Potassium Disorders

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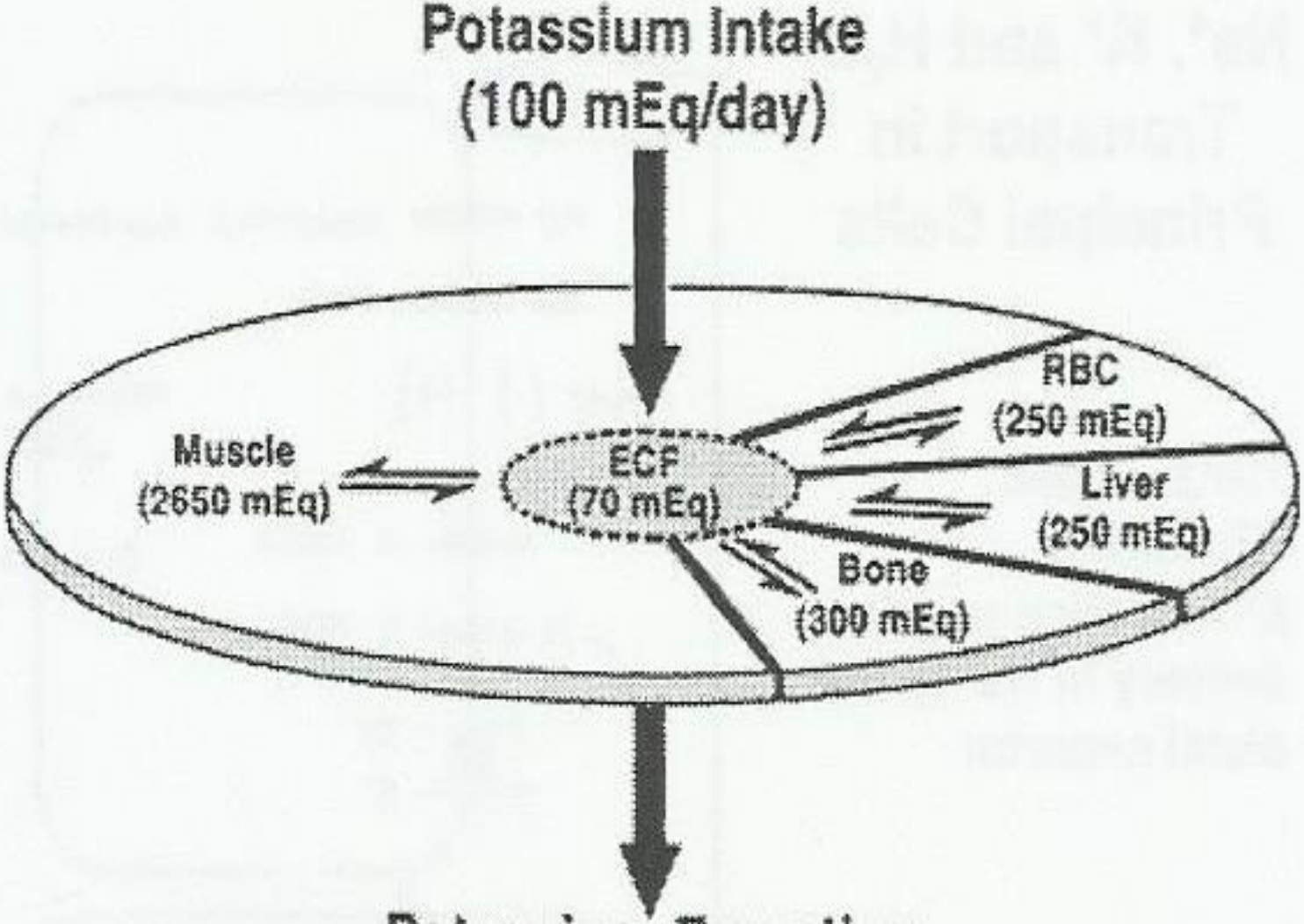
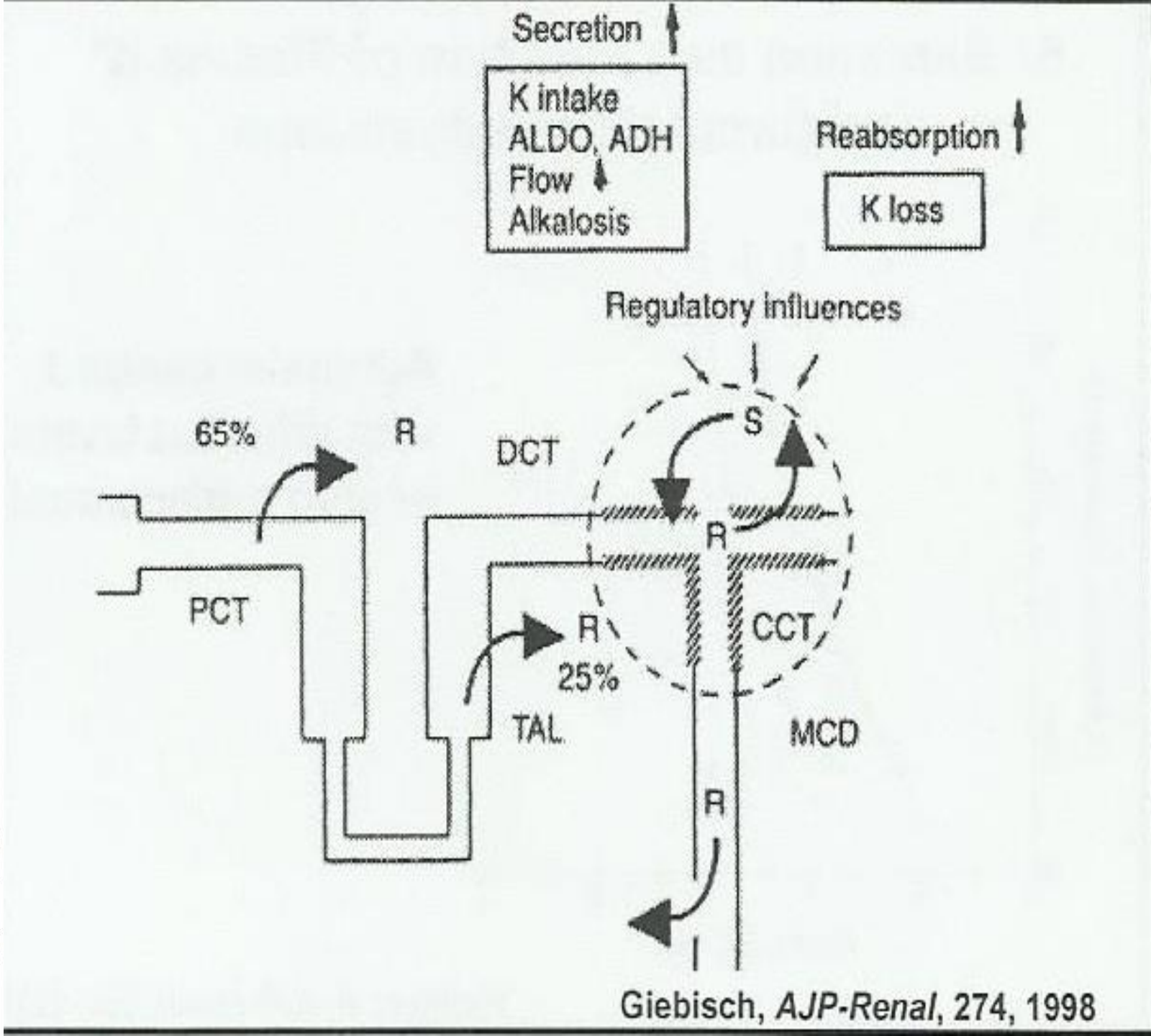
athens-NEPHROLOGY



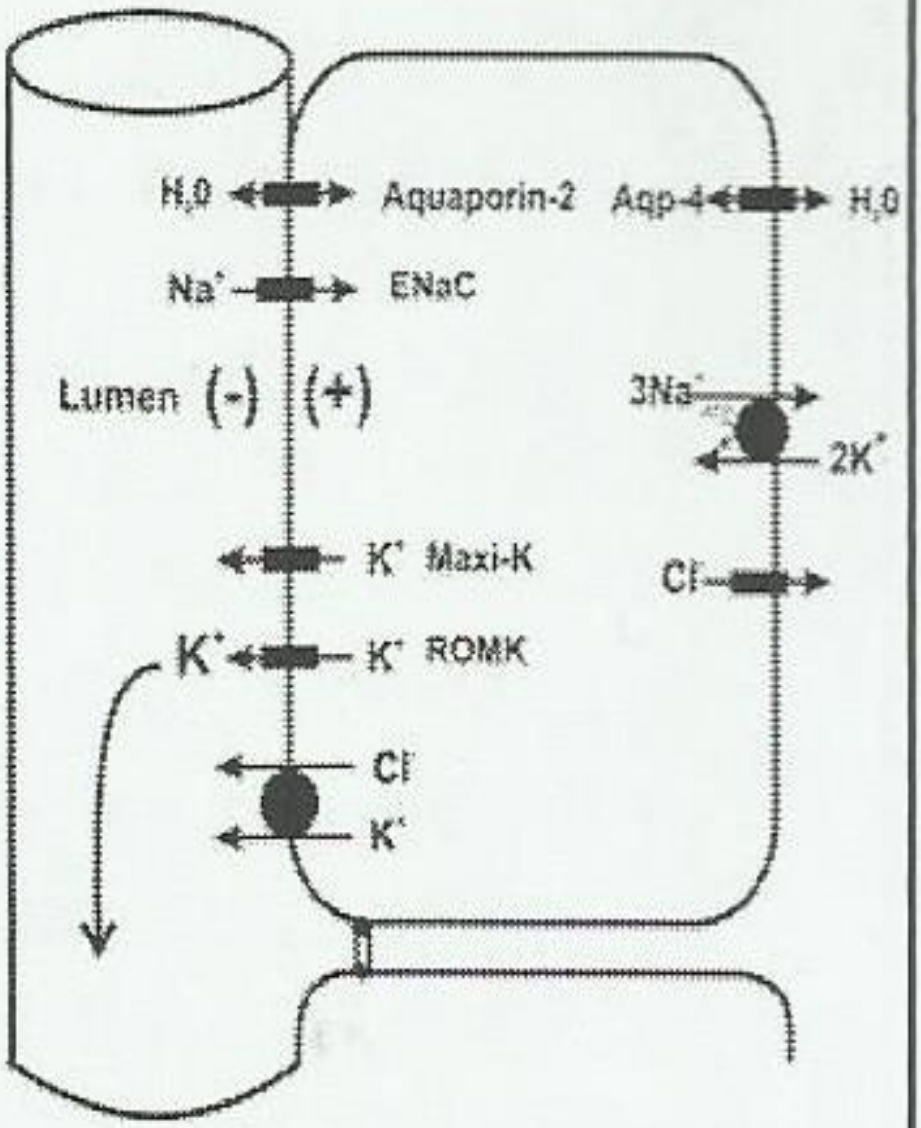
Giebisch, *AJP-Renal*, 274, 1998

Factors Affecting K^+ Shift

Factor	*Transmembrane K^+ Shift*
Insulin	↑ uptake
β-catecholamine	↑ uptake
α-catecholamine	↓ uptake
Acidosis	↓ uptake
Alkalosis	↑ uptake
Hyperosmolarity	↑ efflux

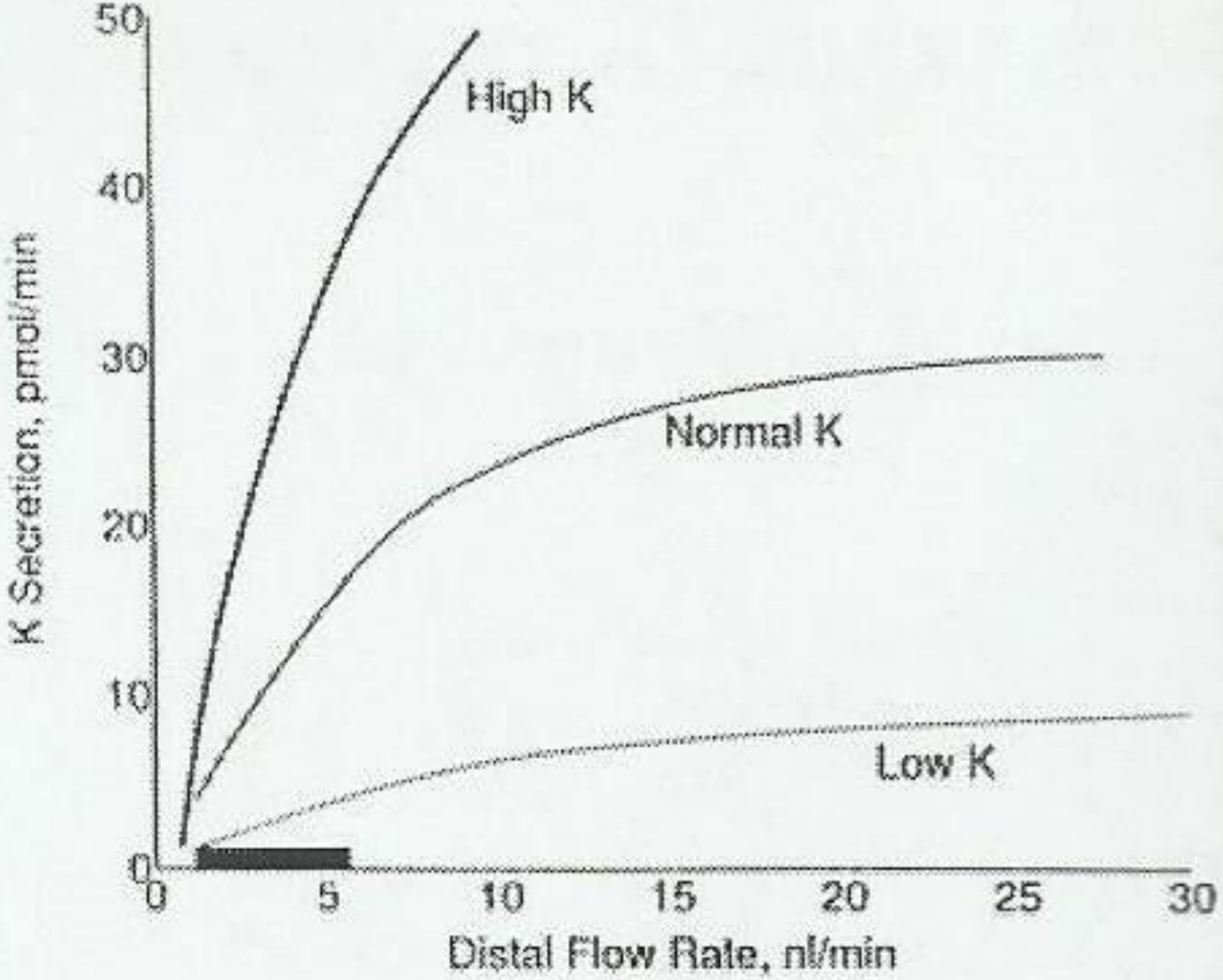

Secretion
K intake
ALDO, ADH
Flow
Alkalosis
Reabsorption
K loss
Regulatory influences
65%
R
DCT
S
R
PCT
R
25%
CCT
TAL
MCD
R
Giebisch, AJP-Renal, 274, 1998

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



ENaC – epithelial Na channel
ROMK – secretory K channel
Maxi-K – flow-activated K channel

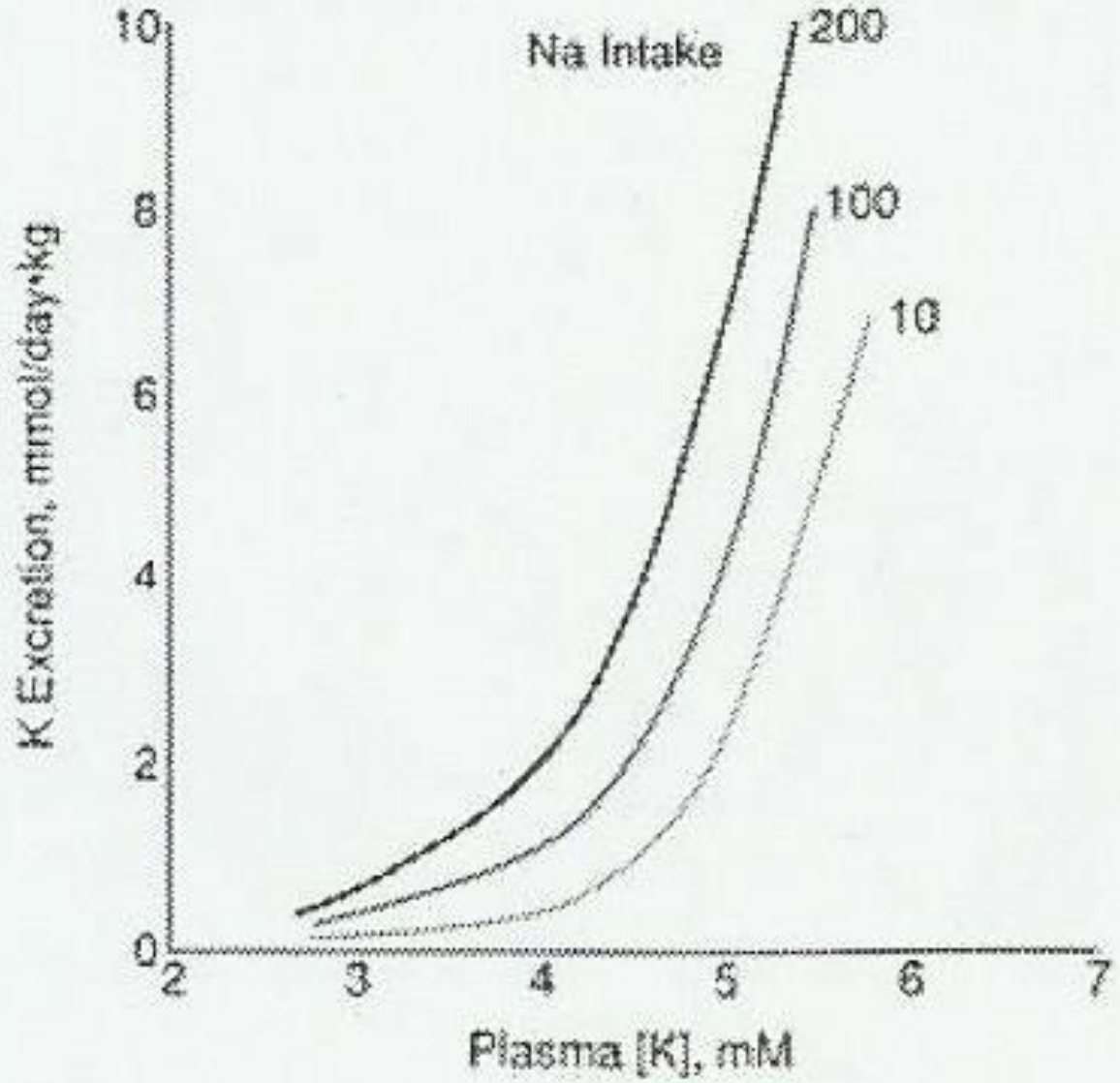
K^+ Secretion is Proportional to Distal Flow



Animals on different K^+ diets

Giebisch, *AJP-Renal*, 274, 1998

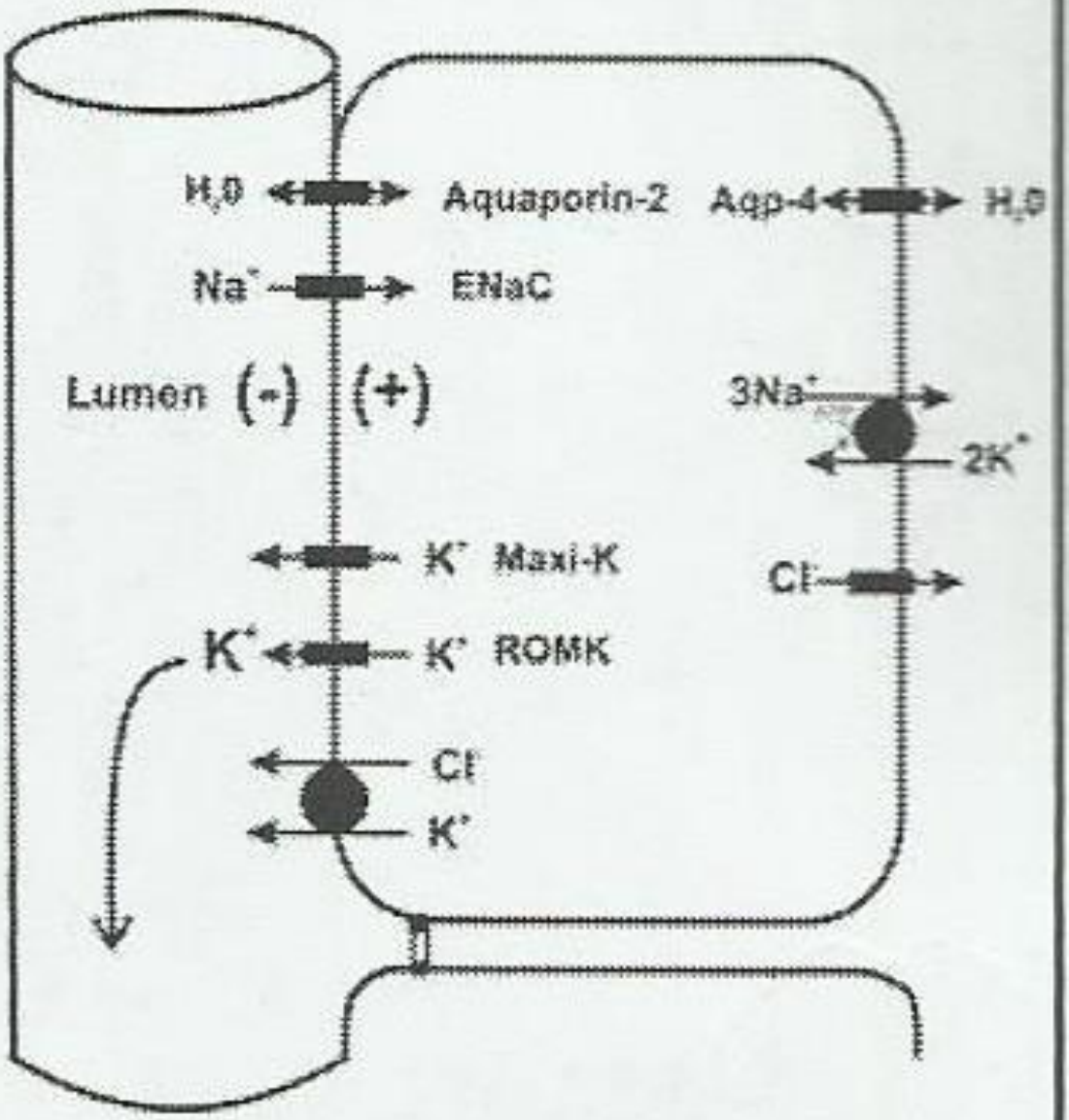
K^+ Excretion is Dependent on Na^+ Intake



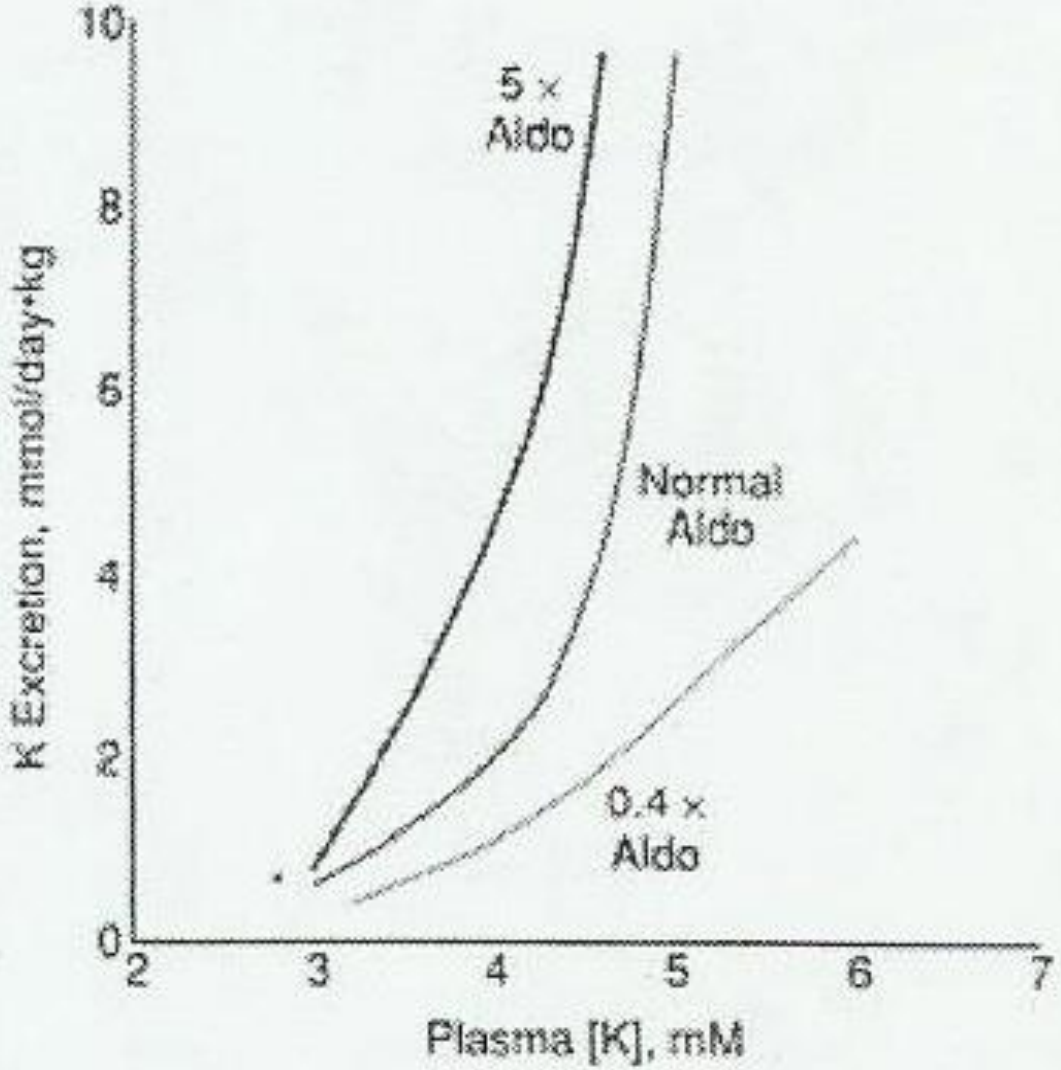
Young et al, *AJP-Renal*, 246, 1984

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

TAKE-HOME MESSAGE:
K^+ excretion requires delivery of Na^+ to the distal nephron



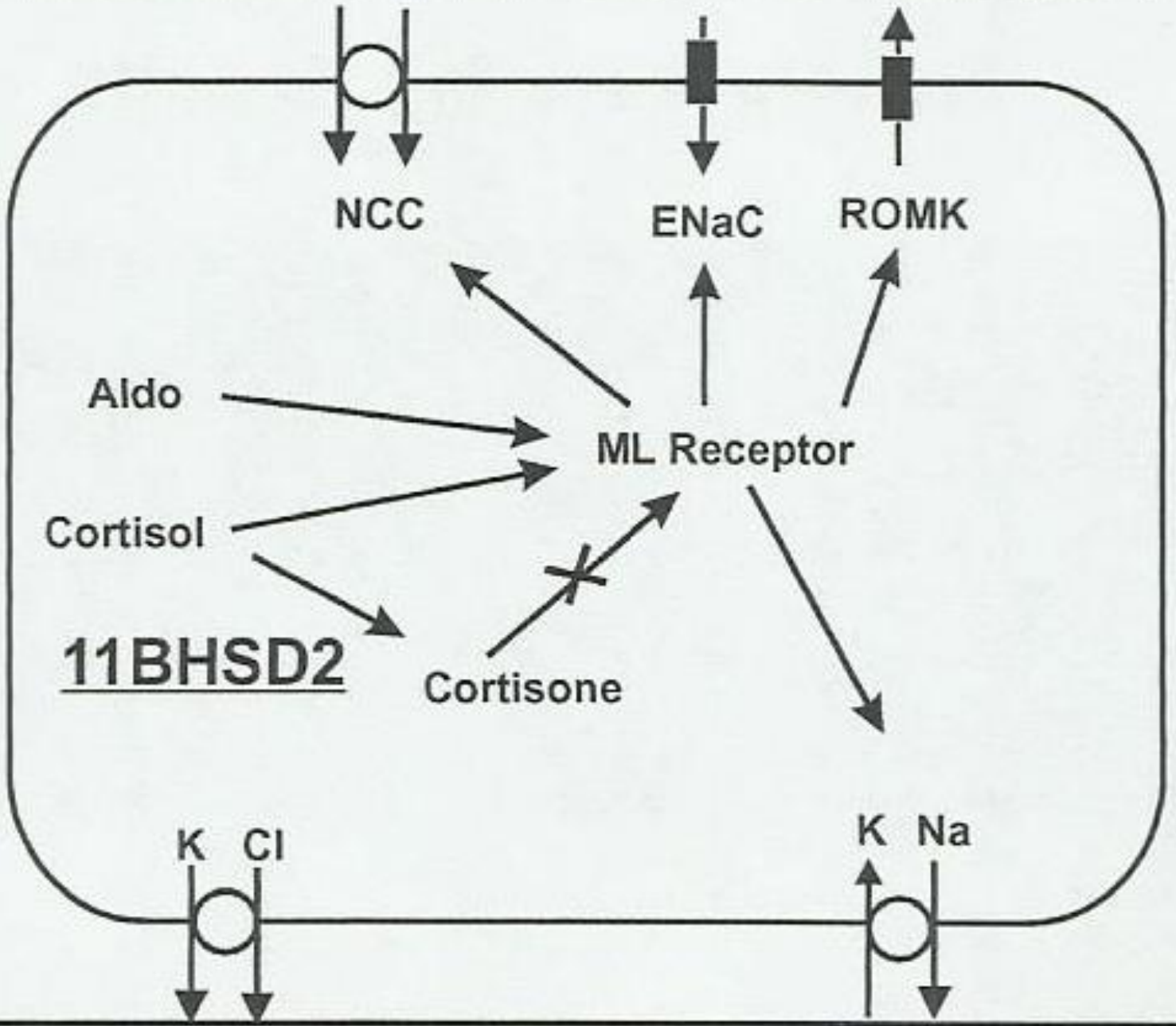
K^+ Excretion as a Function of Plasma K^+ and Circulating Aldosterone



Adrenalectomized with different levels of aldo replacement

Young et al, *AJP-Renal*, 255, 1988

Aldosterone and Distal Ion Transport



Transtubular K^+ Gradient (TTKG)

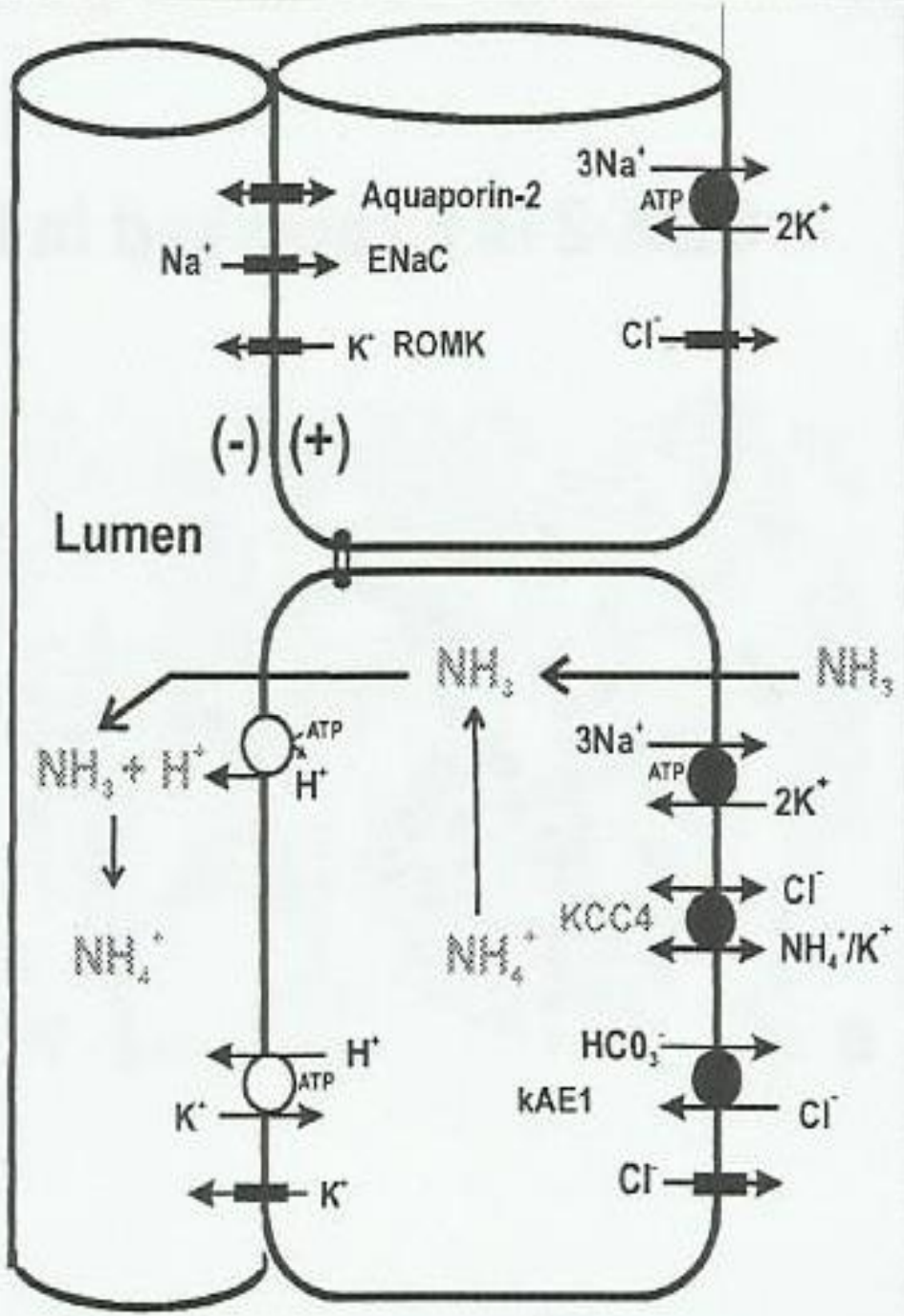
- Useful to assess the renal response to ↓ or ↑ serum K+
- $TTKG = \frac{[\text{urine } K^+ \div (\text{urine Osm} / \text{Plasma Osm})]}{\text{Plasma } K^+}$
- Should be > 7 during hyperkalemia
- Should be < 3 during hypokalemia

- Urine Na^+ to be > 25 mEqu/L; if < 25, distal Na^+ delivery and distal flow rate may be limiting

NH_4^+ Excretion, Renal Collecting Duct

TAKE-HOME MESSAGE:

NH_4^+ excretion also requires delivery of Na^+ to the distal nephron



Causes of Hyperkalemia

- Increased intake
  - K^+ supplements, diet, transfusions, iatrogenic
- Decreased renal excretion
  - Renal disease, particularly with type IV RTA
  - DRUGS
  - Adrenal insufficiency – not universal
- Intra → extracellular shifts
  - Hyperosmolarity
  - Insulinopenia
  - Metabolic acidemia
  - DRUGS
- Artifactual
  - *in vitro* hemolysis, leukocytosis, thrombocytosis
  - "pseudohyperkalemia"

Take A Dietary History!

- 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
  - Fruits: bananas, cantaloupe, oranges, mangos
  - Meats: ground beef, steak, pork, veal, lamb

Hyporeninemic Hypoaldosteronism

- Hyperchloremic acidosis in ~50%, with urine pH classically < 5.5
- Hyperkalemia
- Low plasma renin activity (PRA) and low aldo
- ↓ 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 Type IV RTA

- Diabetic nephropathy
- Acute GN, i.e. nephritic syndrome
- Tubulointerstitial nephropathies, eg. Sickle cell disease
- Drugs, e.g. NSAIDS, cyclosporin, FK-506
- Hereditary causes, e.g. pseudohypoaldosteronism type II

Physiology of Renal Renin Release

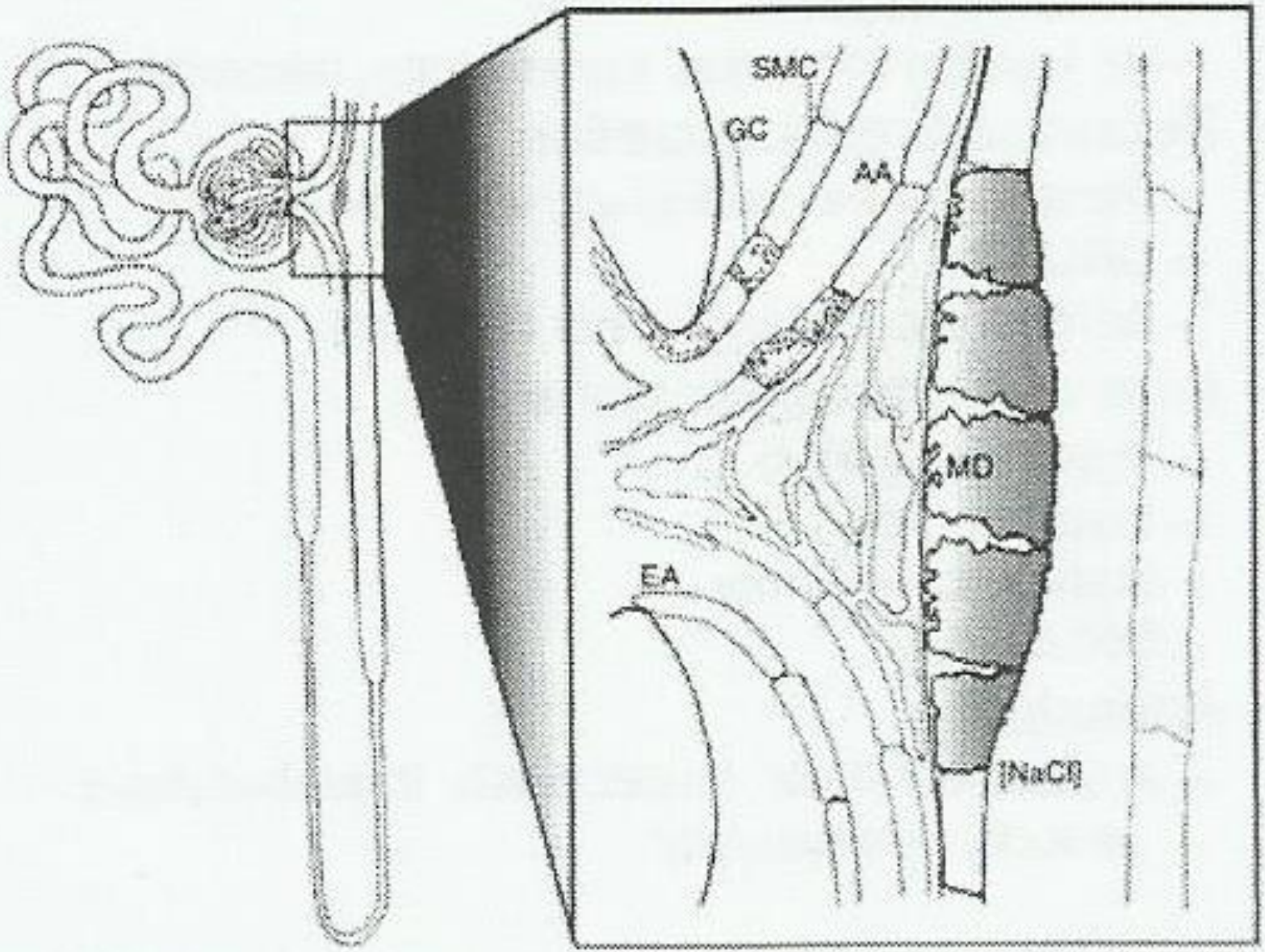
↑ Release:

- **↓ NaCl intake, ↓ ECFV**
- ↓ renal perfusion pressure
- ACE-I, ARBs
- Systemic loop diuretics
- β-adrenergic stimulation, β agonists
- Prostaglandins

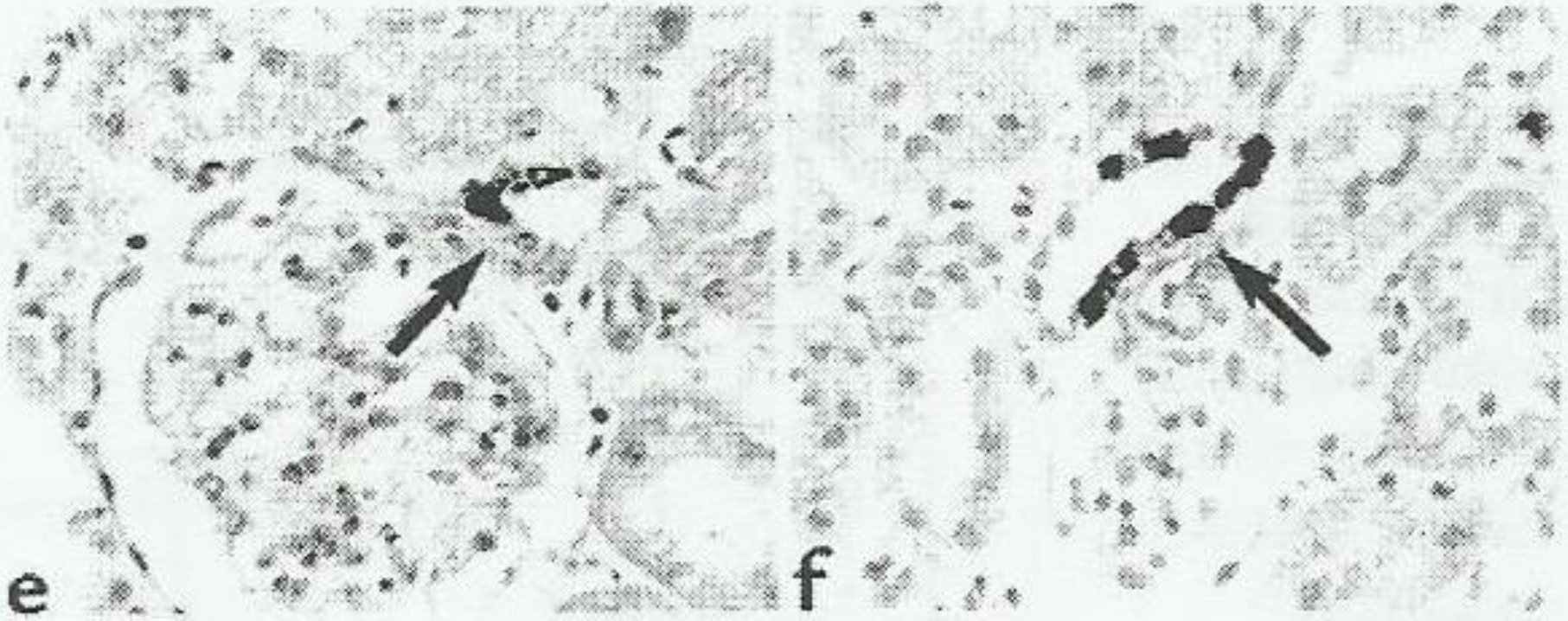
↓ Release:

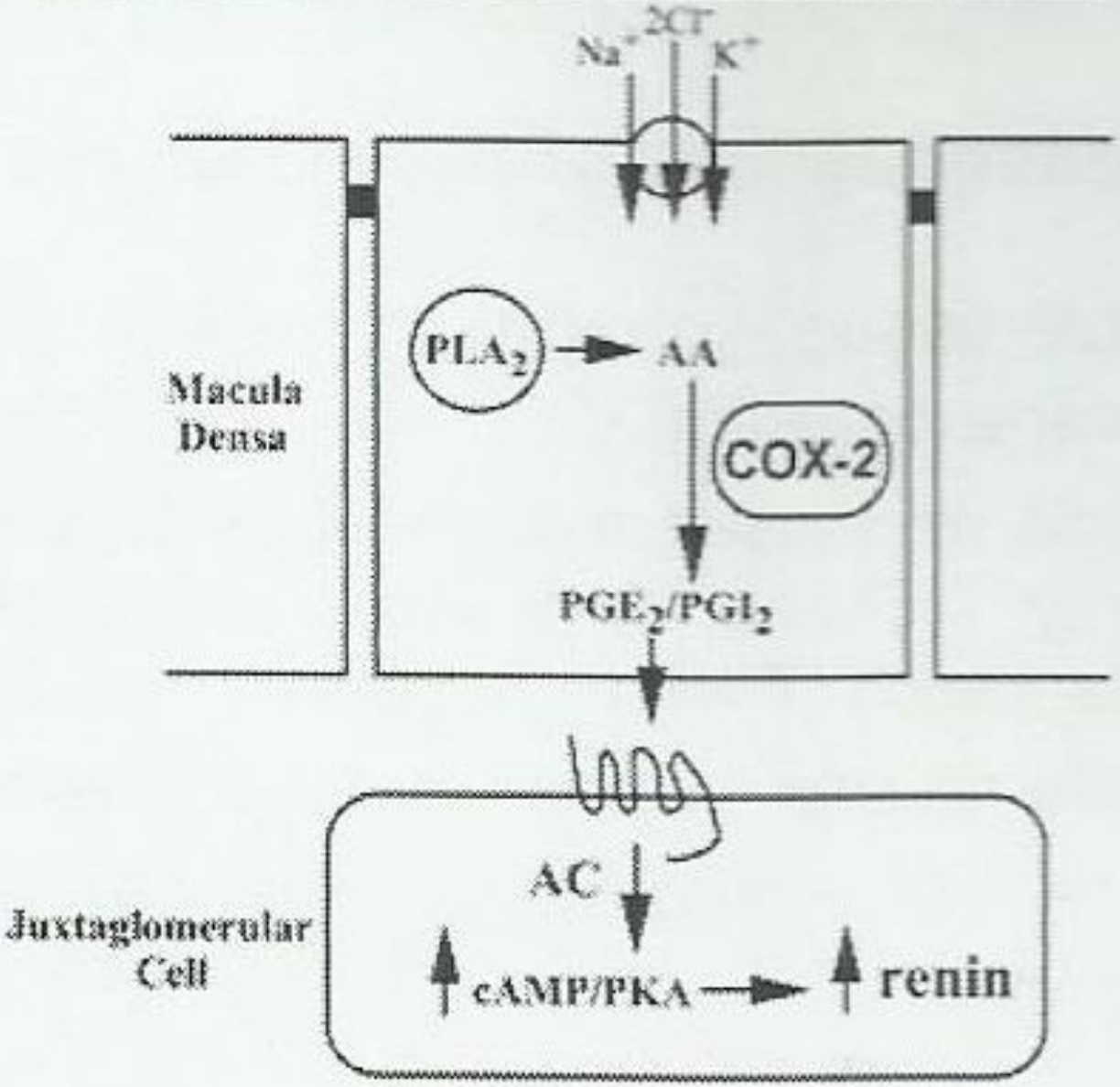
- ↑ NaCl intake, ↑ ECFV
- **↑ ANP/BNP**
- β-antagonists
- NSAIDS
- cyclosporine

The Juxtaglomerular Apparatus, Intra-Renal Source of Renin



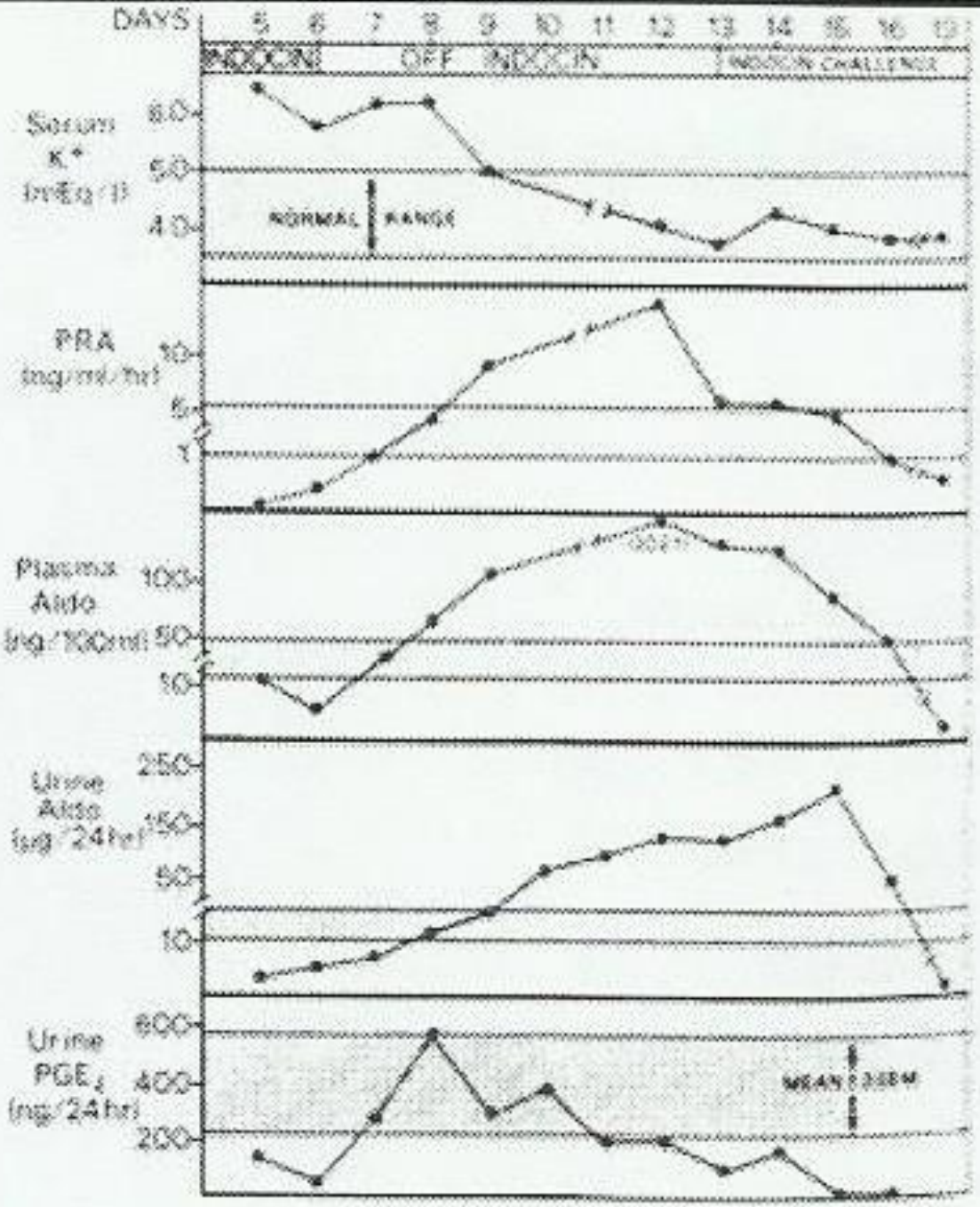
COX-2 is Expressed in the Macula Densa





Harris and Breyer, *AJP-Renal*, 281, 2001

NSAIDs and Type IV RTA



K+

PRA

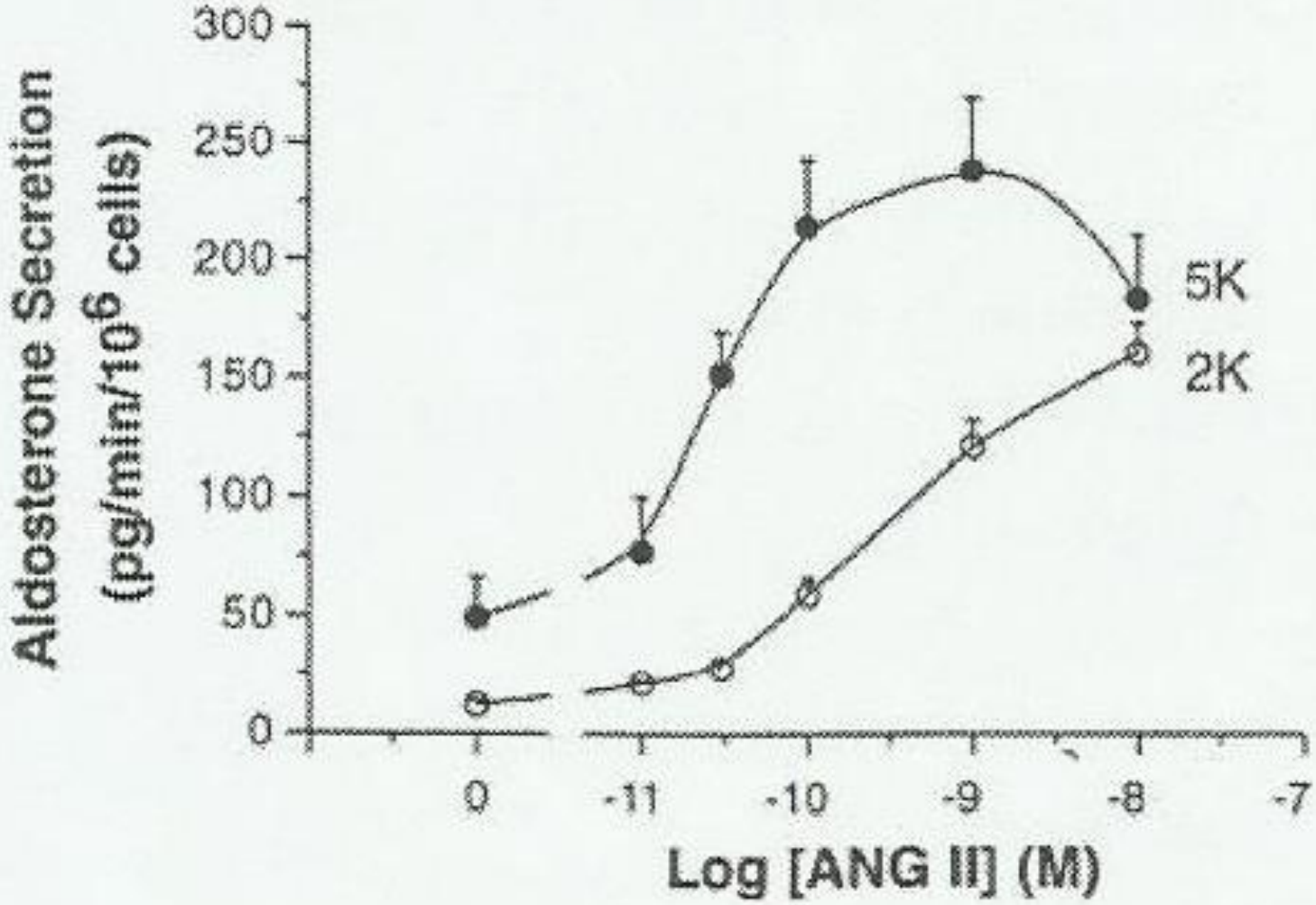
Plasma aldo

Urine aldo

Urine PGE_2

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

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

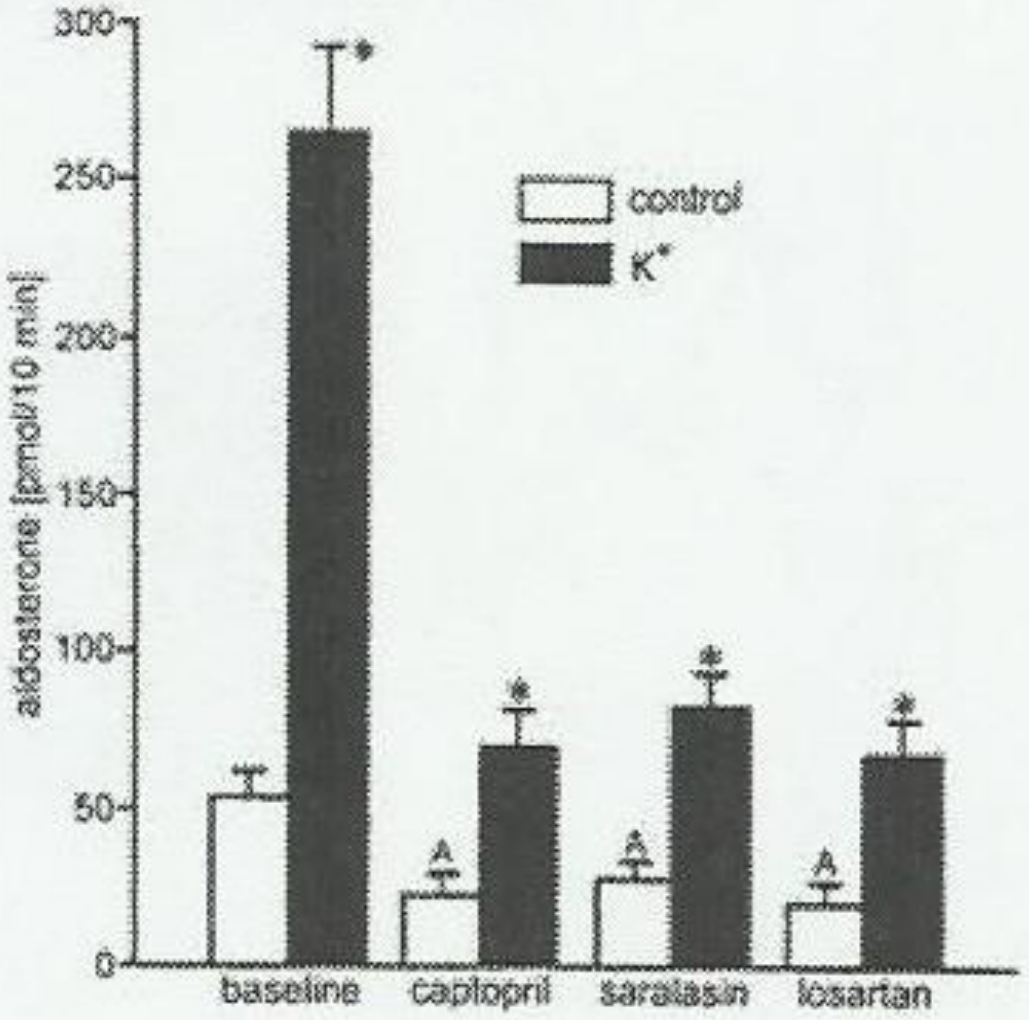


Chen et al, *AJP-Renal*, 276, 1999

An Intact Adrenal RAS is Required For the Responce to Hyperkalemia

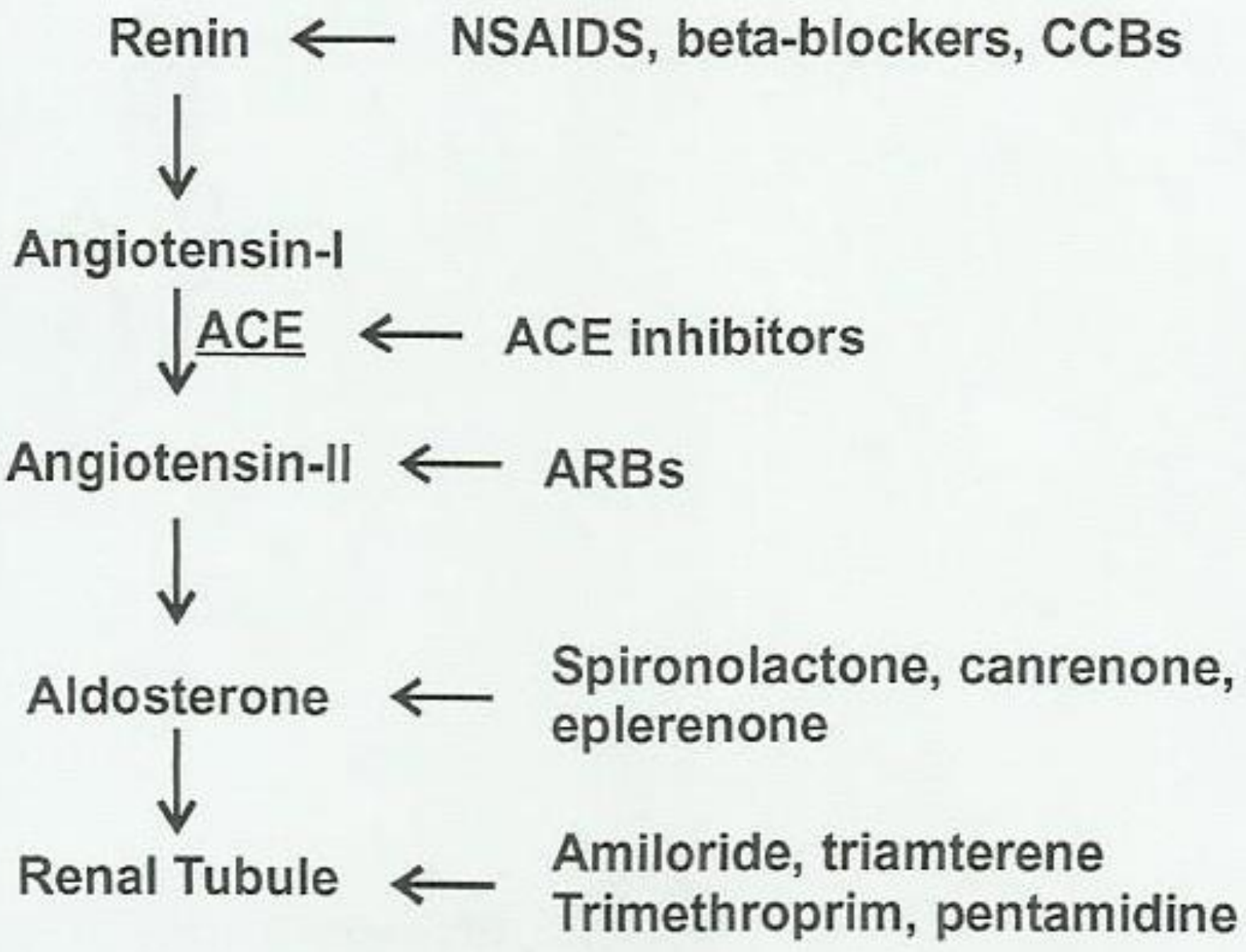
Aldo release from perfused adrenals, NaCl-restricted animals

TAKE-HOME MESSAGE:
RAS inhibition blunts adrenal response to hyperK



Mazzocchi et al, AJP-Renal, 278, 2000

Drugs and the RAS



Hypokalemia

- Pseudohypokalemia – leukocytosis, with uptake of K^+ by WBCs, e.g. in AML
- Redistribution
  - Insulinopenia → DKA
  - Sympathomimetics
  - β_2-agonists, dopamine, theophyline
  - Hypokalemic periodic paralysis, incl. thyrotoxic
  - Acute anabolic state → pernicious anemia
- Non-renal loss → skin, stomach (suctioning), intestine (diarrhea, laxatives)

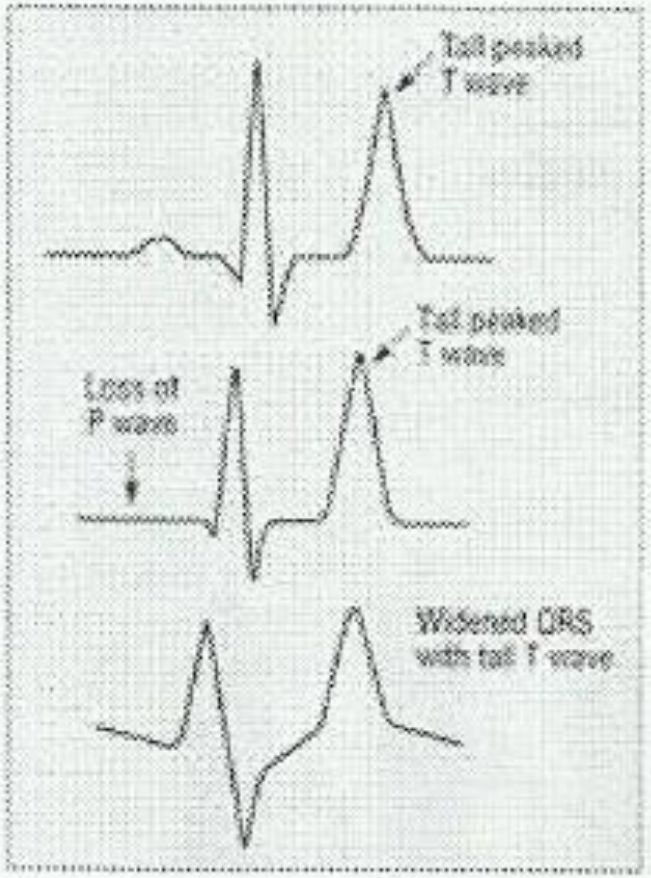
Renal Loss and Hypokalemia

- Drugs
  - Diuretics
  - Antibiotics
    - Penicillin, ampho, AGAs
- Aldosterone excess
- Bicarbonaturia
- **Magnesium deficiency**
- Tubular damage
  - ATN
  - cisplatin
- Intrinsic renal transport defects
  - Liddle's syndrome
  - Bartter's syndrome
  - Gitelman's syndrome

Consequences of Hyperkalemia

- Excitable tissue – change in resting membrane potential
  - Cardiac, decreased myocardial conduction velocity, ↑PR and ↑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



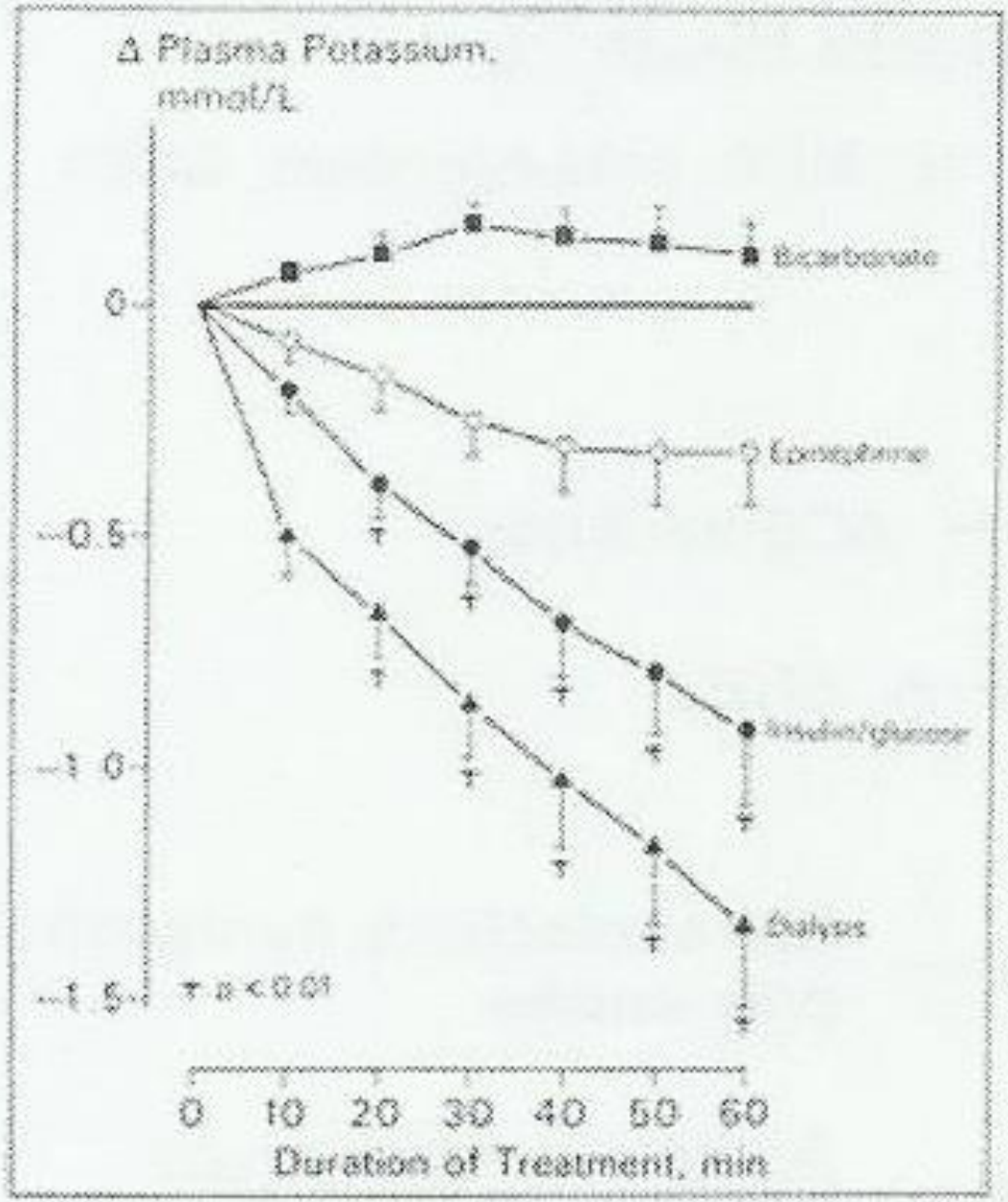
Serum K+	*Major change*
5.5-6.5	Tall peaked T waves
6.5-7.5	Loss of P waves
7.0-8.0	Widening of QRS
8.0-10	Sine wave, ventricular arrhythmia, asystole

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

Treatment of Hyperkalemia

Mechanism	*Therapy*	*Dose*	*Onset*	*Duration*
Stabilize membrane potential	Calcium	10% Ca-gluconate, 10 ml over 10 min.	1-3 min.	30-60 min
Cellular K^+ uptake	Insulin	10 U R with 50 ml of D50, if BS<250	30 min.	4-6 h
	β_2-agonist	nebulized albuterol, 10 mg	30 min.	2-4 h
K^+ removal	Kayexalate	60 g PO in 20% sorbitol	1-2 h	4-6 h
	Hemodialysis		Immediate	



Bicarb Doesn't Work!

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

Insulin and Glucose

- Recommended dose is 10 units of regular insulin followed by 50 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^+

β2-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**

Kayexalate Complications

- Ischemic colitis and colonic necrosis
  - more common in enema form
  - attributed to the sorbitol content
  - post-transplant and post-op patients are at higher risk
- Volume overload
- Reduction in serum calcium
- Iatrogenic hypokalemia
- Interference with lithium absorption

Hemodialysis

- Serum K^+ level reaches a nadir at ~3 hours, but potassium removal continues to the end of the session
- 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 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

Treatment of Hypokalemic Thyrotoxic Paralysis

- K^+ replacement frequently (~50%) accompanied by rebound hyperkalemia.
- Given the hyperadrenergic state induced by thyroxine, high-dose propranolol (3 mg/kg) may be a better treatment.

Figure 2. The clinical approach to hypokalemia[4].
FHPP: familial hypokalemic periodic paralysis; GI: gastrointestinal; TTKG: transtubular potassium gradient; CCD: cortical collecting duct; BP: blood pressure; RTA: renal tubular acidosis; DKA: diabetic ketoacidosis; RAS: renal artery stenosis; RST: renin secreting tumor; HTN: hypertension; PA: primary aldosteronism; GRA: glucocorticoid remediable aldosteronism; AME: apparent mineralocorticoid excess.

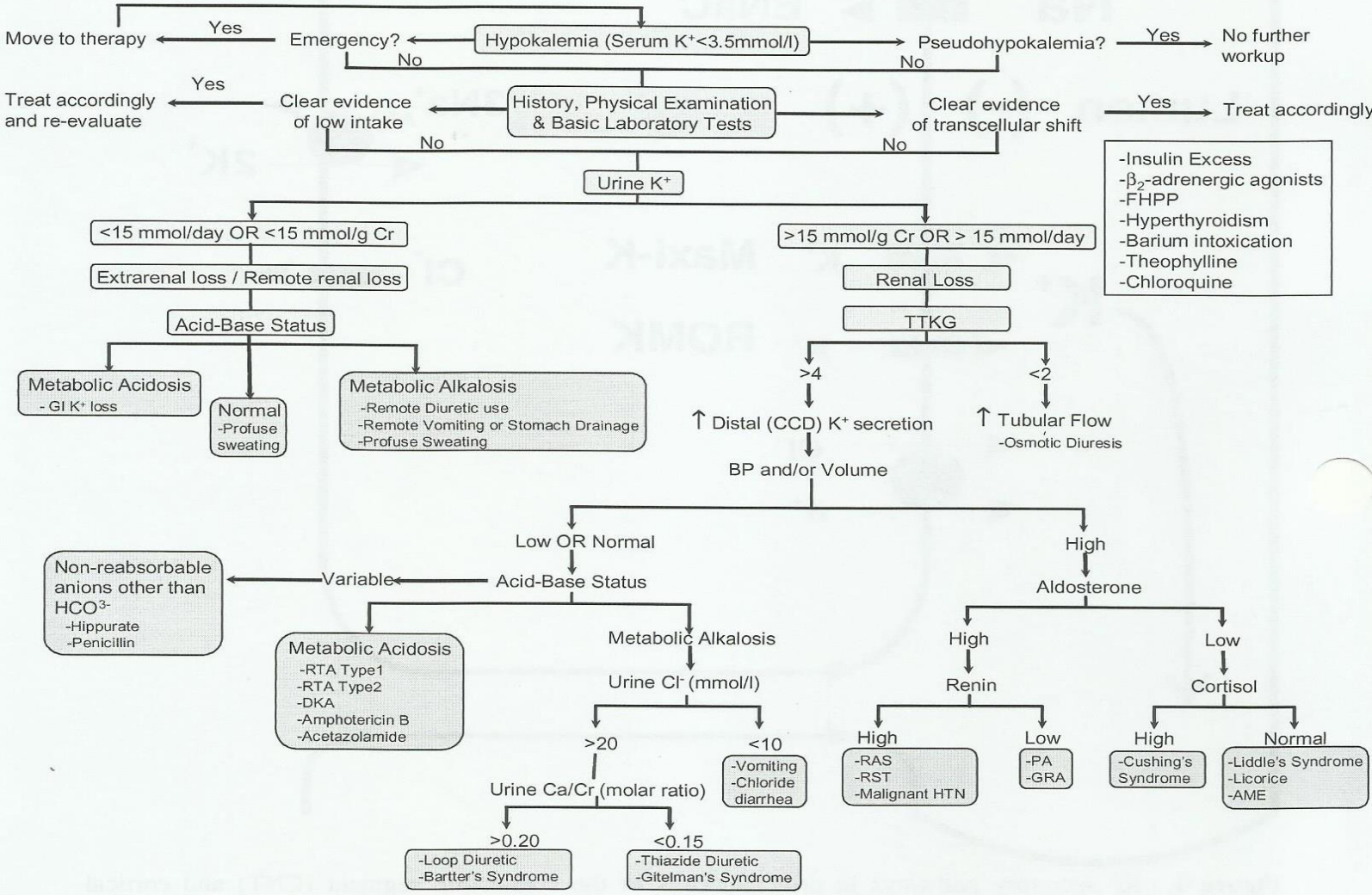


Figure 3. The clinical approach to hyperkalemia[4].
ECG: electrocardiogram; TTKG: transtubular potassium gradient; CCD: cortical collecting duct; GFR: glomerular filtration rate; ECV: effective circulatory volume; acute GN: acute glomerulonephritis; HIV: human immunodeficiency virus; NSAIDs: non-steroidal anti-inflammatory drugs; LMW heparin: low molecular weight heparin; ACE-I: angiotensin converting enzyme inhibitor; ARB: angiotensin II receptor blocker; PHA: pseudohypoaldosteronism; SLE: systemic lupus erythematosus.