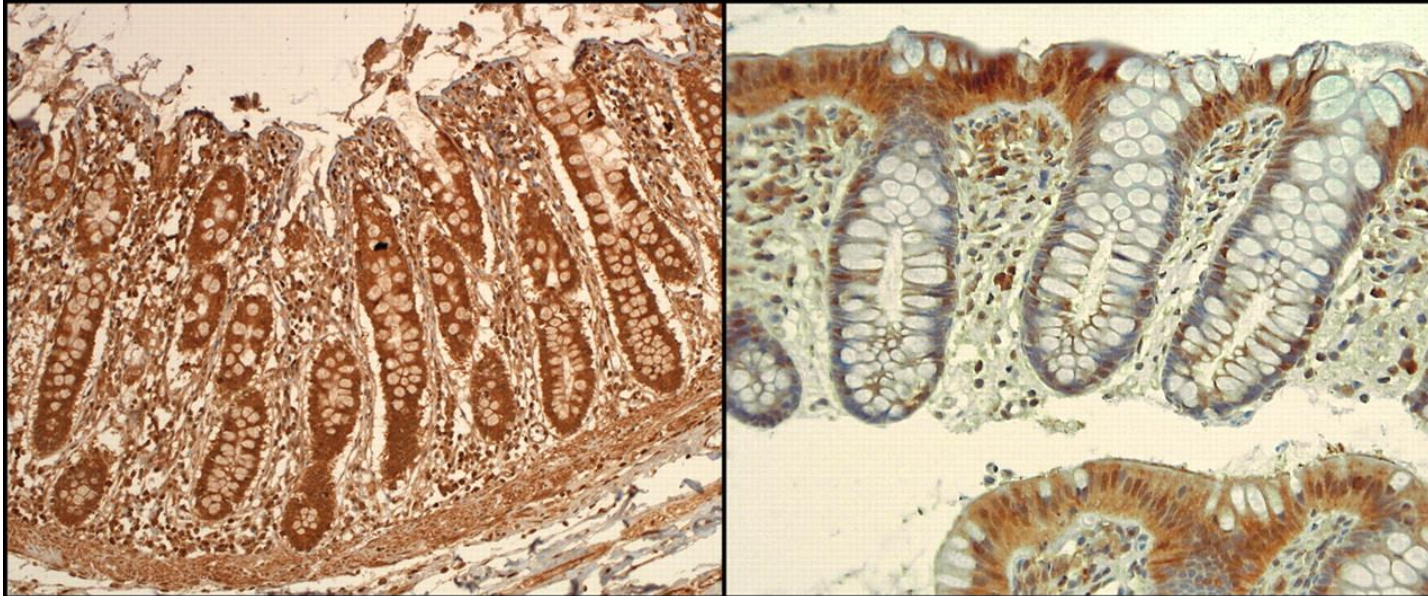
There is an association between (Ogilvie's syndrome) and hypokalemia due to secretory diarrhea with an abnormally high K^+ content. In one patient with concomitant ESRD, immunohistochemistry revealed massive upregulation of the apical BK channel throughout the surface-crypt axes. ? Active stimulation by catecholamines induced by colonic pseudo-obstruction.





Nephrol. Dial. Transplant.
(2008) 23 (10):
3350-3352

Upregulation of BK
secretory K channel



BK Staining: Patient Control

Renal Loss and Hypokalemia

Drugs

- Diuretics
- Antibiotics
 - Non-reabsorbable anions, e.g. Penicillin

Aldosterone excess

Bicarbonaturia

Magnesium deficiency –
inhibition of muscle Na/K-ATPase and ↓ Mg^{2+} -dependent block of ROMK
→ ↑ distal K^+ excretion

Tubular damage

- ATN
- Cisplatin, aminoglycosides, amphotericin

Intrinsic renal transport defects

- Liddle's syndrome
- Bartter's syndrome
- Gitelman's syndrome
- Hereditary dRTA



Hypokalemia and Hypertension

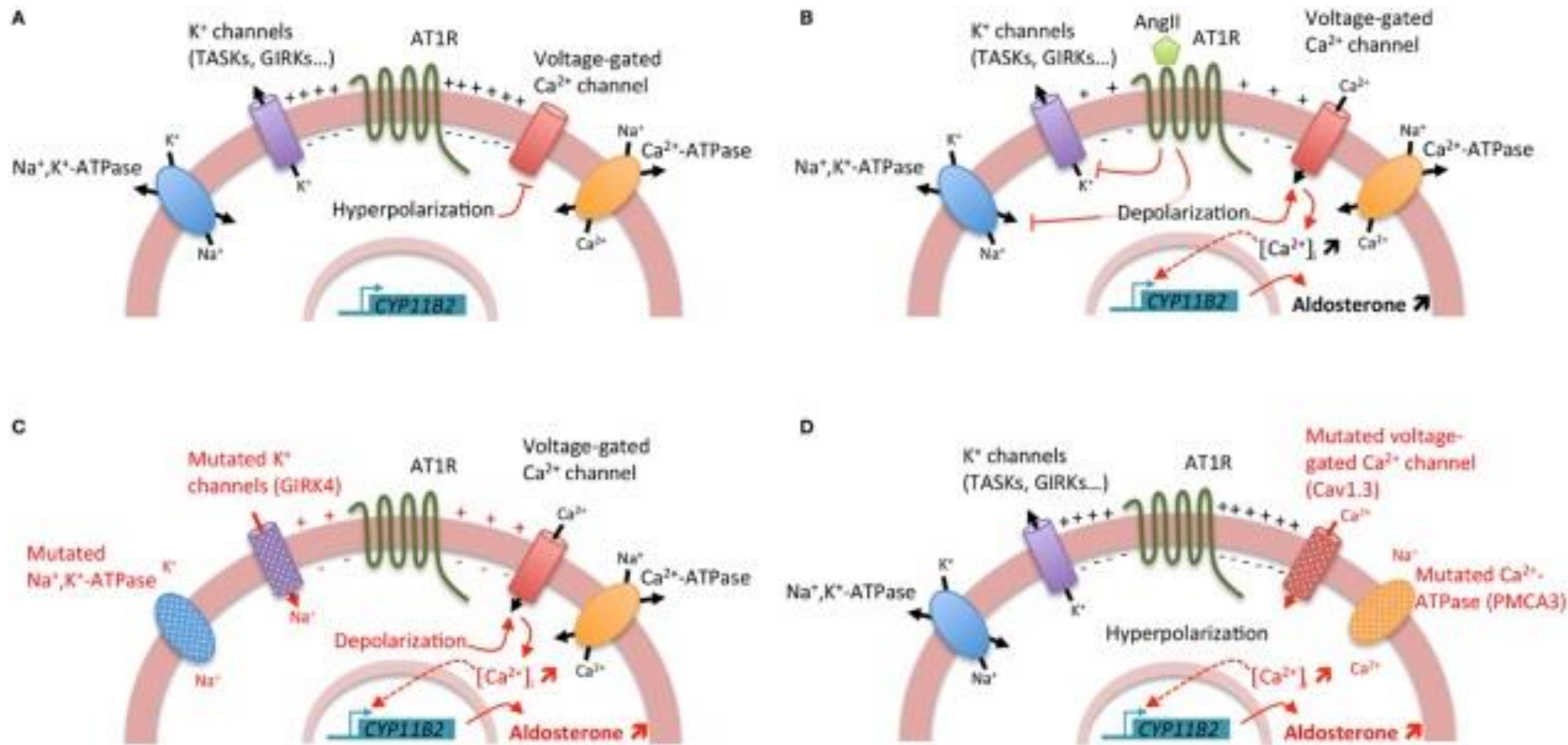
Common

- aldosterone-producing adenoma, bilateral adrenal hyperplasia

< Common

- familial hyperaldosteronism, including GRA (Glucocorticoid remedial aldosteronism)
- adrenocortical carcinoma
- renovascular disease
- Liddle's syndrome
- 11 β HS2 inhibition/deficiency – licorice/S.A.M.E.
- Ectopic ACTH





- A) Zona glomerulosa cells are strongly hyperpolarized (-80 mV) due to K channel activity
- B) Ang-II depolarizes cells by inhibiting K channels and Na/K-ATPase, leading to depolarization. Depolarization activates Ca²⁺ channels, increasing intracellular Ca²⁺ and activating CYP11B2 transcription to generate more aldo.
- C) Acquired mutations in GIRK4/KCNJ5 induce Na⁺ conductivity, depolarizing the cell. Acquired mutations in Na/K-ATPase have the same effect.
- D) Acquired mutations in calcium transport proteins increase intracellular Ca²⁺

Screening and Confirmatory Testing, Primary Hyperaldosteronism

Aldosterone (PAC) to renin (PRA) ratio

- Check when normokalemic, $[K^+] > 4.0$ mEq/L
- Beware of drug effects during evaluation, switch to RAAS-neutral drugs (verapamil, alpha blockers, hydralazine)

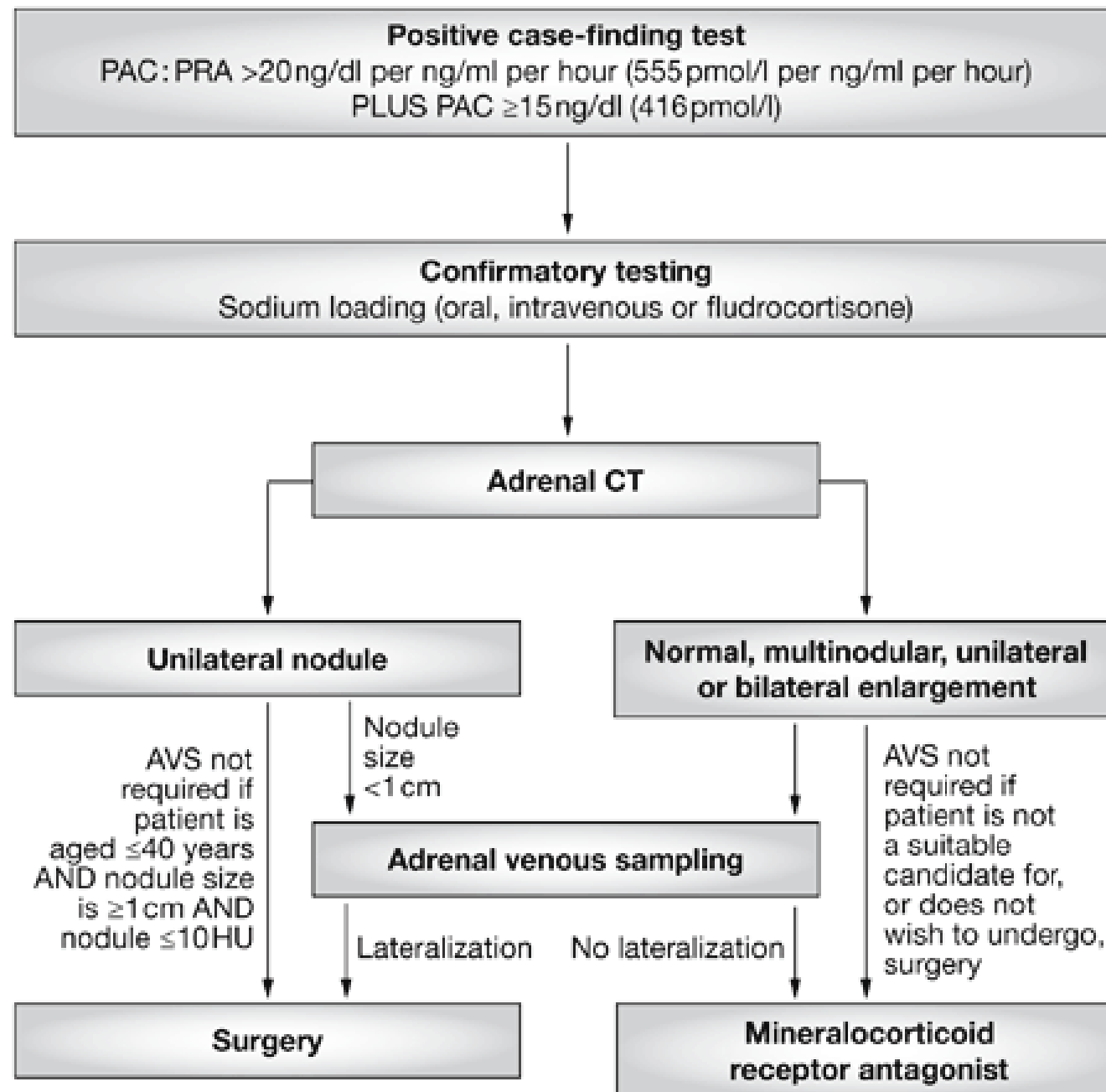
24 hour aldosterone secretion

Salt suppression testing

- Oral to >200 milliEq/day for 3 days, followed by PAC:PRA and 24 hr urine aldo
- IV saline, 2 liters/4 hours, pre- and post-PAC:PRA

Imaging +/- adrenal vein sampling (AVS)





Consequences of Hyperkalemia

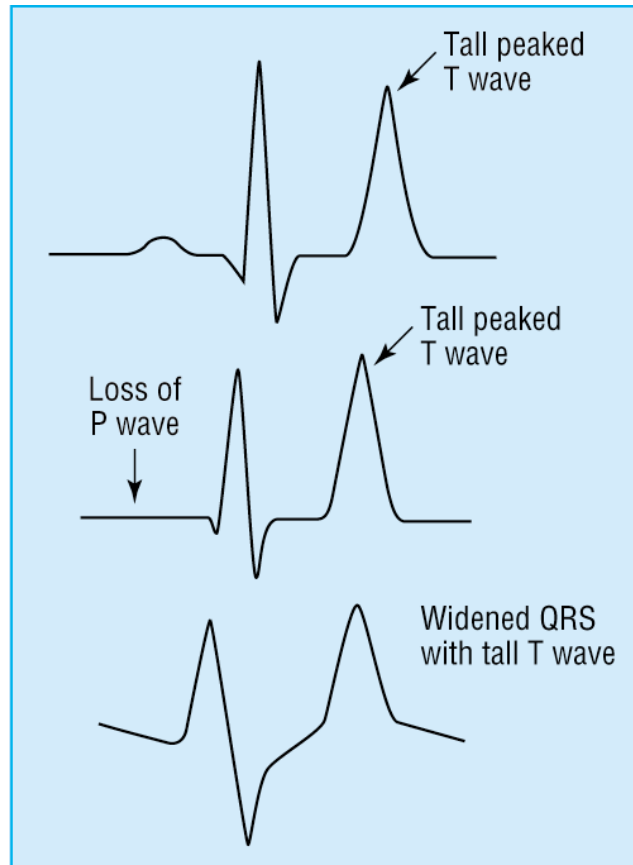
Excitable tissue – change in resting membrane potential

- Cardiac, decreased myocardial conduction velocity, $\uparrow$ PR and $\uparrow$ QRS and increased rate of repolarization (T wave changes)
- Skeletal muscle – weakness, fatigue, paralysis

Kidney – decreased ability to secrete NH_4^+ → acidosis



Typical Electrocardiographic Features of Hyperkalemia



<i>Serum K⁺</i>	<i>Major change</i>
5.5-6.5	Tall peaked T waves
6.5-7.5	Loss of P waves
7.0-8.0	Widening of QRS
8.0-10	Sine wave, ventricular arrhythmia, asystole

Caveats: ECGs and Hyperkalemia

Remember, “the first symptom of hyperkalemia is death.....”

ECG changes are not sensitive, particularly in ESRD

Peaked T's in other disorders

Atypical ECGs

- Complete heart block
- Intraventricular conduction delays
- QRS axis shift
- Brugada sign - pseudo-RBBB and “coved” ST ↑

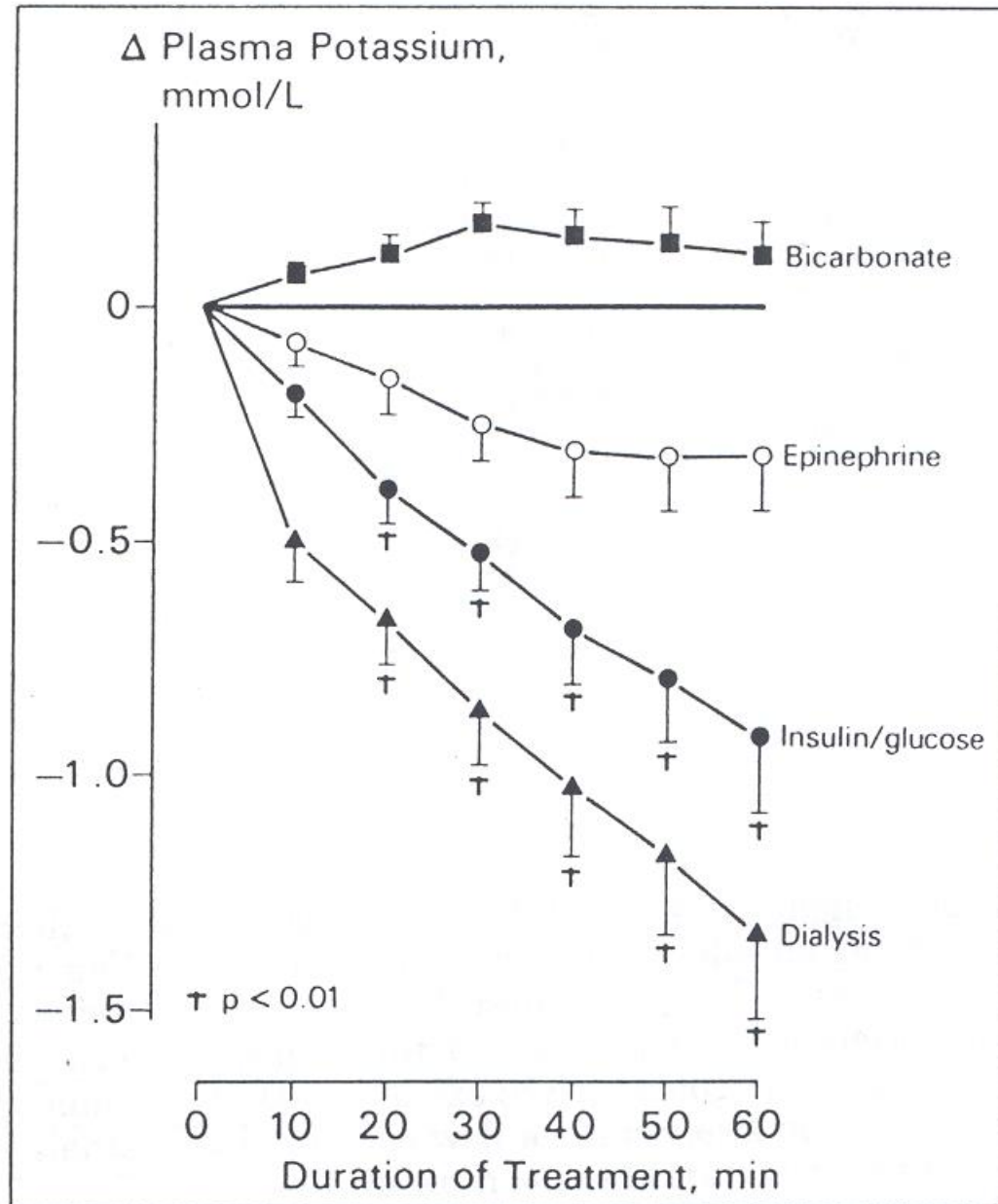


Treatment of Hyperkalemia

<i>Mechanism</i>	<i>Therapy</i>	<i>Dose</i>	<i>Onset</i>	<i>Duration</i>
<i>Stabilize membrane potential</i>	Calcium	10% Ca-gluconate, 10 ml over 10 min.	1-3 min.	30-60 min
	Insulin	10 U R with 50 ml of D50, if BS<250	30 min.	4-6 h
<i>Cellular K⁺ uptake</i>	β_2 -agonist	nebulized albuterol, 10 mg	30 min.	2-4 h
	Potassium Binders	Agent-specific	hours	?
<i>K⁺ removal</i>	Hemodialysis		Immediate	



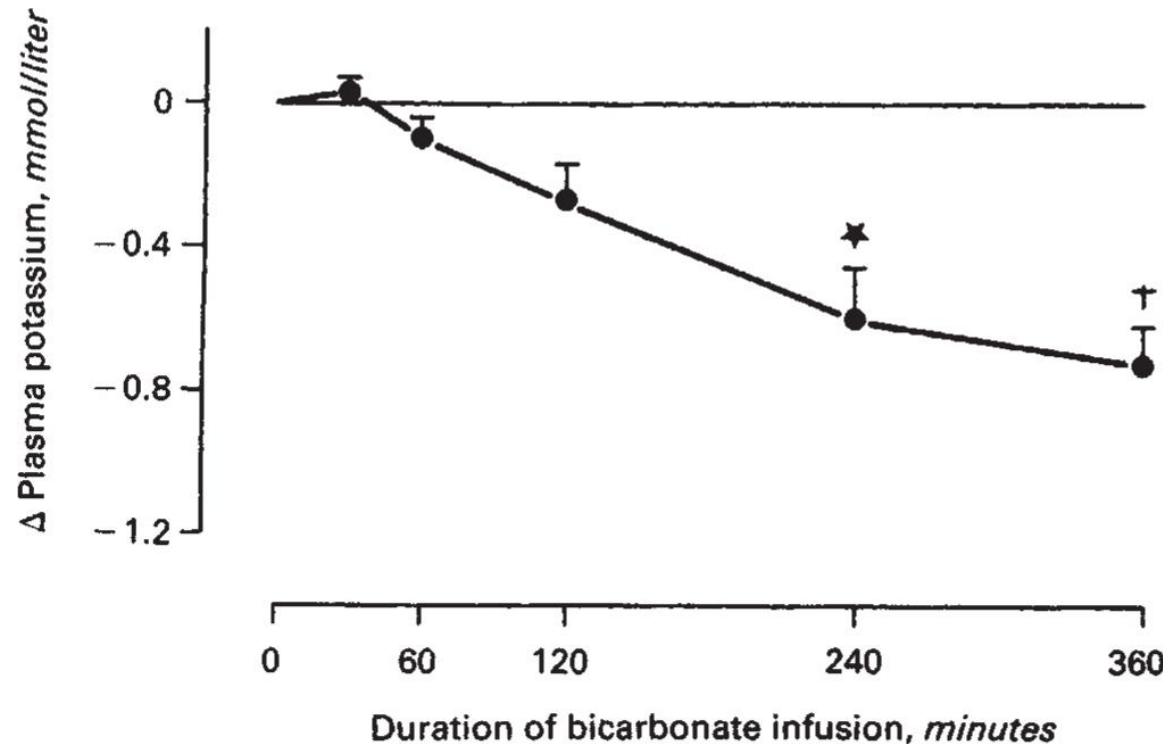
Hypertonic Bicarb Is Acutely Ineffective



Blumberg et al, *Am J Med*, 85, 1988



Sustained, Isotonic Bicarbonate Infusions are Modestly Effective in ESRD



ESRD patients.
mean [K] 6.0 mEq/l,
mean [HCO₃] 17 mEq/l

Hypertonic → isotonic
infusion, 390 mmole
in 1190 ml

Insulin and Glucose

Threshold of >6.5 mEq/L without ECG changes.
Recommended dose is 10 units of regular insulin
followed by 25 g of 50% glucose

Followed by 10% dextrose infusion at a rate of 50-75 ml/hour (to prevent hypoglycemia)

In hyperglycemic patients (glucose > 200 - 250 mg/dl)
insulin alone is enough

D50W alone should be avoided → hyperosmolality
can increase K^+ , primarily in predisposed patients
(e.g. DM with type IV RTA)



β_2 -Adrenergic Agonists (Inhaled)

10-20 mg of nebulized albuterol in 4 ml of normal saline, inhaled over 10 minutes

Hypokalemic effect starts in 30 minutes, peaks at 90 minutes and lasts for 2-6 hours

Reduces K^+ level by 0.5-1.0 mmol/L

Synergistic with insulin, but ineffective as the sole agent in ESRD

Use with caution in ischemic HR, monitor HR closely

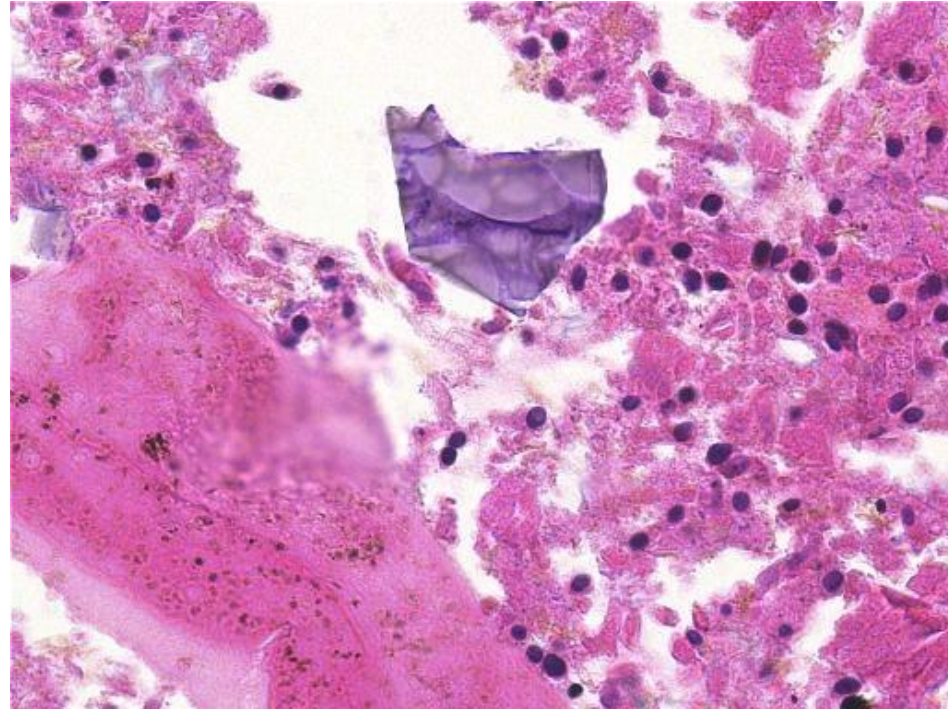


Sodium Polystyrene Sulphate (Kayexalate) Can Cause Bowel Necrosis



necrotic small bowel

Boston case, 2011



SPS crystal, duodenum

The Available Alternatives....

The NEW ENGLAND JOURNAL *of* MEDICINE

ESTABLISHED IN 1812

JANUARY 15, 2015

VOL. 372 NO. 3

Patiromer in Patients with Kidney Disease and Hyperkalemia Receiving RAAS Inhibitors

Matthew R. Weir, M.D., George L. Bakris, M.D., David A. Bushinsky, M.D., Martha R. Mayo, Pharm.D.,
Dahlia Garza, M.D., Yuri Stasiv, Ph.D., Janet Wittes, Ph.D., Heidi Christ-Schmidt, M.S.E., Lance Berman, M.D.,
and Bertram Pitt, M.D., for the OPAL-HK Investigators*

The NEW ENGLAND JOURNAL *of* MEDICINE

ORIGINAL ARTICLE

Sodium Zirconium Cyclosilicate in Hyperkalemia

David K. Packham, M.B., B.S., M.D., Henrik S. Rasmussen, M.D., Ph.D.,
Philip T. Lavin, Ph.D., Mohamed A. El-Shahawy, M.D., M.P.H.,
Simon D. Roger, M.D., Geoffrey Block, M.D., Wajeh Qunibi, M.D.,
Pablo Pergola, M.D., Ph.D., and Bhupinder Singh, M.D.



Patiromer

- Chief adverse event is hypomagnesemia (4.3% incidence of magnesium <1.2 mg/dL in AMETHYST-DN).
- Concerns re drug interactions, but only documented for ciprofloxacin, metformin, and thyroxine; can obviate if dosed 3 hours between/before other drugs.
- Can cause hypercalcemia, due to an increase in GI absorption.
- Demonstrated to reduce circulating aldosterone; ? role in managing aldosterone breakthrough.

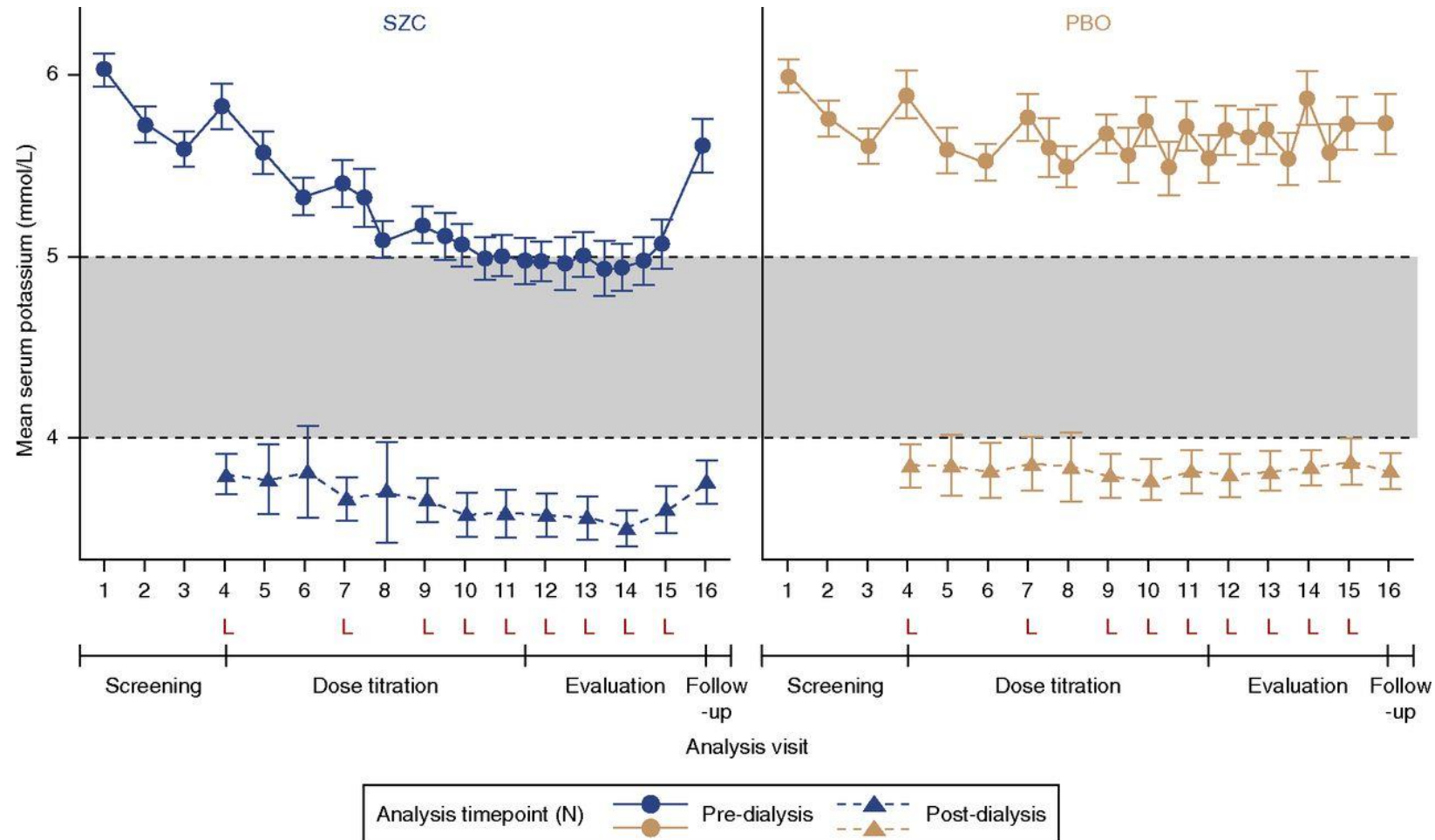


Sodium Zirconium Cyclosilicate (SZC, ZS-9)

- Selective for K^+ and NH_4^+ - no binding to magnesium or calcium.
- Associated increase in serum bicarbonate.
- No drug interactions.
- Rapid onset: After one 10-g dose serum $[K^+]$ declines by ~0.4 mEq/L at 1 hour, by ~0.6 mmol per liter at 2 hours, and by ~0.7 mEq/L at four hours.
- May contribute to edema, presumably due to Na^+ load.



SZC in Hyperkalemic HD Patients



RCT of 196 patients Fishbane et al, JASN 2019



Hemodialysis

The only therapy that can reliably normalize hyperK within 4 hours.

Serum K^+ reaches a nadir at ~3 hours, but removal continues to end of HD Rx.

The amount of K^+ removed depends on:

- type and surface area of the dialyzer
- blood flow rate
- dialysate flow rate
- dialysis duration
- serum:dialysate K^+ gradient



The Serum - Dialysate Gradient

Dialysates with lower K^+ concentration are more effective, but may lead to rebound hypertension

Dialysates with very low K^+ concentration (0 or 1 mmol/L) should be used cautiously, given the risk of arrhythmia

Graded reduction in K^+ concentration is effective, with ↓ arrhythmia, and is the standard of care at BWH

Continuous cardiac monitoring is recommended when using very low K^+ concentration dialysates



Consequences of Hypokalemia

Arrhythmias

Muscles – weakness, paralysis, myopathy

Metabolic alkalosis

Insulin resistance

HYPERTENSION

Polydipsia, polyuria, nephrogenic DI

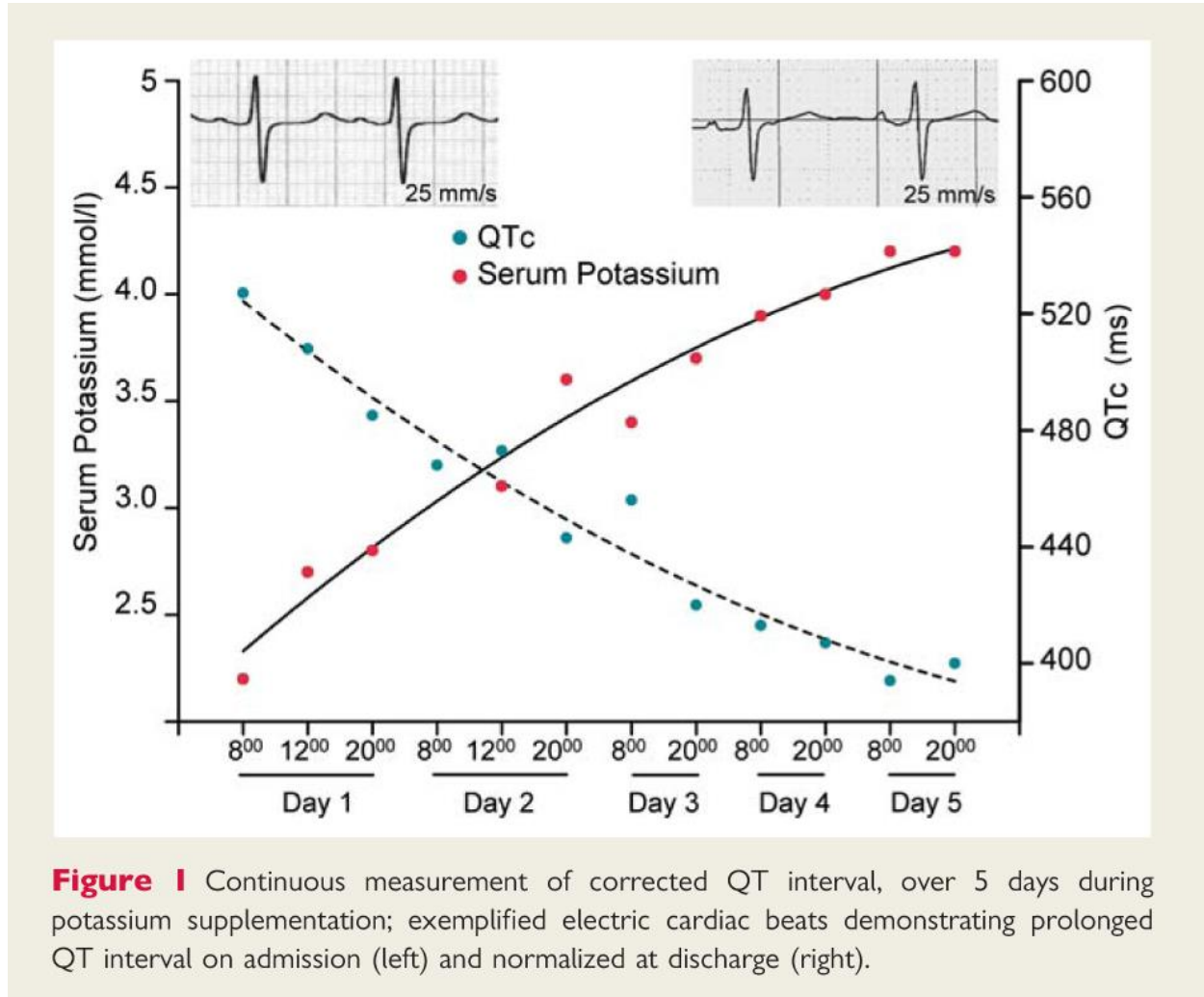
Structural renal disease – AKI, ESRD

Predisposition to

- Rhabdomyolysis
- Hepatic encephalopathy

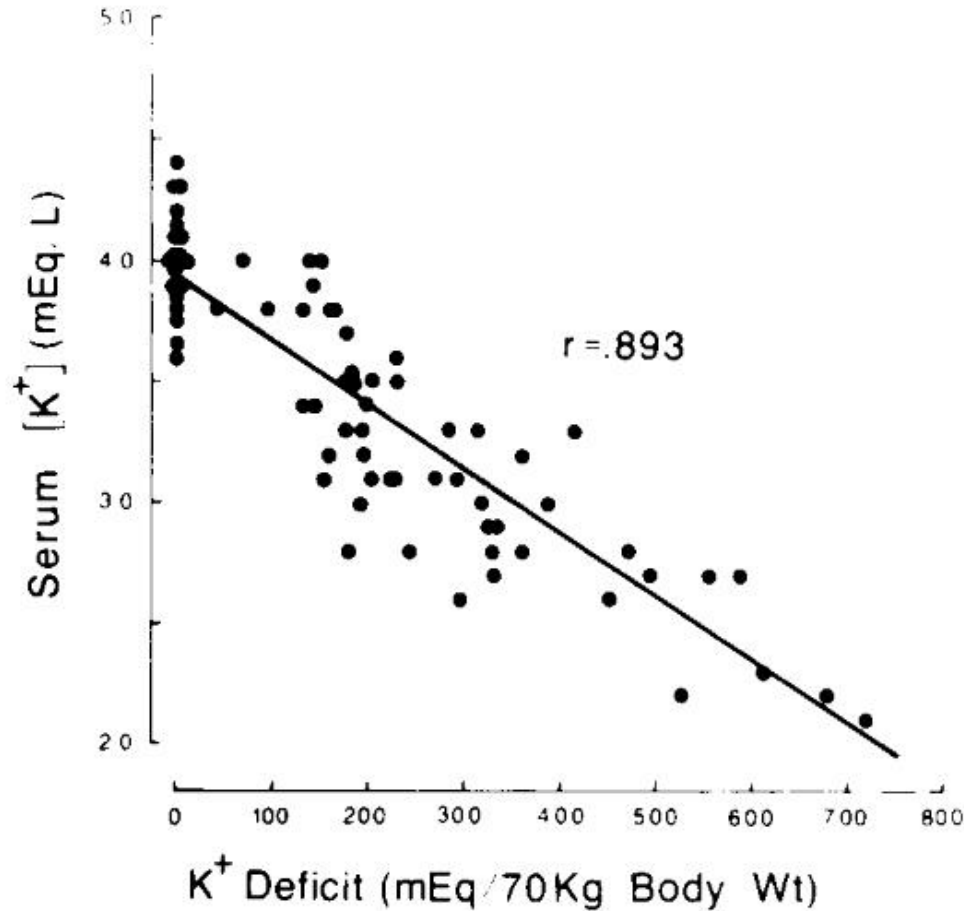


QTc and Serum [K⁺]



Case report,
hypokalemia
with LQT

Estimate the Deficit!



↓ in $[K^+]$ of
0.27 mM per
100 mEq
deficit

Pooled studies of K^+ deprivation

Sterns et al, *Medicine*, 1981



Treatment of Hypokalemia

Look for sequelae – ECG, motor power, etc., →
telemetry for ECG changes, symptomatic hypokalemia
requiring aggressive Rx

First replete magnesium

Usually oral therapy, preferably K-Cl

Replete deficit over days, monitor $[K^+]$ q4-6h to monitor
Rx and avoid transient hyperkalemia

IV can be given safely at 10 mEq/hour, but up to 40-
60 mEq/hr in a monitored setting – need central line, ?
preferably femoral

DO NOT USE DEXTROSE SOLUTIONS

→ acute ↓ in K^+ , due to the induced insulin
release



Question #3

32 yo Latin American male admitted with weakness and a K of 2.0

HPI: The patient has been very healthy until 2 months PTA, when he developed leg weakness. This weakness has fluctuated, and is more severe at night-time. He denies drug abuse, laxative abuse, is on no medications.

ROS: no nausea, no vomiting or diarrhea.

SH: Taxi driver, married with one child

FH: 10 siblings, mother has DM, one sister has thyroid disease.



Physical Exam

Temp 97.2 bp 176/96 HR 102, RR 16

HEENT normal

JVP visible and not elevated, good peripheral pulses, no edema

S1, S2 normal, no murmurs

Abdomen – soft, non-tender, no organomegaly

Neuro – decreased DTRs, otherwise normal



	Admission:	5 months PTA:
Na	139	143
K	<u>2.0</u>	3.8
Cl	105	107
HCO ₃ ⁻	26	29
BUN	11	16
Creat	0.6	1.0
Glu	145	136
PO4	<u>1.2</u>	
Ca	8.8	8.8
Mg	<u>1.3</u>	1.9
Alb	3.8	
Posm	290	TTKG = 2.0
UOsm	590	
UK	10	



Which of the following is likely to be abnormal in this patient?

- A. TSH level
- B. Genetic sequence of the gene encoding the Na/K-ATPase alpha-1 subunit
- C. Genetic sequence of the gene encoding a muscle-specific K⁺ channel
- D. A & C
- E. A, B & C



Mutations in Potassium Channel Kir2.6 Cause Susceptibility to Thyrotoxic Hypokalemic Periodic Paralysis

Devon P. Ryan,^{1,2,14} Magnus R. Dias da Silva,^{2,14,15} Tuck Wah Soong,^{4,8} Bertrand Fontaine,⁵ Matt R. Donaldson,^{2,16} Annie W.C. Kung,⁶ Wallaya Jongjaroenprasert,⁷ Mui Cheng Liang,⁸ Daphne H.C. Khoo,¹⁰ Jin Seng Cheah,⁹ Su Chin Ho,¹¹ Harold S. Bernstein,¹¹ Rui M.B. Maciel,¹² Robert H. Brown, Jr.,¹³ and Louis J. Ptáček^{1,2,3,*}

¹Neuroscience Graduate Program

²Department of Neurology

³Howard Hughes Medical Institute

University of California, San Francisco, San Francisco, CA, 94158, USA

⁴Ion Channel and Transporter Laboratory, National Neuroscience Institute, Singapore 308433, Republic of Singapore

⁵INSERM, Université Pierre et Marie Curie-UPMC, UMRS 546, and Assistance Publique-Hôpitaux de Paris, Centre de Référence des Canalopathies Musculaires, Groupe Hospitalier Pitié-Salpêtrière, 75013 Paris, France

⁶Department of Medicine, University of Hong Kong, Queen Mary Hospital, Hong Kong SAR, China

⁷Department of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok 10400, Thailand

⁸Department of Physiology

⁹Department of Medicine

Yong Loo Lin School of Medicine, National University of Singapore, Singapore 308433, Republic of Singapore

¹⁰Department of Clinical Research, Singapore General Hospital, Singapore 169608, Republic of Singapore

¹¹Cardiovascular Research Institute, University of California, San Francisco, San Francisco, CA 94143-0130, USA

¹²Department of Medicine, Division of Endocrinology, Universidade Federal de São Paulo, São Paulo 04039-032, Brazil

¹³Massachusetts General Hospital, 16th Street, Navy Yard, Charlestown, MA 02129, USA

¹⁴These authors contributed equally to this work

¹⁵Present address: Department of Biochemistry, Universidade Federal de São Paulo, São Paulo 04044-020, Brazil

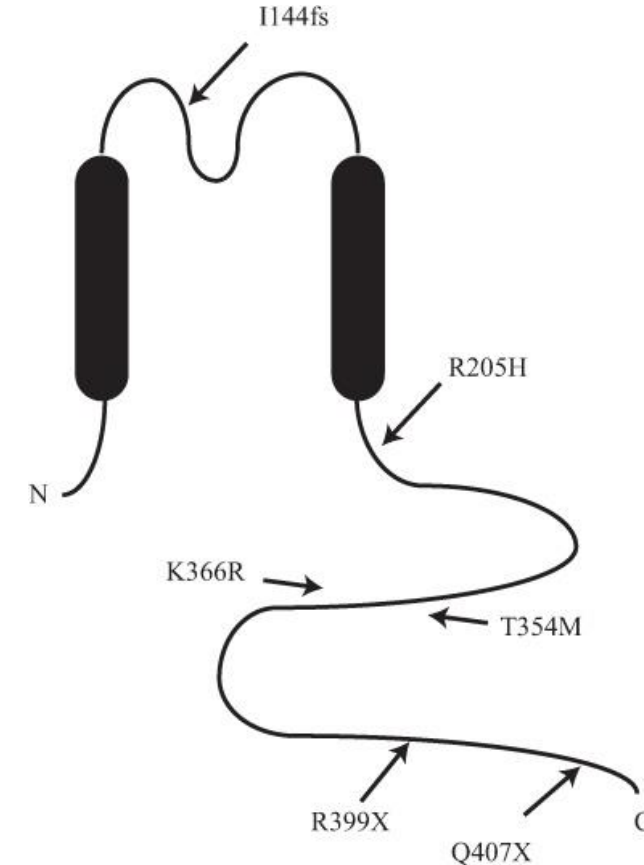
¹⁶Present address: Department of Dermatology, Texas Tech University, Lubbock, TX 79409, USA

*Correspondence: ljp@ucsf.edu

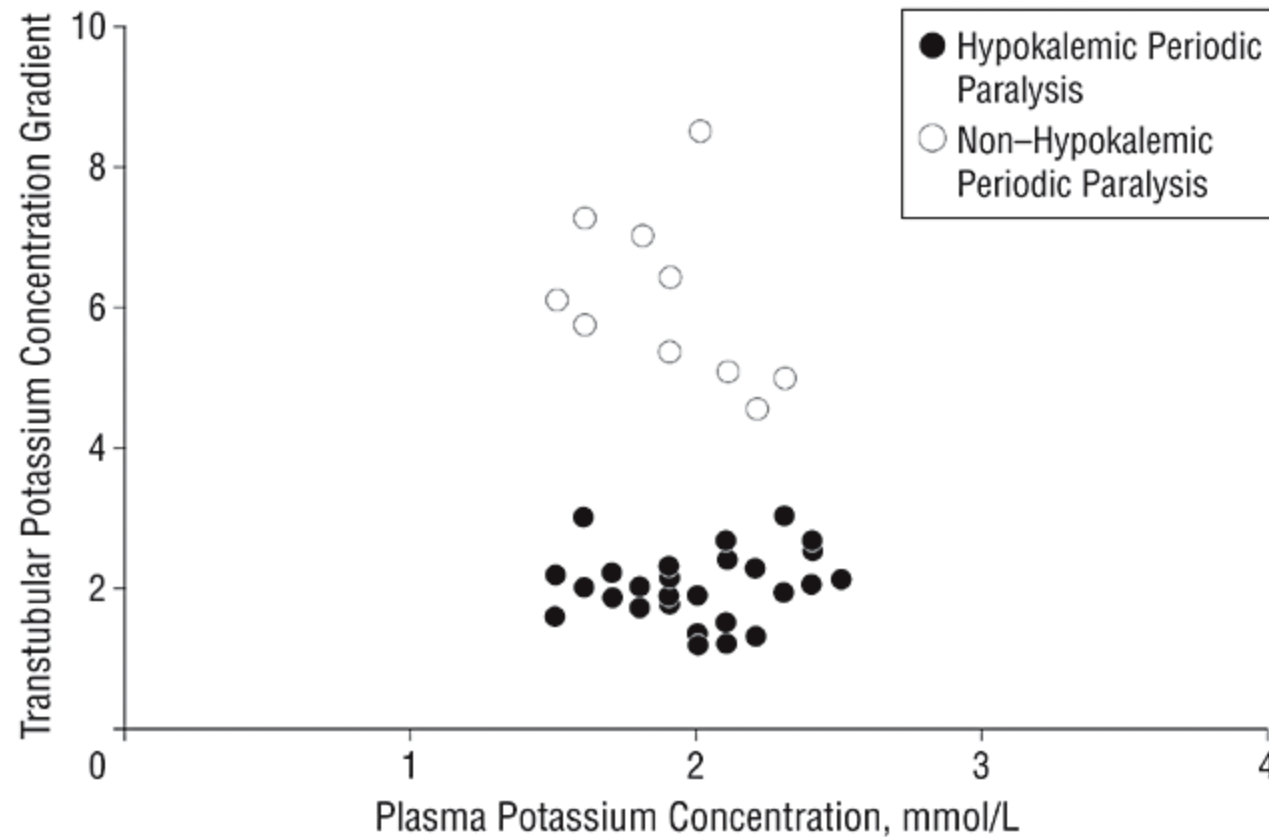
DOI 10.1016/j.cell.2009.12.024

Cell 140, 88–98, January 8, 2010 ©

Point mutations in a muscle-specific, thyroid-induced K⁺ channel detected in multiple unrelated patients with TPP, primarily non-Asian in origin.

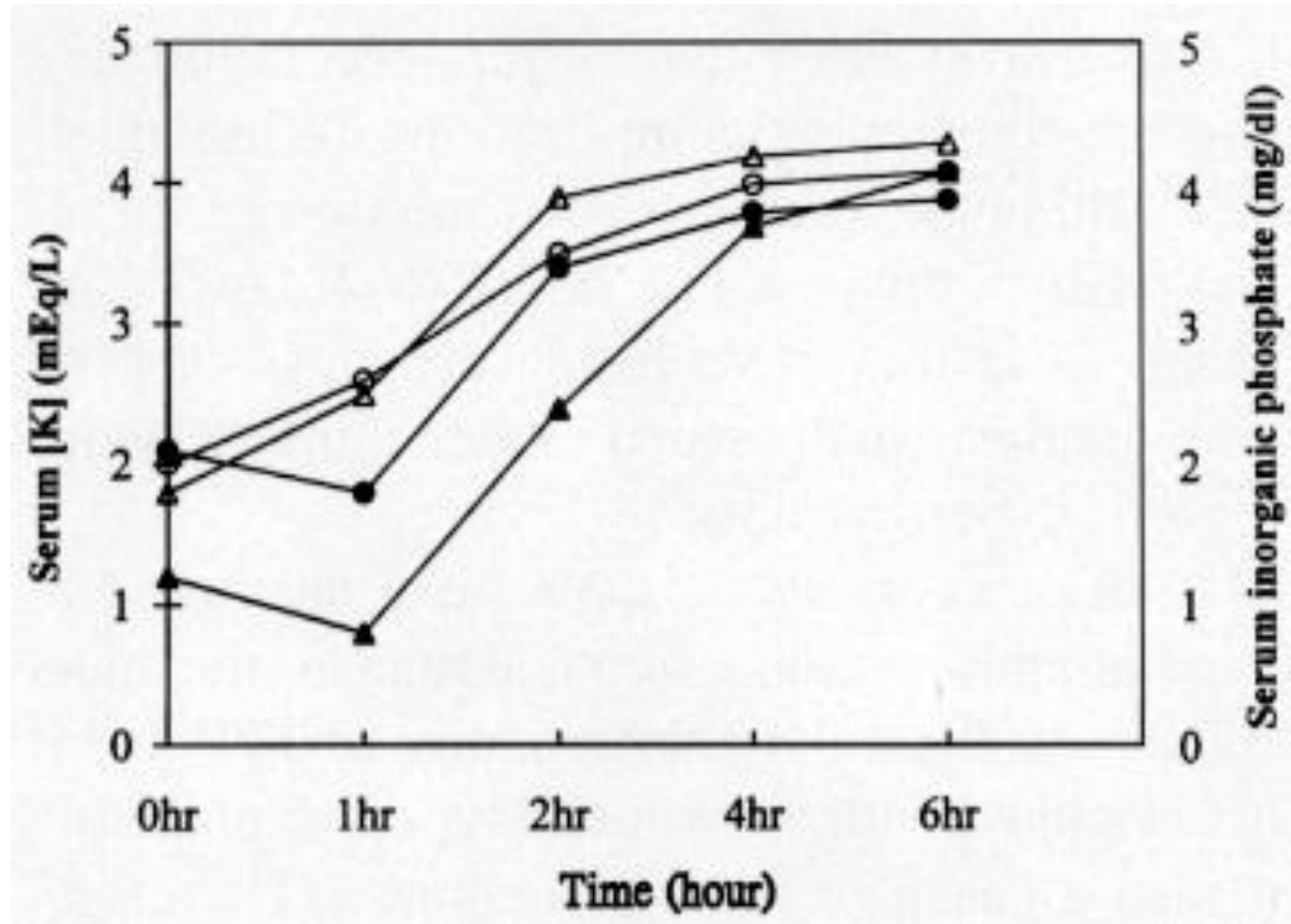


Use of the TTKG in Hypokalemic Paralysis



Lin et al, *Arch Int Med*, 2004

Response of Serum K⁺ and Phosphate to High-Dose Propranolol in TPP



TAKE HOME MESSAGES

Regulation of renal renin release and adrenal aldosterone release.

The aldosterone paradox.

New developments in hyperaldosteronism and thyrotoxic periodic paralysis.

Treatment issues in hypokalemia.

New K^+ binders for hyperkalemia.



REFERENCES

- **Mount, D.B.**, “Fluid and Electrolyte Disturbances”, *Harrison’s Principles of Internal Medicine*, 21st edition, McGraw Hill, 2022, 295-311
- **Mount, D.B. and Dubose**, , “Fluid & Electrolyte Imbalances and of Acid-Base Disturbances: Interpretation and Management – Case Discussions”, *Harrison’s Principles of Internal Medicine*, 21st edition, McGraw Hill, 2022, E-chapter
- **Mount, D.B.** “Disorders of Potassium Balance”, *The Kidney*, 11th Edition, (Brenner and Rector), W.B. Saunders & Company, 2020, 537-579
- McCormack J.A., **Mount D.B.**, Ellison D. H. “Transport of Sodium, Chloride, and Potassium”, *The Kidney*, 11th Edition, (Brenner and Rector), W.B. Saunders & Company, 2020, 156-198



REFERENCES

- **Mount, D.B.** “Advances in chronic potassium control; prognostic implications for CKD”. NephSAP, 2017:16(1): 1-9
- **Mount, D.B.** “Treatment and prevention of hyperkalemia”. UpToDate, Waltham, MA, 2016.
- **Mount, D.B.** “Causes of hypokalemia”. UpToDate, Waltham, MA, 2016.
- **Mount, D.B.** “Clinical manifestations and treatment of hypokalemia”. UpToDate, Waltham, MA, 2016.
- **Mount, D.B.** “Causes and evaluation of hyperkalemia”. UpToDate, Waltham, MA, 2016.
- **Mount, D.B..** “Case Studies in Electrolyte and Acid-Base Disorders”, *Core Concepts in the Disorders of Fluid, Electrolytes and Acid-Base Balance*, 1st edition (ed. Mount and Singh), Springer et al, 2012

