Diuretic Resistance
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Diuretic Resistance: When What You are Doing Stops Working

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Disclosures

- None, just working for The Man like all of us

A disease is not a disease unless it affects the kidneys

Joel Chinitz M.D. Philadelphia

A good heart and set of kidneys can withstand all but the most woefully incompetent fluid regime

Gottlieb AJ, *The Whole Internists Catalogue,* W.B. Saunders, 1980

Objectives

- Understand where in the kidney each class of diuretics work
- Discuss how the body responds to chronic diuretic therapy
- Discuss the causes of diuretic resistance
- Discuss strategies to overcome diuretic resistance

Resting Fluid Balance

Minimal obligatory water intake	
Ingested	500 ml
Water in food	600 ml
Water from oxidation	500 ml
Total	1600 ml/day

Minimal obligatory water output	
Urine	500 ml
Skin	500 ml
Respiratory	400 ml
Stool	200 ml
Total	1600 ml/ day

Sodium and Water in the Kidney

- 99% of filtered sodium is reabsorbed
- 1% excreted
- 99-99.5% of filtered water is reabsorbed
- 0.5-1% excreted
- In states of excess sodium and water-more excretion
- In dehydration-body holds onto sodium and water

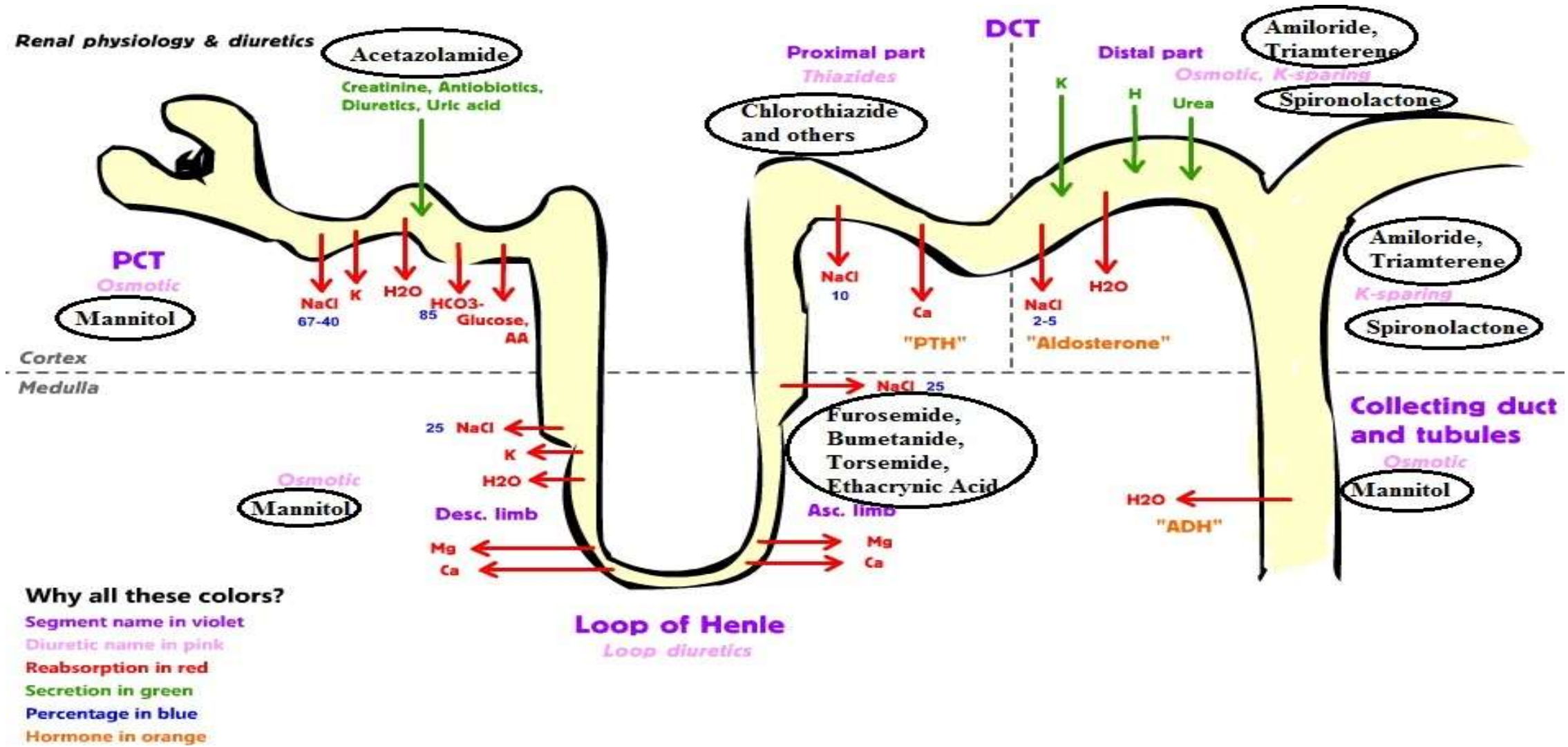
Diuretics Definition

- A substance that will increase the output of urine

Sites of Action on the Nephron

- Proximal Tubule: Carbonic anhydrase inhibitors and Sodium Glucose Luminal Cotransporter inhibitors (SGLT-2)
- Thick Ascending Limb: Loop diuretics
- Distal Tubule: Thiazides
- Distal Tubule/Collecting Duct: Potassium sparing, mineralocorticoid receptor blockers
- Multi-segmental: Osmotic diuretics

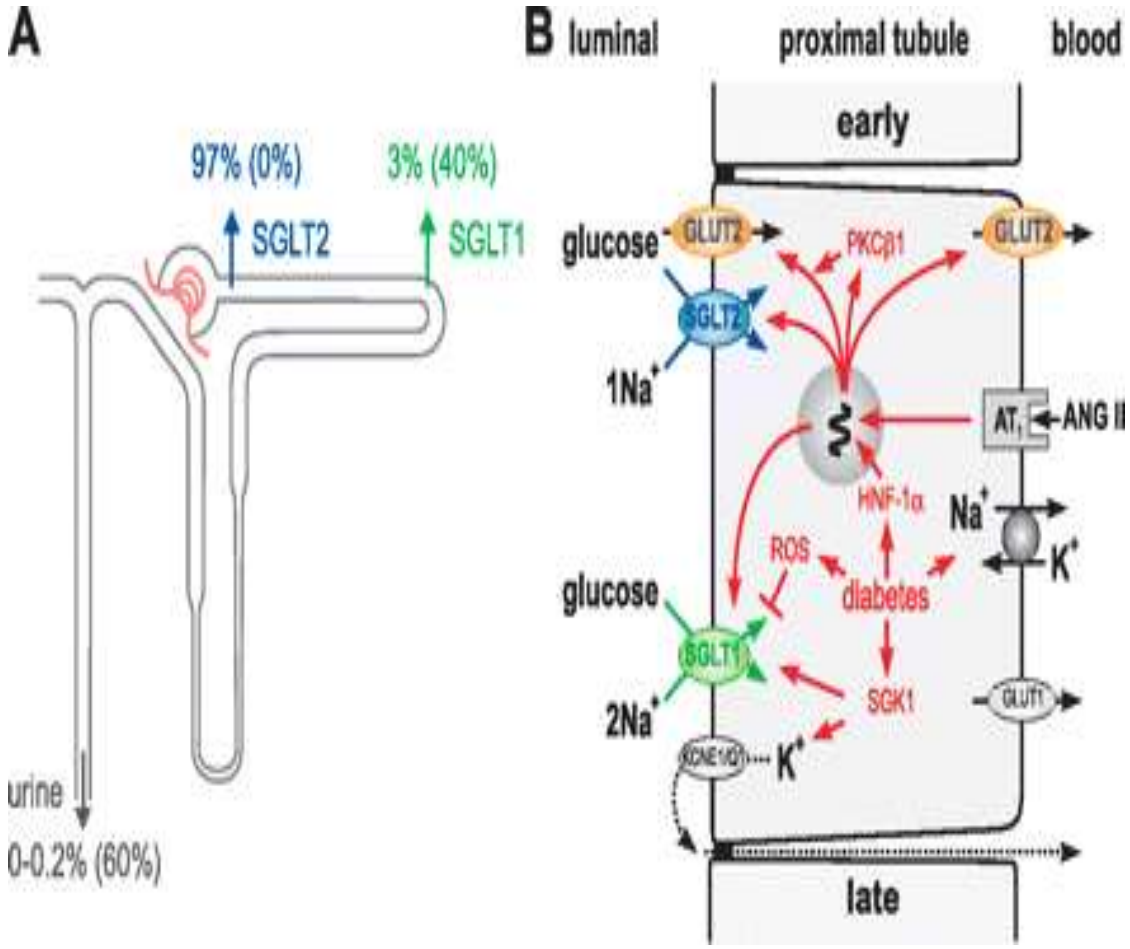
Diuretic Actions on the Nephron

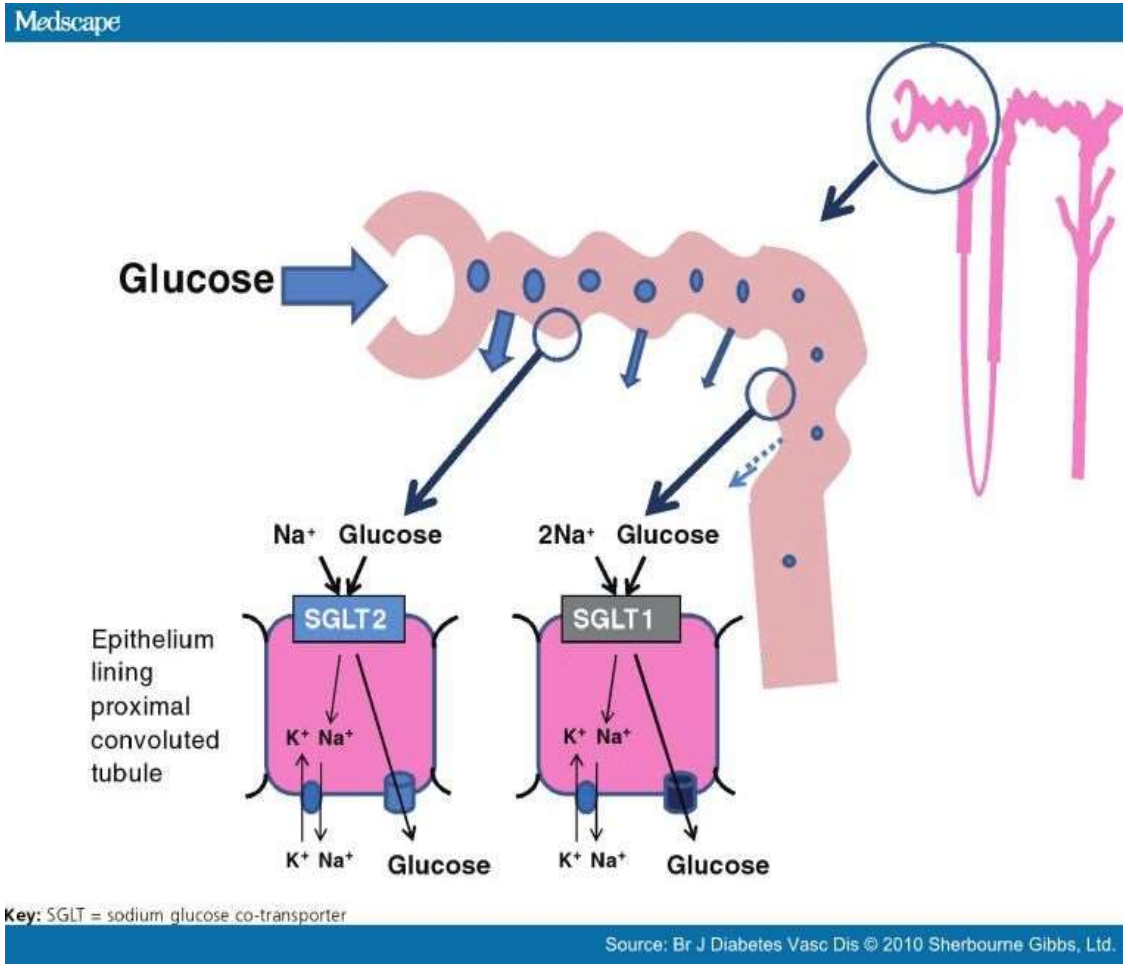


SGLT-2 Inhibitors

- Although not classified as a diuretic per se, they *decrease* reabsorption of sodium along with glucose in the proximal tubule leading to loss of sodium and water along with glucose in the urine.
- By blocking SGLT-1/2 the Sodium and Glucose is passed dpwnstream

MOA of SGLT-2's





Diuretic Effects of SGLT-2's

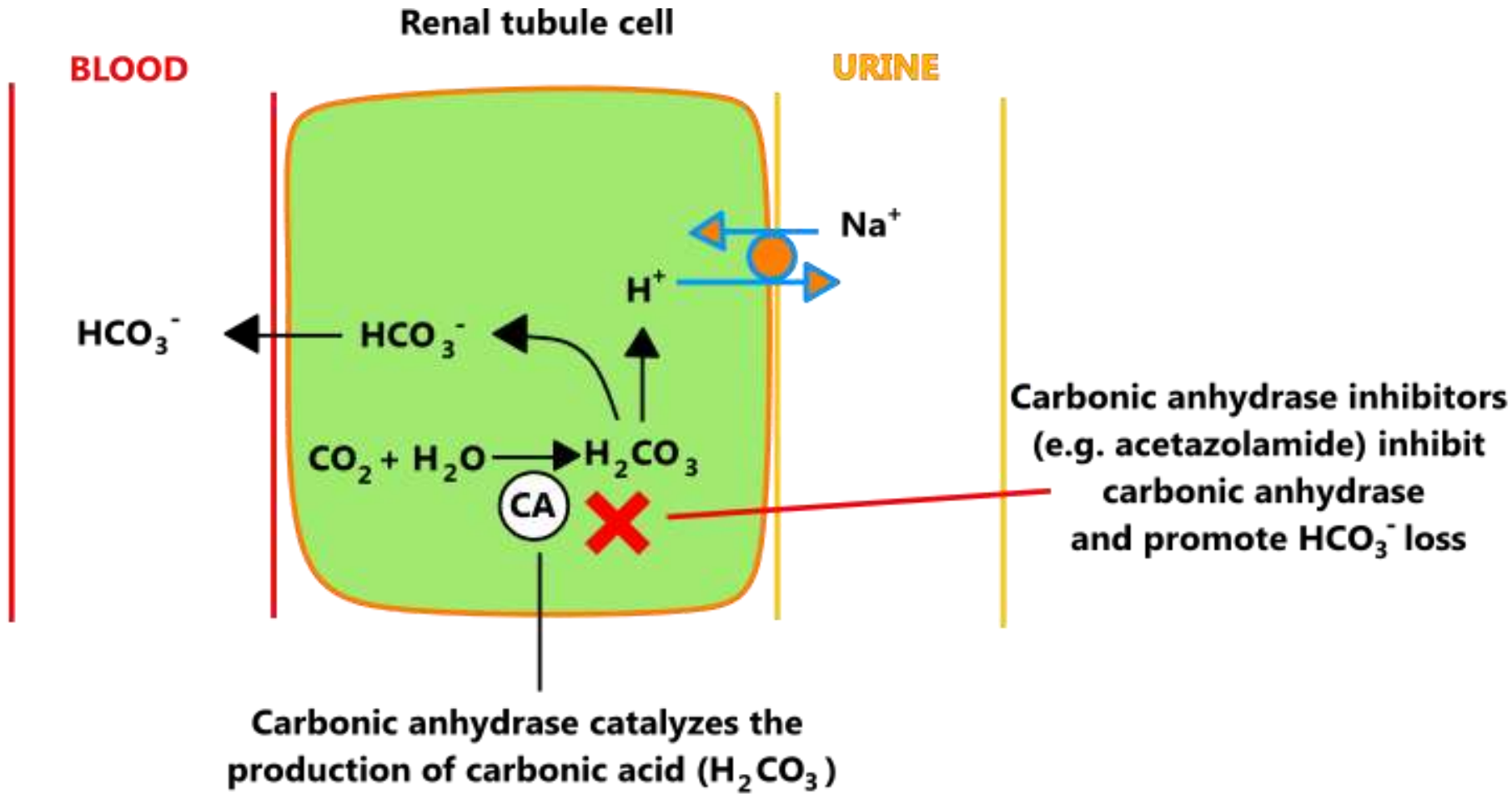
- Decreased sodium reabsorption and osmotic diuretic effects
- 1.5-6kg weight loss, partially due to sodium and water loss
- ~4.45 mm Hg SBP decrease in SGLT-2 treated patients

Diabetes Care 2015;38: 2344-2353.

Carbonic Anhydrase Inhibitors

- *Weak diuretic* action leads to loss of Na, Cl and Bicarbonate in the urine leading to metabolic acidosis (induces a Proximal Type 2 RTA)
- Volume loss leads to *hypokalemia*
- *Indications*: glaucoma, altitude sickness (additive to respiratory alkalosis), idiopathic intracranial hypertension, epilepsy (topiramate), chronic metabolic alkalosis
- Acetazolamide (Diamox)
- Maybe considered as last resort add-on diuretic therapy

Carbonic Anhydrase Inhibitors

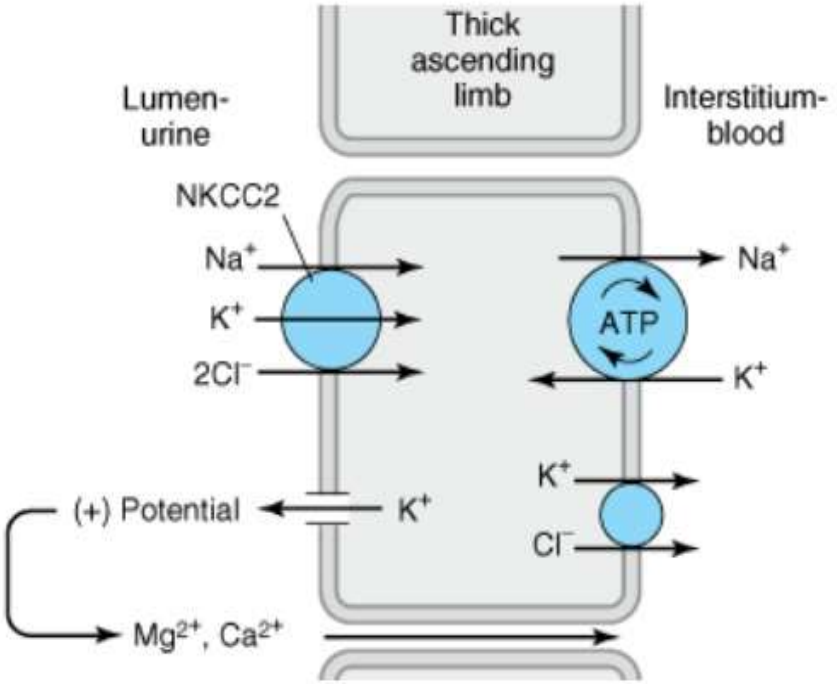


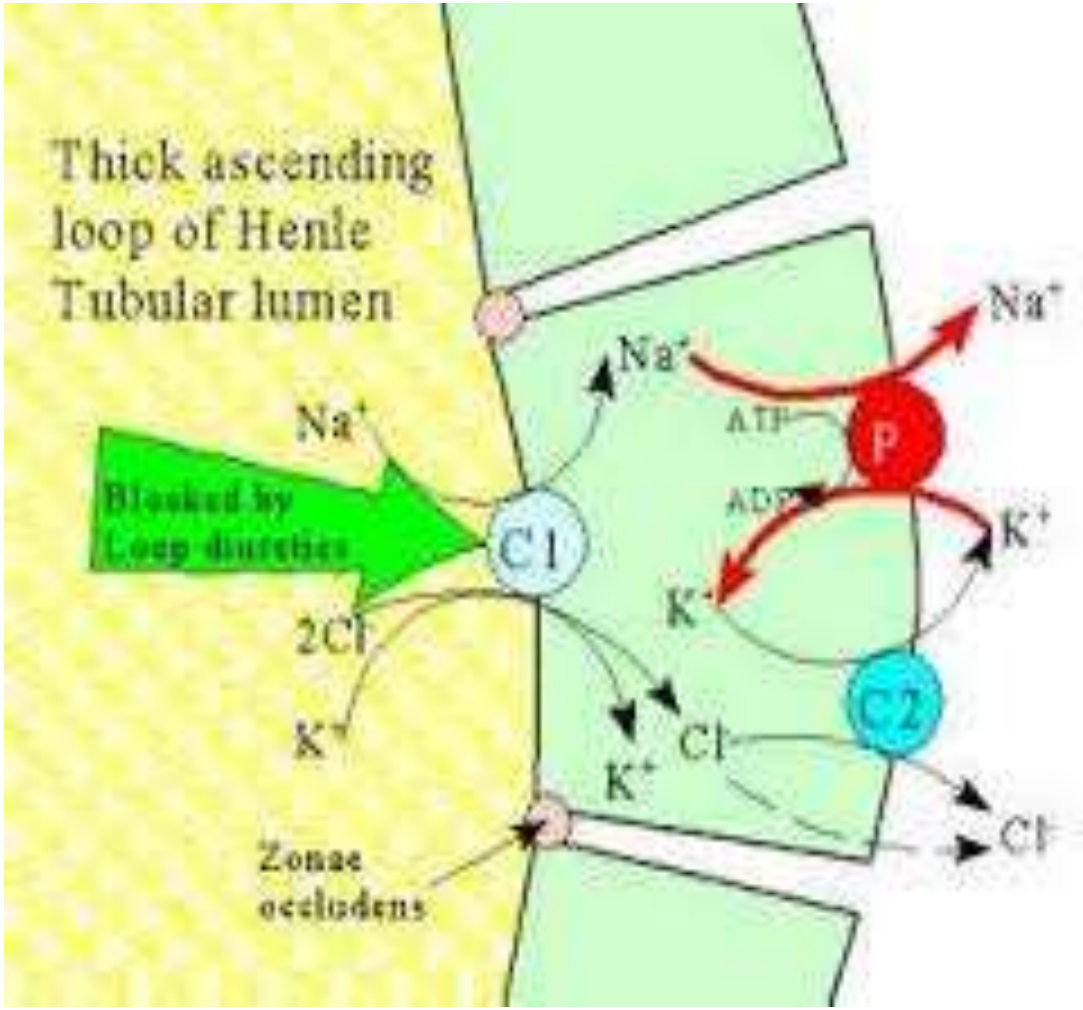
Reference [5]

Loop Diuretics

- Powerful medications used to mobilize fluid in CHF, cirrhosis, hypertension, CKD and nephrotic syndrome
- “High ceiling”-significant increased urine output up to a point
- Loop diuretics need to be *bound* to albumin and *secreted* in the *proximal* tubule. It then competes with Chloride, thus blocking the Na/K/2CL Symporter/Cotransporter (NKCCT-2) in the *Thick Ascending Limb* (TAL)

MOA Loop Diuretics





Loop Diuretics

- *The Na/K/2Cl* (NKCCT-2) symporter is responsible for 20-40% of the reabsorption of Na, K and Cl.
- By blocking the NKCCT-2 sodium is sent downstream and excreted
- Euvolemic patients will have a urine Na content of ~75 mEq/l=1/2 NS
- Also leads to loss of Magnesium and Calcium

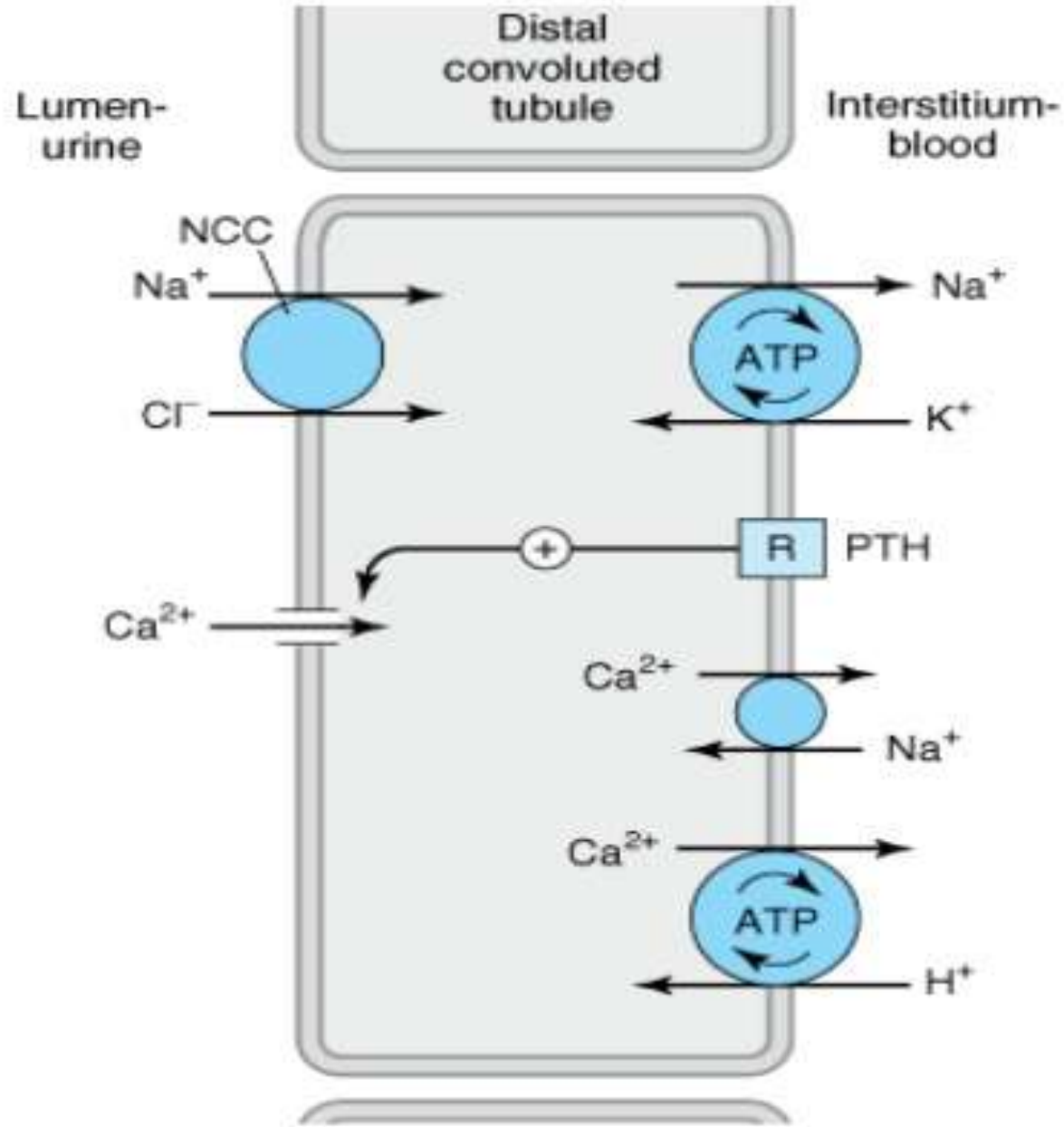
Loop diuretics

- Furosemide, torsemide, bumetanide, *ethacrynic acid* (only agent that can be used in a patient with a *true sulfa allergy*)
- *Variable* oral *absorption* from the *GI tract* can influence diuretic actions, torsemide has an advantage of *consistent* GI uptake
- In *advanced CHF or CKD* doses need to be *increased* for therapeutic effect and frequency e.g. Q8-12 hours
- Chronic therapy will lead to *decreased effect* due to hypertrophy of Na receptors distally/downstream
- Increase calcium loss in the urine in hypercalcuria

Thiazide and Thiazide-like Diuretics

- Medications that *inhibit* the actions of the *Sodium Chloride Cotransporter/ Symporter* (NCCT) in the early segment of the Distal Convoluted Tubule, sending Sodium downstream
- Responsible of about 3-5% of Na reabsorption
- Long term effects hypotensive effects may be due to arteriolar vasodilation
- When combined with loop diuretic can diminish diuretic resistance
- However, thiazides can lead to greater degree of hyponatremia as compared to loop diuretics

Mechanism of Action of Thiazide



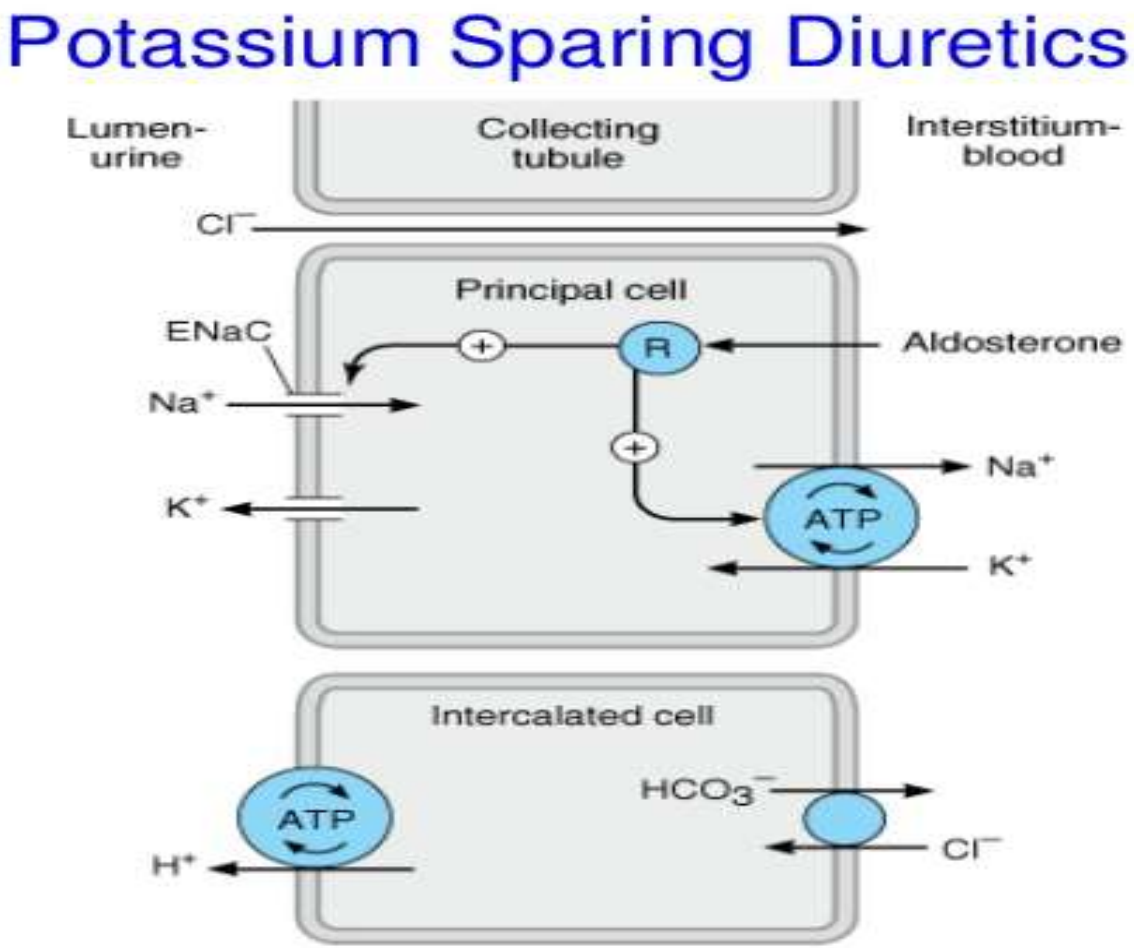
Thiazides

- Enhanced Calcium reabsorption can prevent renal lithiasis
- Thiazides *augment* the effect of most classes of antihypertensives
- Clinically Chlorthalidone and Indapamide are *more* effective than HCTZ in part due to longer $T_{1/2}$
- Use: HTN-1st or 2nd line medication, CHF, edematous states, prevention of calcium stones
- Effective to a GFR of 30 ml/min
- Metolazone is no more effective than Chlorthalidone

Potassium Sparing Diuretics

- *Block Epithelial Sodium Channel* (ENaC) in the Principal cells of the Collecting Duct, thus *no Sodium reabsorbed* into the cell *or Potassium is secreted* into the lumen, thus Sodium is passed downstream
- Responsible for ~3% of Sodium reabsorption
- Mild metabolic acidosis and hyperkalemia, mimics a Distal Type 4 RTA
- Can be used in combination with other classes in diuretic resistance

Potassium Sparing Diuretics



Potassium Sparing Diuretics

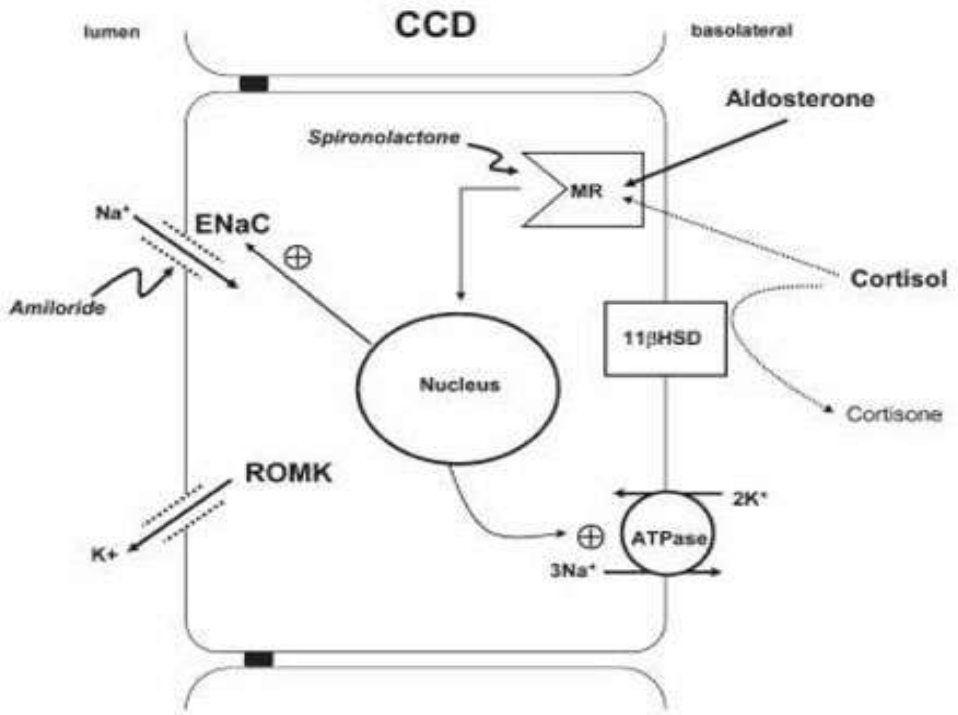
- Amiloride, triamterene, trimethoprim (part of Bactrim), may be combined with a thiazide
- Use: HTN, may prevent toxic effect of Lithium, CHF, edematous states

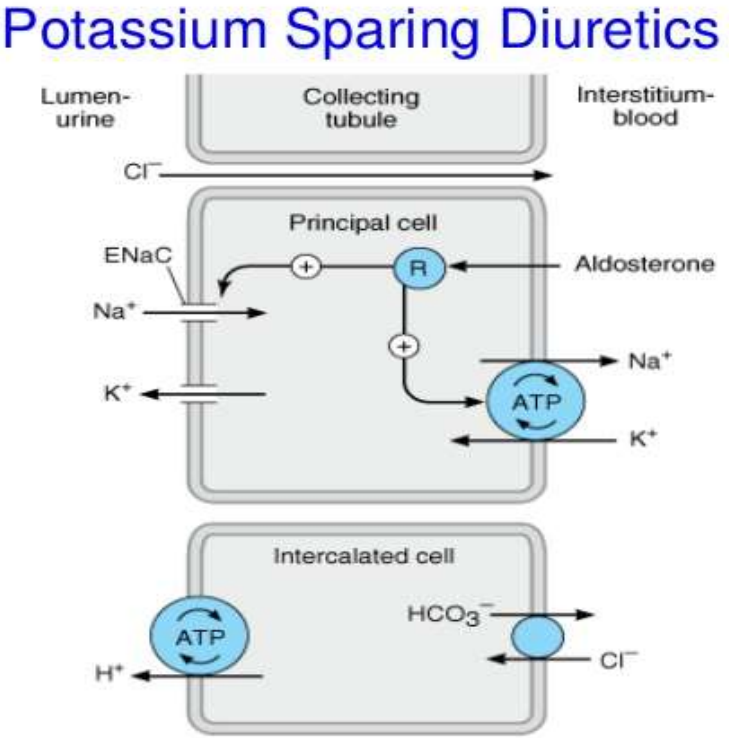
Mineralocorticoid Receptor Antagonists (MRAs)

- Block the effects of aldosterone and similar mineralocorticoids
- Act of the MCR in the Principal cells of the Collecting Duct and other sites, preventing Sodium reabsorption and passing it downstream
- Similar MOA as Potassium sparing diuretics
- Spironolactone and Eplerenone
- *Used* in HTN, CHF, CKD, Cirrhosis
- Hyperkalemia and metabolic acidosis as with K sparing diuretics
- *Improved* survival in CHF, even w/ worsening CKD

Cardiorenal Med 2017;7:128-136. *NEJM* 1999;341:709-717(RALES Study)

MRAs MOA


lumen
CCD
basolateral
Aldosterone
Spironolactone
MR
Na+
ENaC
Amiloride
Cortisol
11βHSD
Nucleus
Cortisone
ROMK
K+
2K+
ATPase
3Na+

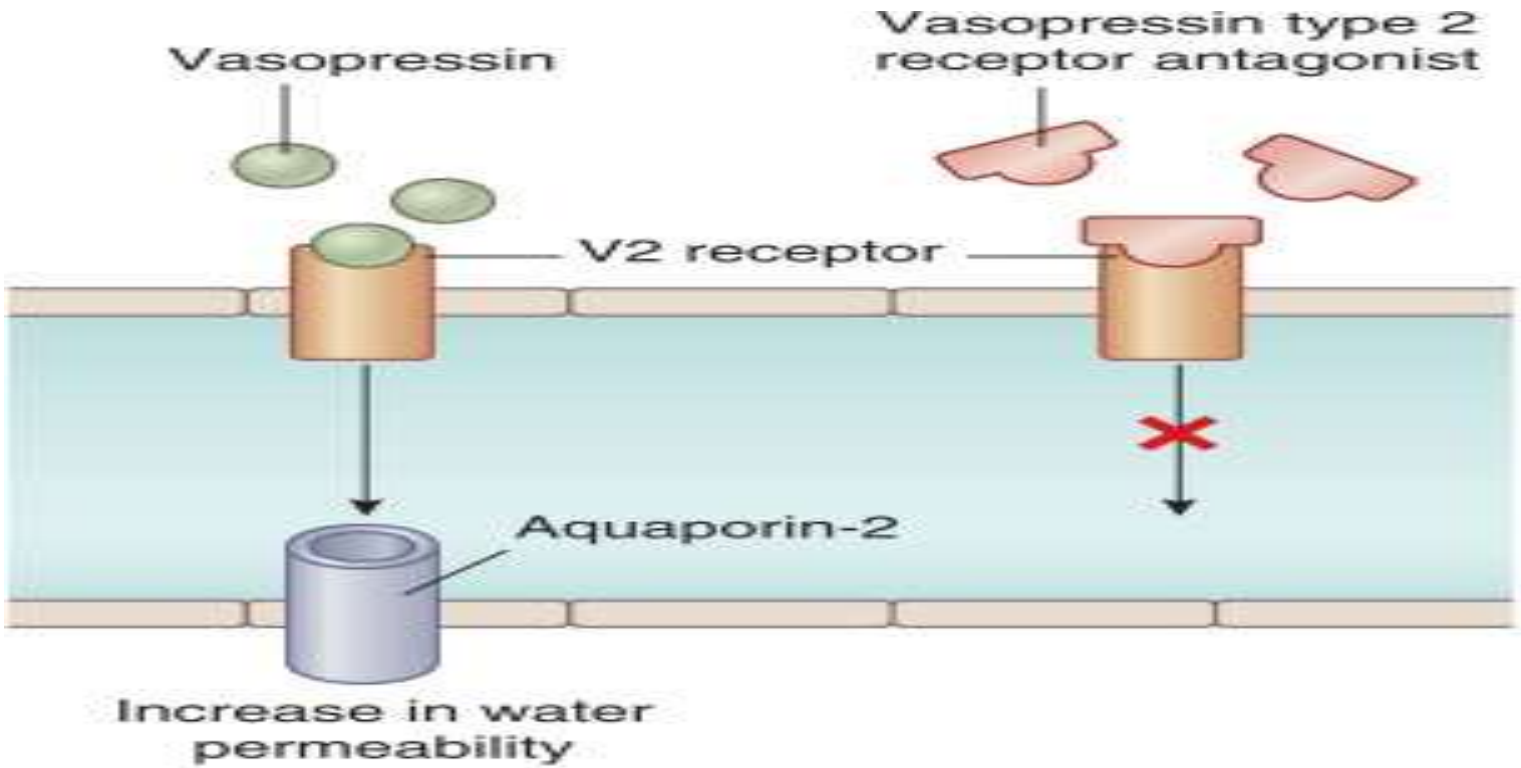

Potassium Sparing Diuretics
Lumen-urine
Collecting tubule
Interstitium-blood
Cl⁻
Principal cell
ENaC
R
Aldosterone
Na+
K+
ATP
Na+
K+
Intercalated cell
ATP
HCO3⁻
Cl⁻
H+

Vasopressin Receptor Antagonists(VRA)

- *Block* the actions of Antidiuretic Hormone at the V_1 and/or V_2 receptors leading to a free water diuresis (induces a nephrogenic diabetes insipidus)
- Tolvaptan V_2 Concerns about liver and renal effects
- Conivaptan V_{1a} and V_2
- EVEREST Trial-Tolvaptan in ADCHF-*no* long term benefit vs placebo, though some short term fluid/symptom improvement was noted in treatment arm

Eur Heart J 2009;30:2233-2240

How VRAs Work



- Concentrated urine
- Decreased free water clearance
- Lowering of serum sodium

- Dilute urine
- Increased free water clearance
- Raising of serum sodium

Vasopressin Receptor Antagonists

- Use: SIADH, Cirrhosis/ESLD, CHF, polycystic kidney disease
- BUT-may lead to overcorrection of hyponatremia and CNS damage (FDA black box warning)
- Not sure where this class of medications will fit in clinically

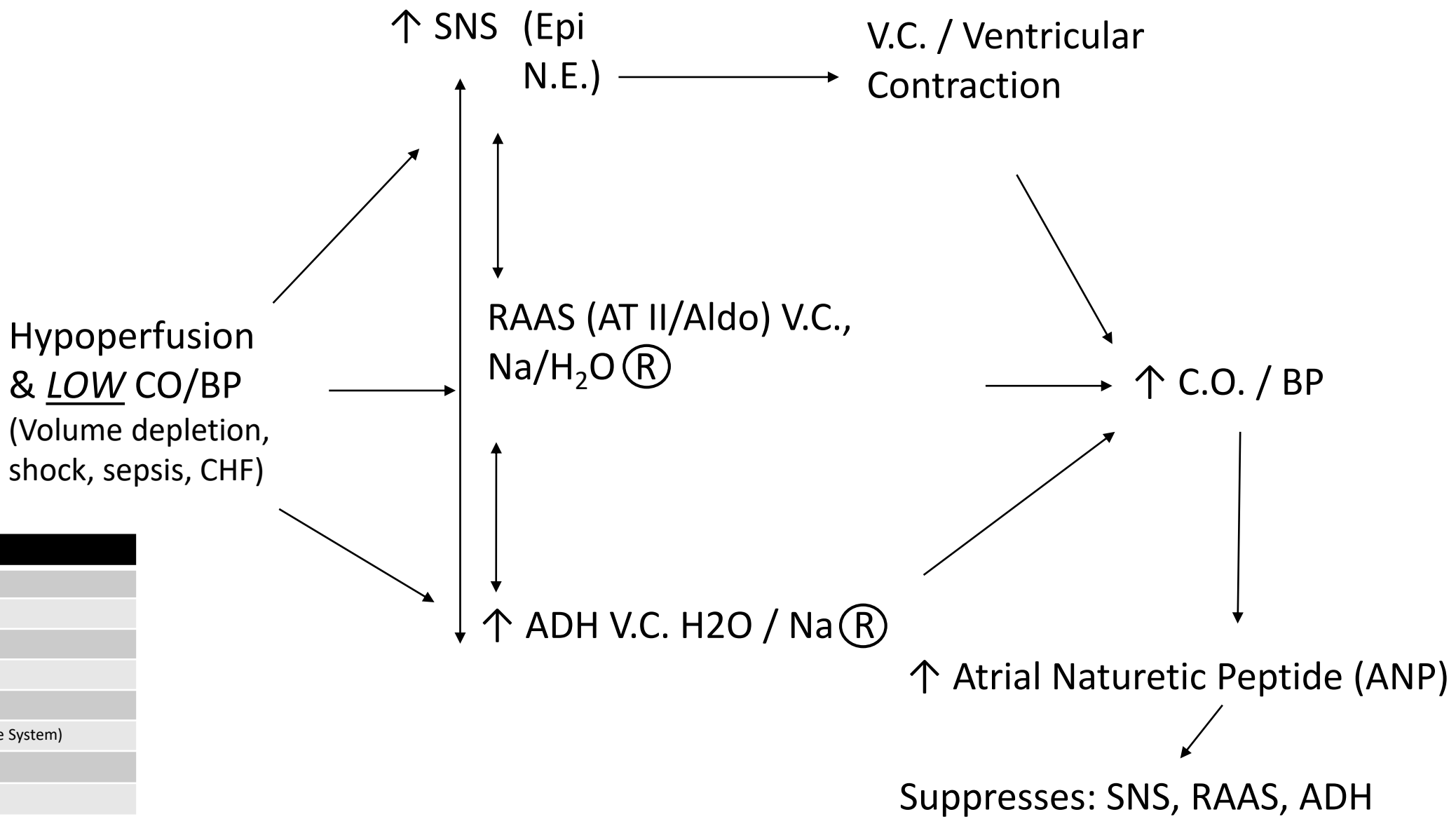
Diuretic Resistance

- Definition: the inability to mobilize and excrete excessive extracellular fluid, usually due to under dosage or failure of current diuretic regime.

Causes of Diuretic Resistance

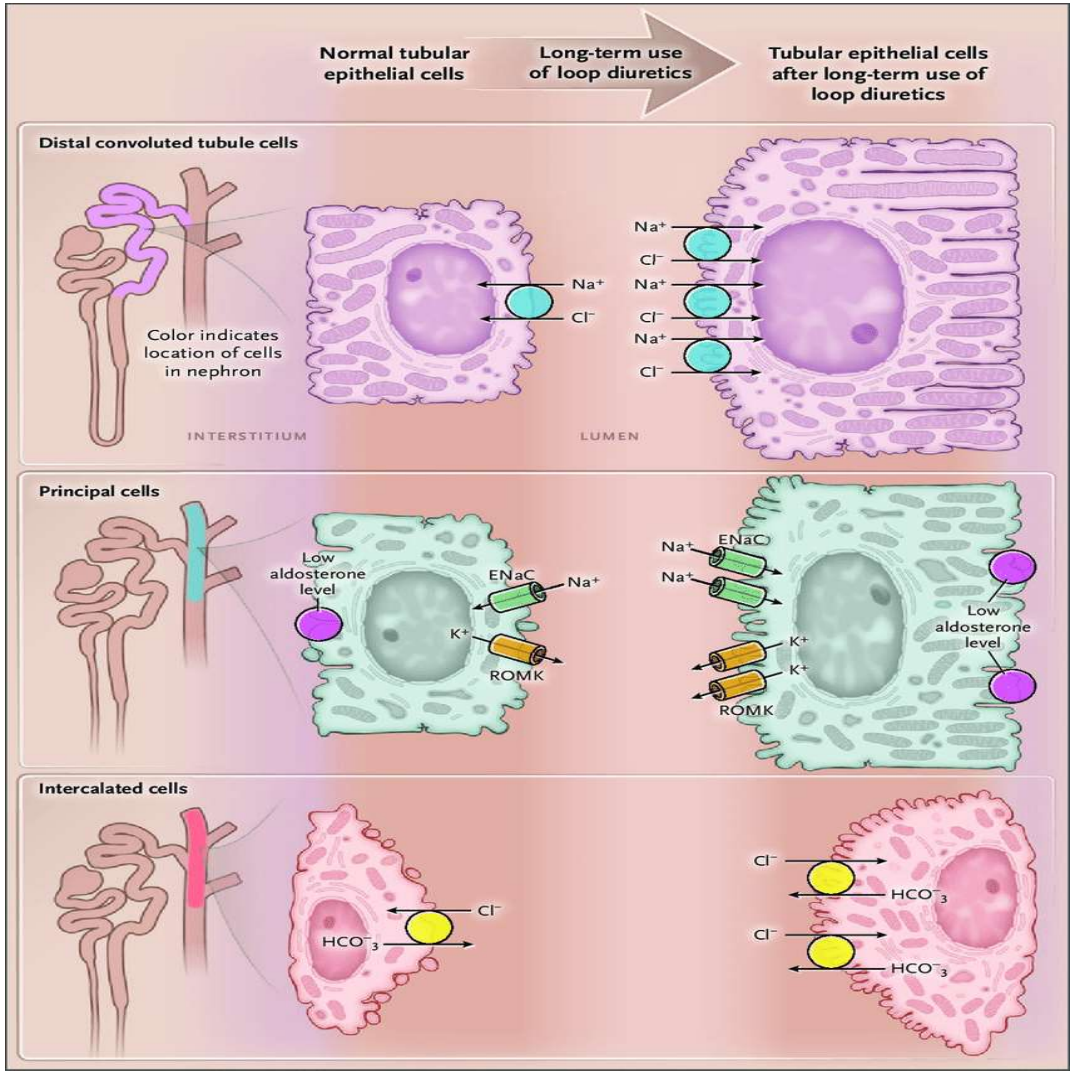
- Increased sodium reabsorption at other sites in the kidney downstream (remodeling)
- Under dosage and frequency
- Excess salt intake
- Hypoalbuminemia
- Decreased gut absorption
- Decreased diuretic secretion in urine
- Decompensated heart function and/or renal function
- NSAIDs and other medications

How the Body Responds to Volume Depletion and CHF



Glossary	
SNS	Sympathetic Nervous System
Epi	Epinephrine
N.E.	Norepinephrine
V.C.	Vasoconstriction
Ⓡ	Reabsorption
RAAS	(Renin Angiotensin Aldosterone System)
ADH	Antidiuretic Hormone
ANP	Atrial Naturetic Peptide

How the Kidney Adapts to Chronic Diuretic Therapy-Nephron Remodeling



- Sodium uptake from the tubule of blocked by a diuretic
- More sodium is delivered distally, and the is an <u>increase</u> in the number of sodium coupled <u>exchangers</u> to reabsorb the excess sodium in the tubule
- *The body never wants to lose sodium or water-no matter how badly it needs to*

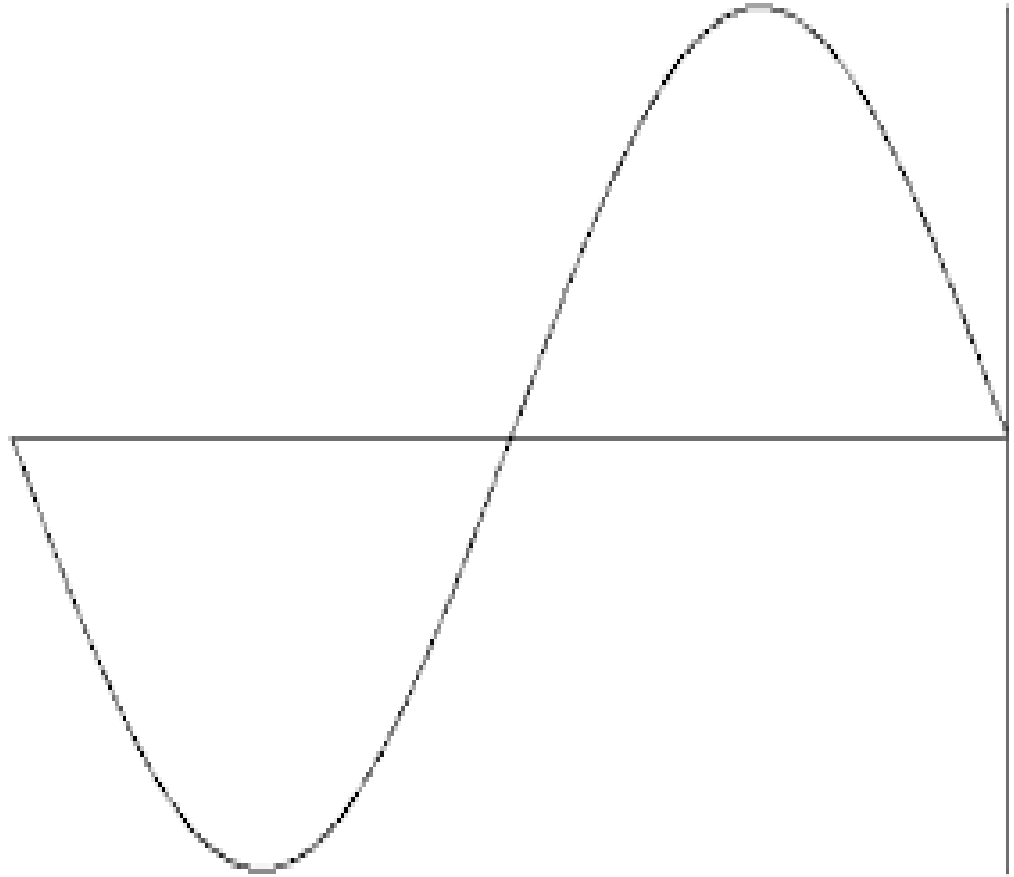
NEJM 2018; 378:684-685

Underdosage

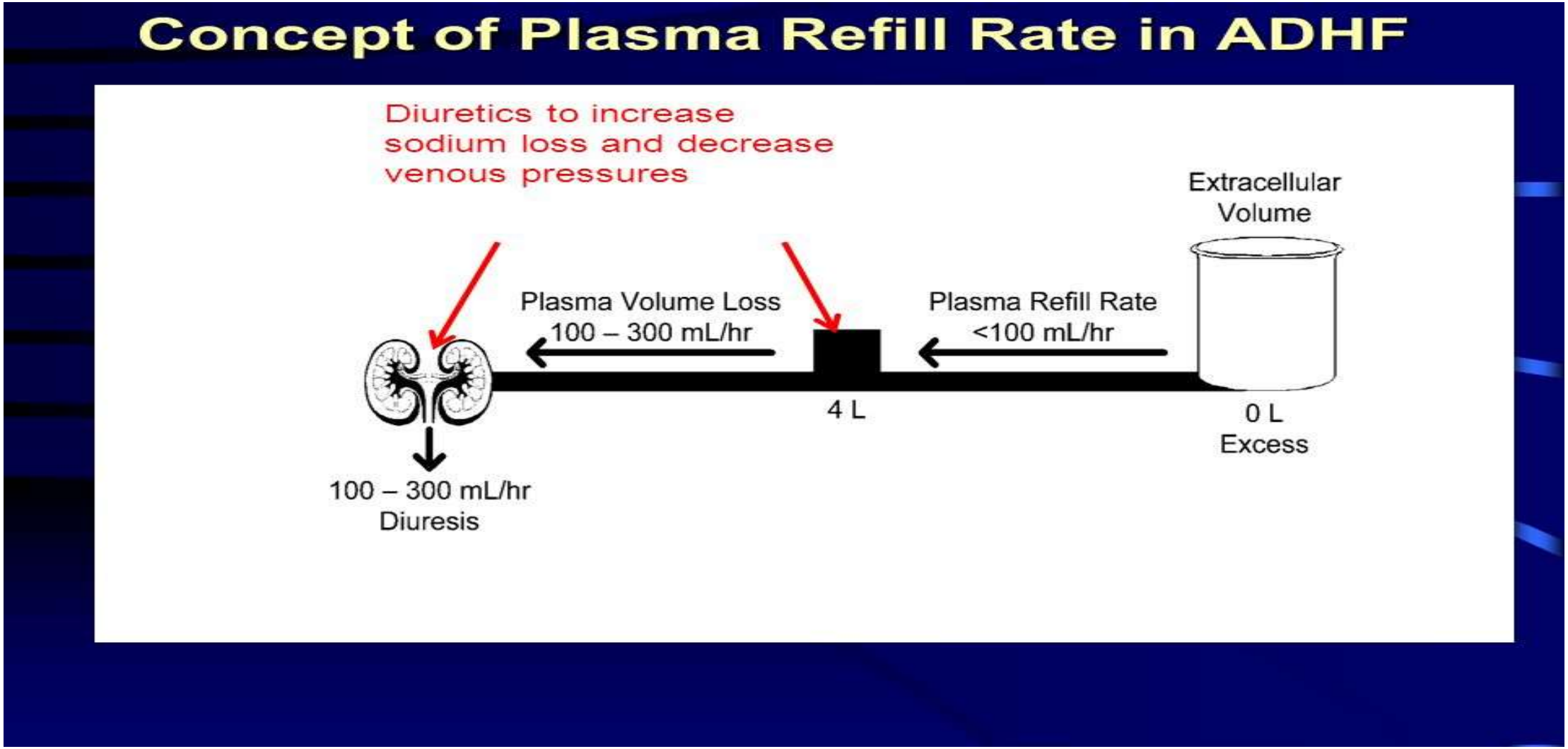
- Threshold rate: Dose of diuretic must overcome the reabsorption at other sites. In chronic diuretic therapy, especially with loops, there is hypertrophy of the distal cells (Na/Cl symporter and ENaC) to increase sodium reabsorption eventually negating the original dose.
- Diuretic Braking: Diminished diuretic effect with subsequent dosages
- Maximum effective dose: dose at which loop Na/Cl transport will be completely inhibited

Once Daily Diuretic Dosage-No Net Fluid Loss

- Initial diuretic effect for several hours leads to enhanced sodium and water reabsorption with no net fluid loss



Refill in Diuretic Therapy



Underdosage

Rule of thumb:

- Increase dose-IV 2x oral dose minimum

AND

Increase frequency Q 8, or 12 hours

- Increase dose in CKD-don’t send a baby in to do a grown-up’s job!
- 20mg of Lasix with a creatinine of 3.2 mg/dl will have little effect

Excess Salt Intake

Recent data has challenged severe salt restriction, no randomized trials have looked at this in CHF

- Will negate the effects of diuretics and most antihypertensive agents
- Think SALT not just sodium, 3-4 gm/da (???)
- If 24 hour urine sodium >100 mEq/l=non compliance
- In a review of 32 studies a “J-shaped curve” of increased CV Risk in daily Na intake <2.5 gm/day and > 6.0 gm/day

Curr Hypertens Rep. 2012;14:193-201

NSAID/Cox-2 Inhibitor Use

- NSAIDs and COX-2 inhibit prostaglandins that vasodilate the afferent arteriole, resulting in vasoconstriction and decreased glomerular perfusion
- Certain prostaglandins have naturetic actions, inhibited by these meds
- Can cause AKI
- PPI’s, herbal medications i.e. licorice root mimics hyperaldosteronism

Hypoalbuminemia

- Albumin less than 2.2 g/dl leads to low oncotic pressure and extravasation of fluid into tissues
- Generalized edema from CHF, cirrhosis, nephrotic syndrome, low oncotic pressure and malnutrition impair absorption of oral diuretics
- Torsemide has more consistent gut absorption in CHF, thus better diuretic action

Clin Pharmacol Ther 1995;57:601-609

Future Cardiol 2012; 169:707-728

Decreased Diuretic Secretion in the Kidney

- Hypoperfusion from hypotension or CHF
- Worsening renal function, NSAIDs compete with diuretics for secretion
- 95% protein bound (low albumin=less diuretic binding)
- Loop diuretics *bind* to *albumin* and are *absorbed* in the proximal tubule cell and then *secreted* as a *free diuretic*
- The free diuretic goes to the thick ascending limb where is *competes* with *chloride* at the Na/K/2 Cl pump
- *Low oncotic pressure* leads to diminished binding of albumin to the loop diuretic, thus limited uptake and action

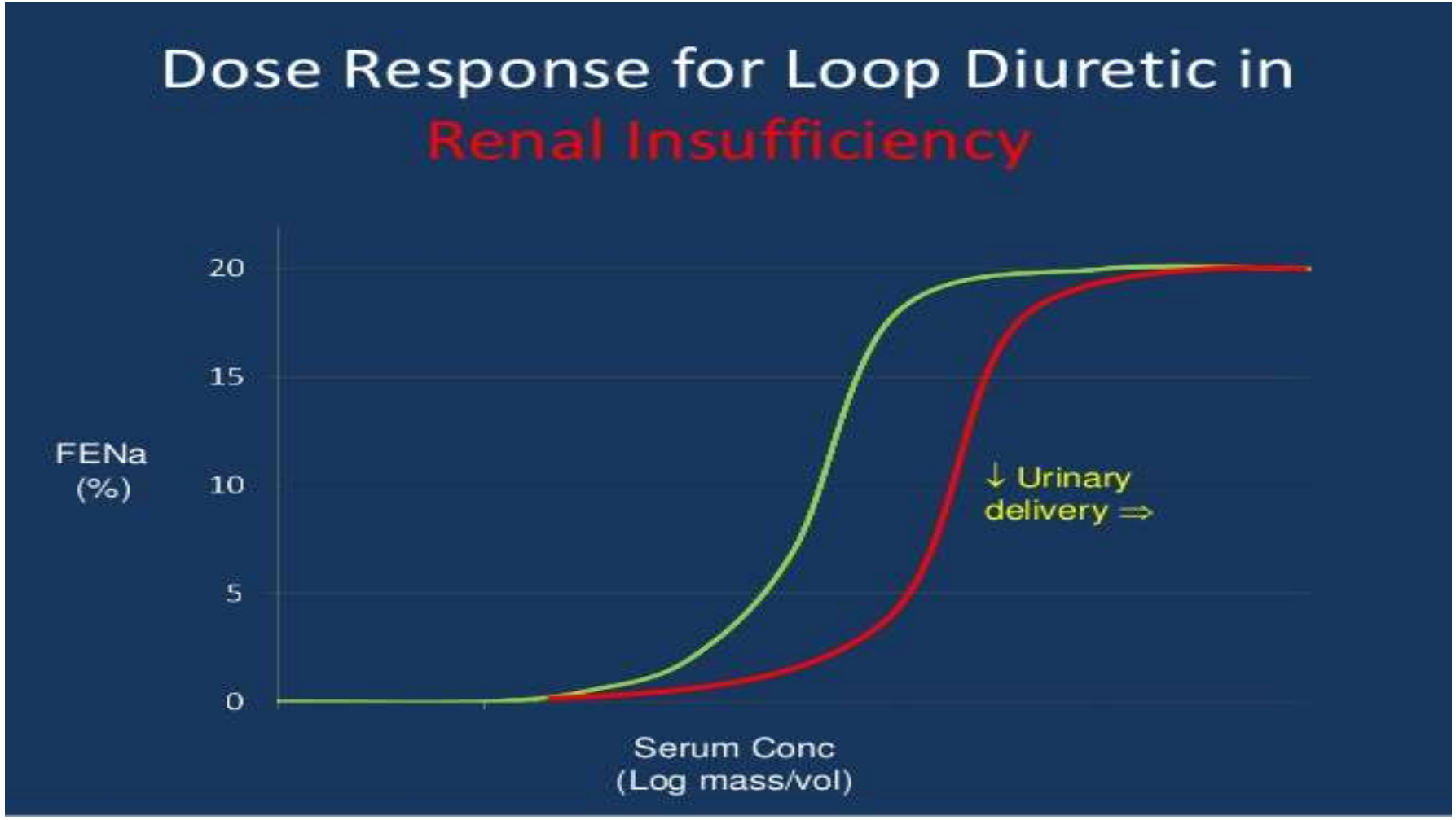
Ellison *N Engl J Med* 2018;377:1964-1975

Decreased Diuretic Secretion in the Kidney

- Increased dose needed in CKD or AKI
- Albumin supplementation when level is <2.2g/dl (?)
- Posture: supine *more* diuretic effect, upright-increased NE and renin/aldosterone-*less* diuretic effect
- Continuous infusion vs bolus (maybe/maybe not-DOSE trial 2011)

Felkner *N Engl J Med* 2011;364:797-805

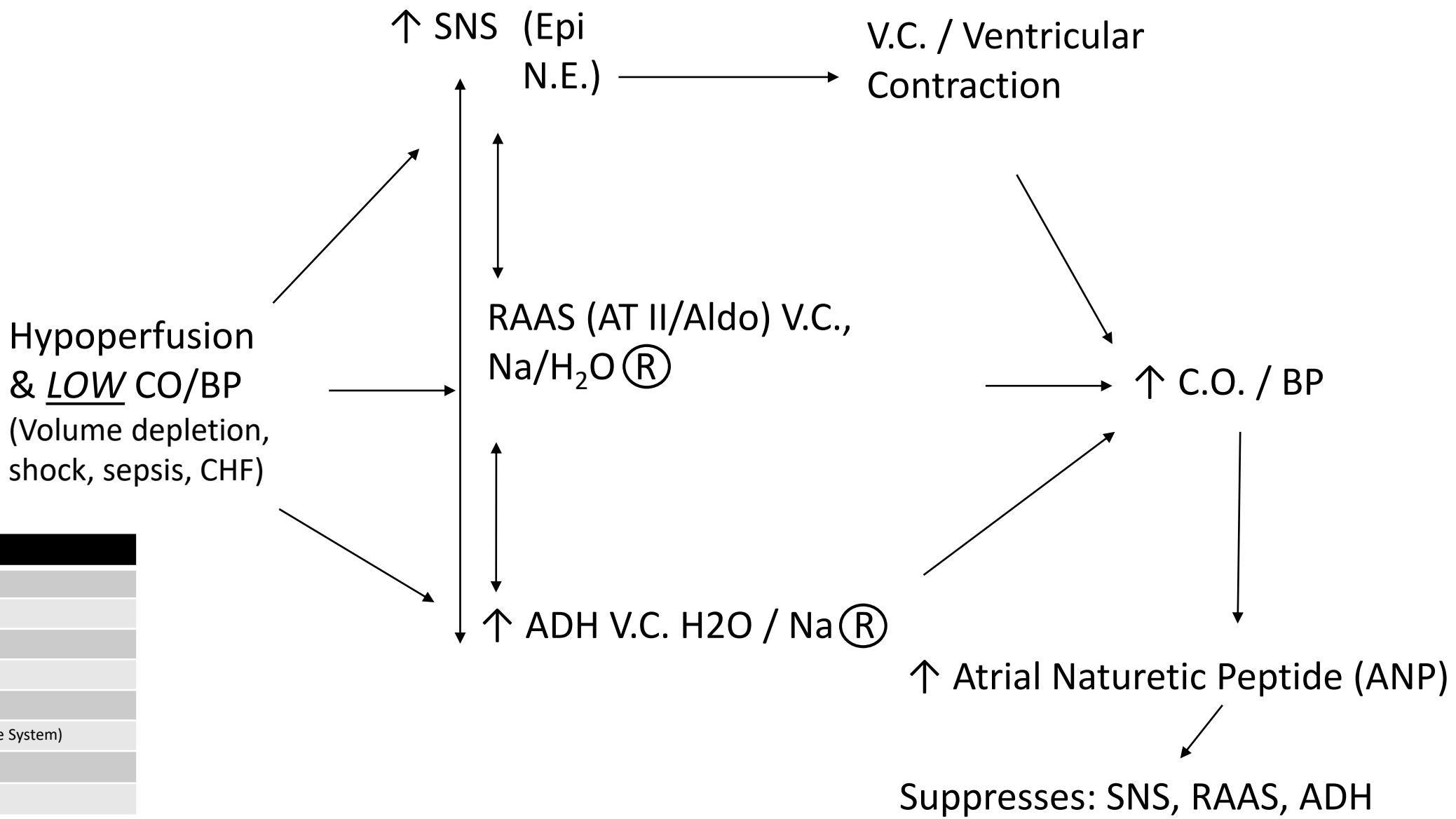
Renal Insufficiency and Diuretic Resistance



Decompensated CHF/CKD/AKI

- Diminished perfusion of the kidney leads to *perceived* volume depletion and increased catecholamines, RAAS activity, and ADH with *enhanced* sodium and water reabsorption
- *Treat/Tweak CHF*: ACE-I/ARB/MRA, adrenergic blockage (carvedilol), nitrates
- Blood pressure control
- Nutrition-salt restriction improved diet

How the Body Responds to Volume Depletion and CHF



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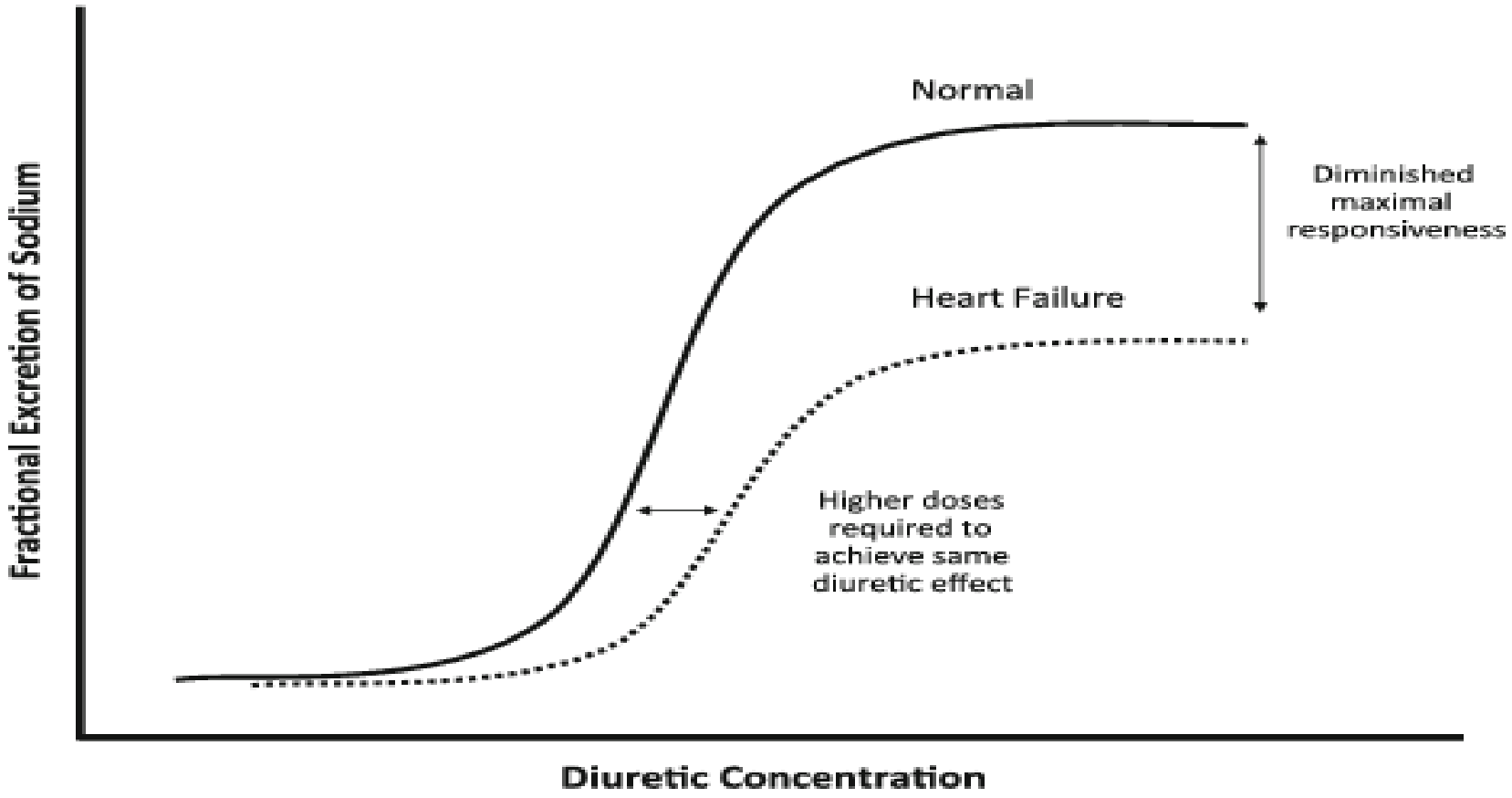
Diuretic Resistance in Decompensated CHF



Approach to a Diuretic Resistant Patient

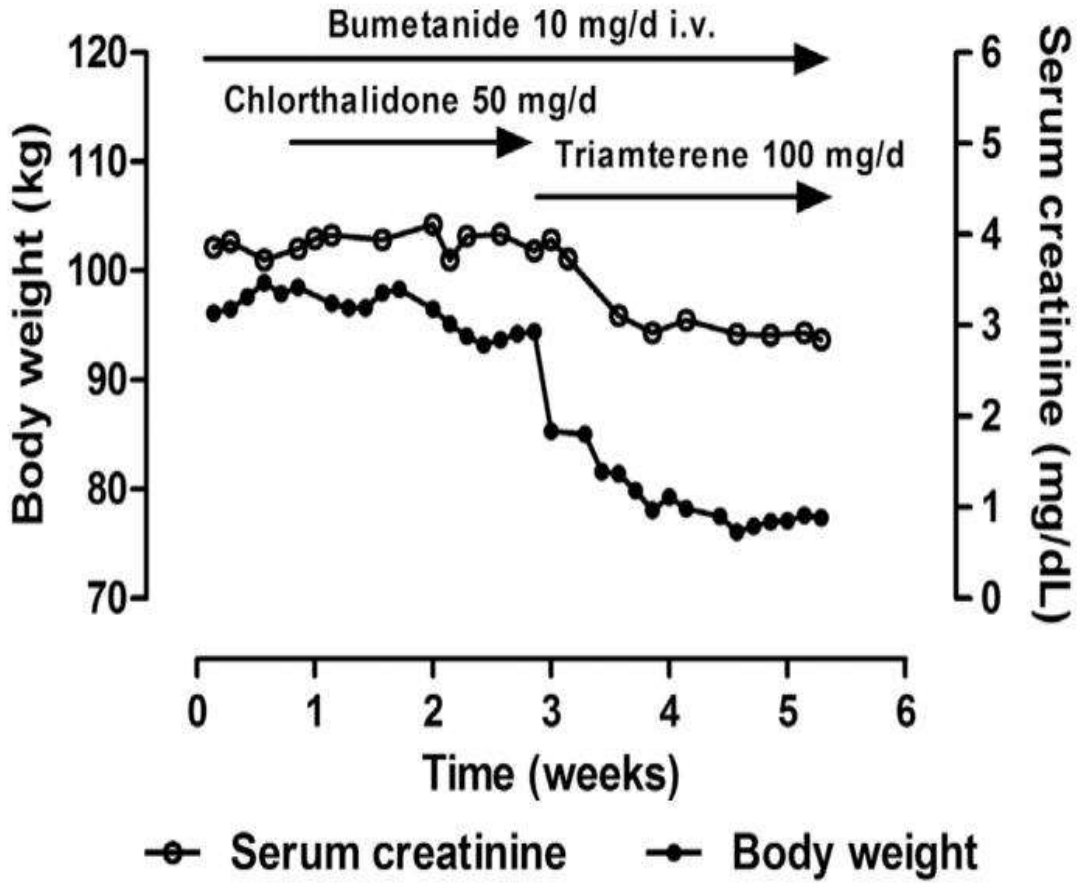
- Are they taking the medication and as directed?
- Salt intake-just because is does not taste salty does not mean it is low sodium chloride
- Other medications: herbal meds-NSAIDs, PPI's, COX-2 inhibitors, licorice root, herbal products-mimics hyperaldosteronism
- Worsening: renal, cardiac, liver function or any combination of
- Hypothyroidism (amiodarone?)

Approach to a Diuretic Resistant Patient (2)

- Increase the dose *and* frequency of the loop diuretic
- *Consider* oral *torsemide* over oral furosemide (better gut absorption, longer $T_{1/2}$)
- *Add* a thiazide (chlorthalidone, indapamide or metolazone)
- *Add* a mineralocorticoid receptor blocker or K-sparing agent (spironolactone, eplerenone, amiloride or triamterene)
- Address *other* treatments, adrenergic blockade, ACE-I or ARB, but not together
- *Compression* of LE's with ACE wraps and SCDs
- *Paracentesis*: decreases intraabdominal pressure

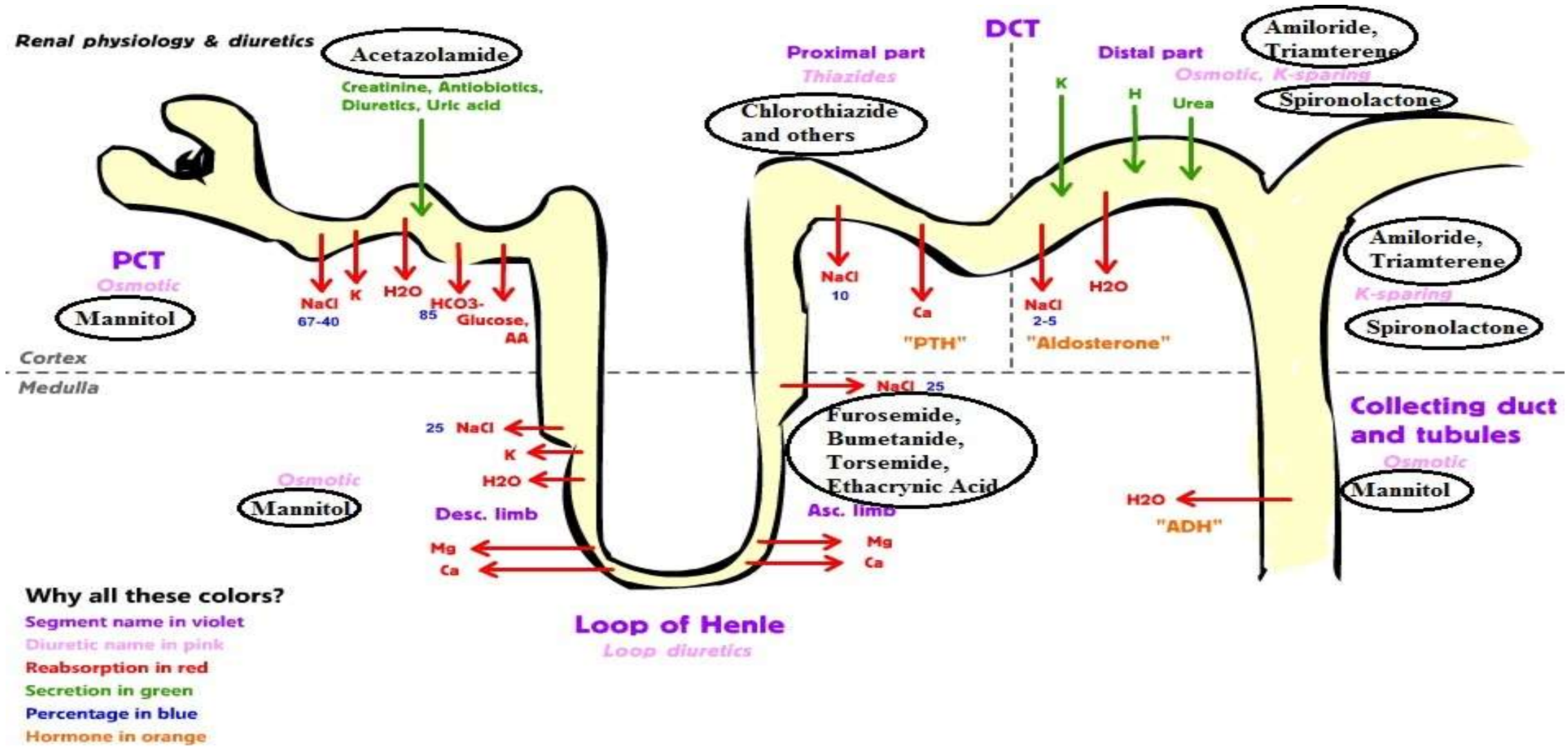
Effects of Sequential Nephron Segment Blockade on Diuretic Resistance

- Improved creatinine
- Fluid mobilization/loss
- 3 segments blocked: TAL, NCCT, ENaC



Am J Kidney Dis 2017;69: 136-142

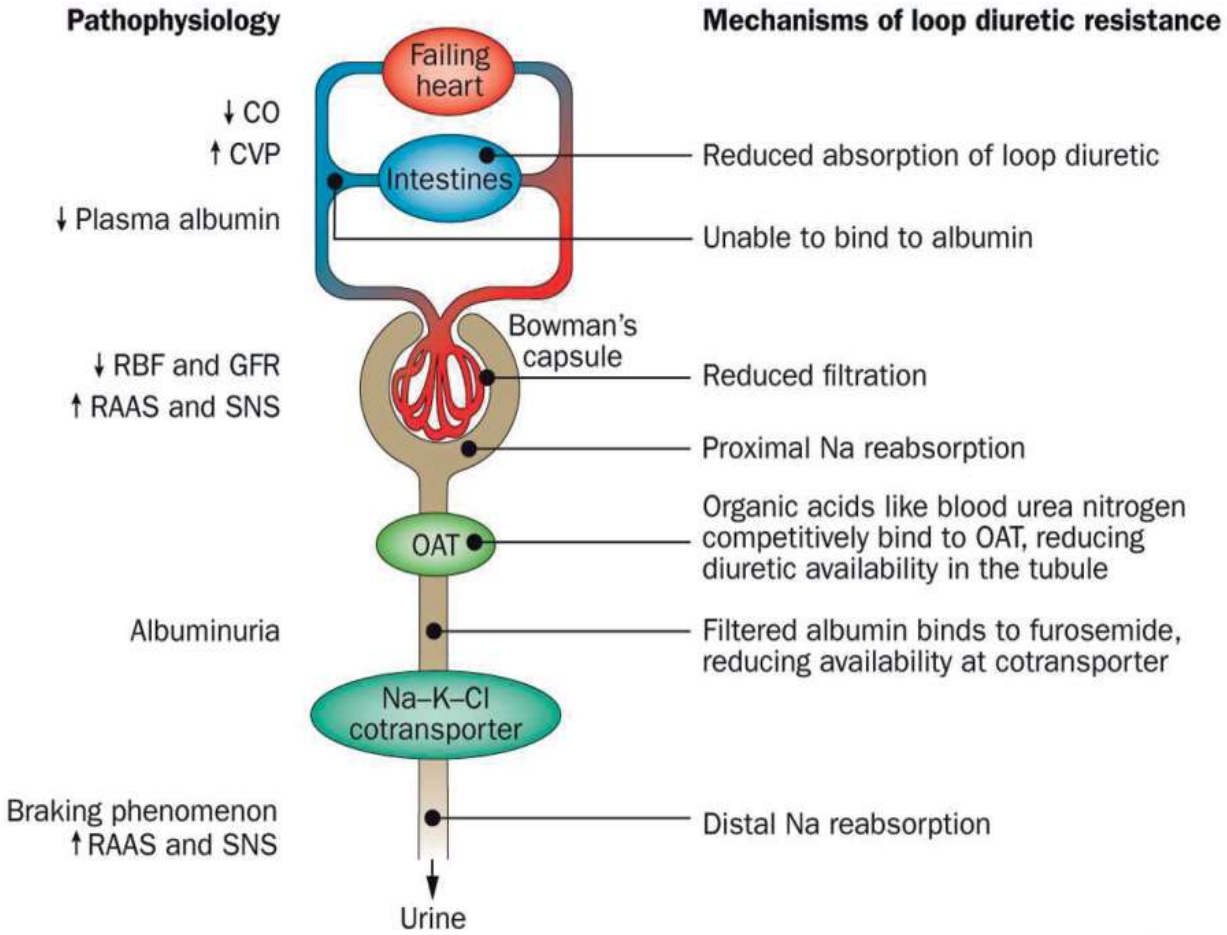
Diuretic Actions on the Nephron



When Maximum Therapy Fails

- Isolated ultrafiltration/dialysis: iso-osmotic fluid removal
- Can correct underlying acidosis which can improve cardiac function
- Correction of anemia
- Don’t overlook salt intake!

Summary of Diuretic Resistance



Remember

- The body *never* wants to lose salt or water, no matter how desperately it needs to
- Sequentially blocking sodium and water reabsorption with help to attenuate this normal physiological response-think breaking links of the chain

Thank you

Questions?

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