Renal Tubular Acidosis

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Summary

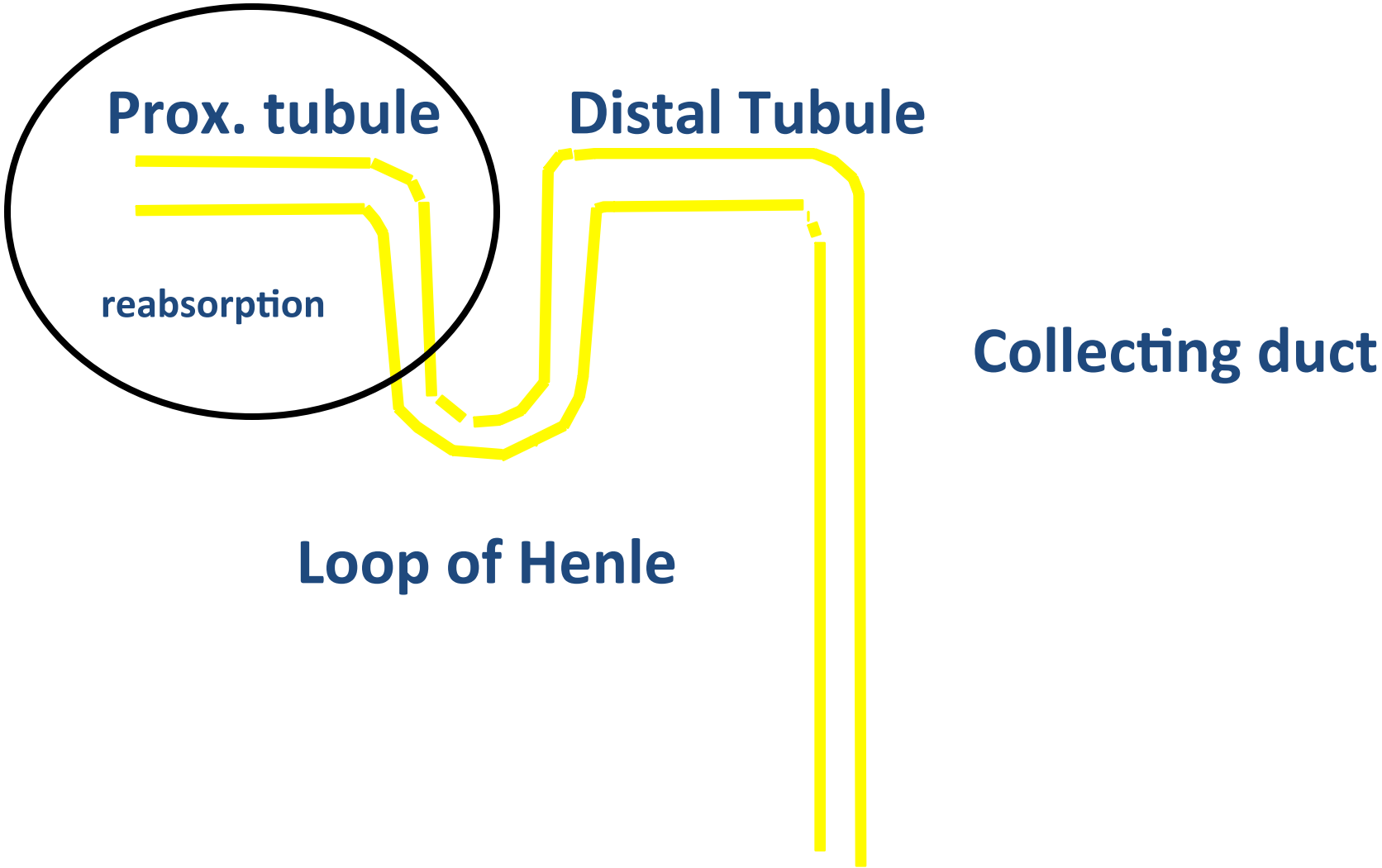
- Review of renal tubule physiology
- Types of RTA's
- Why they are named the way they are
- Subtypes
- Comparison and constrasting of RTA's
- Treatment

Glomerular Physiology

- Filtration
  - Filtration membrane
    - Endothlial cell layer
    - Basement membrane
    - Epithelial cell layer
    - Electrical charge – negative
- Clearance = waste product removal
- Ultrafiltration = water removal

Renal Tubule Physiology

Overview

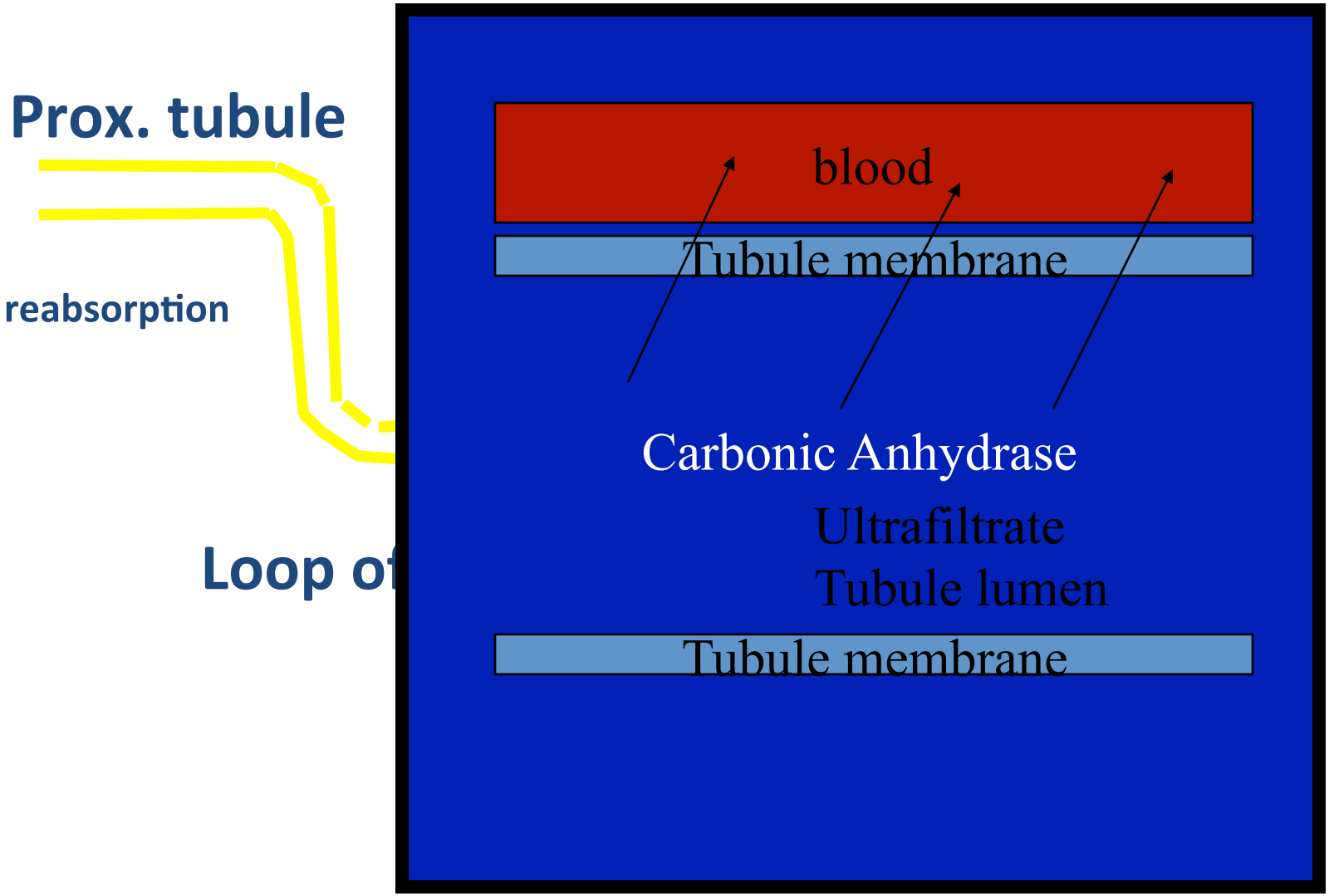


Proximal Tubule

- Function: Reabsorption
- Features:
- Brush border with cilia
- Carbonic Anhydrase for reclaiming Bicarb
- Filtration Fraction
- Pathology: Renal tubular Acidosis

Renal Tubule Physiology

Overview



Renal Tubule Physiology

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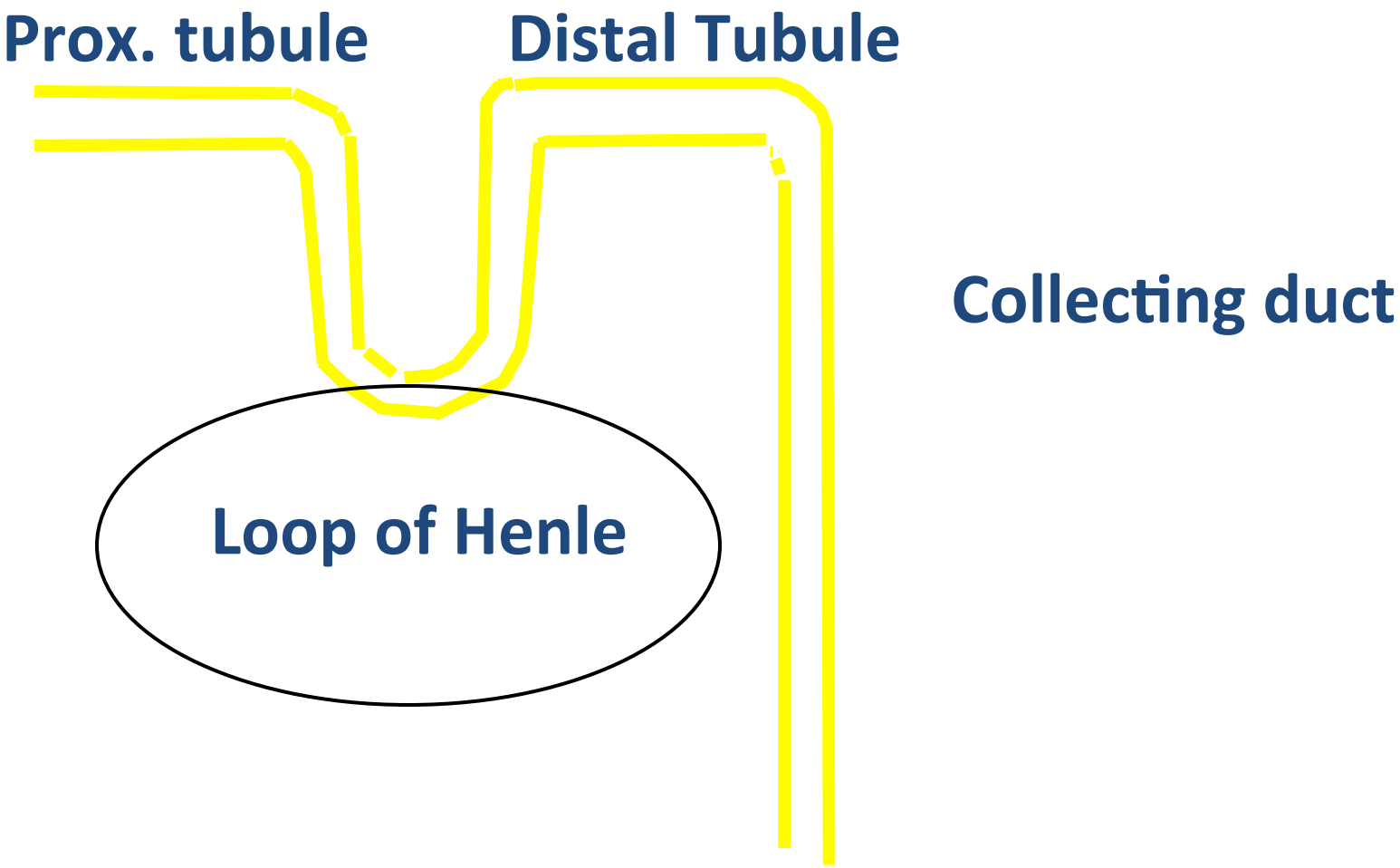

Renal Tubule Physiology

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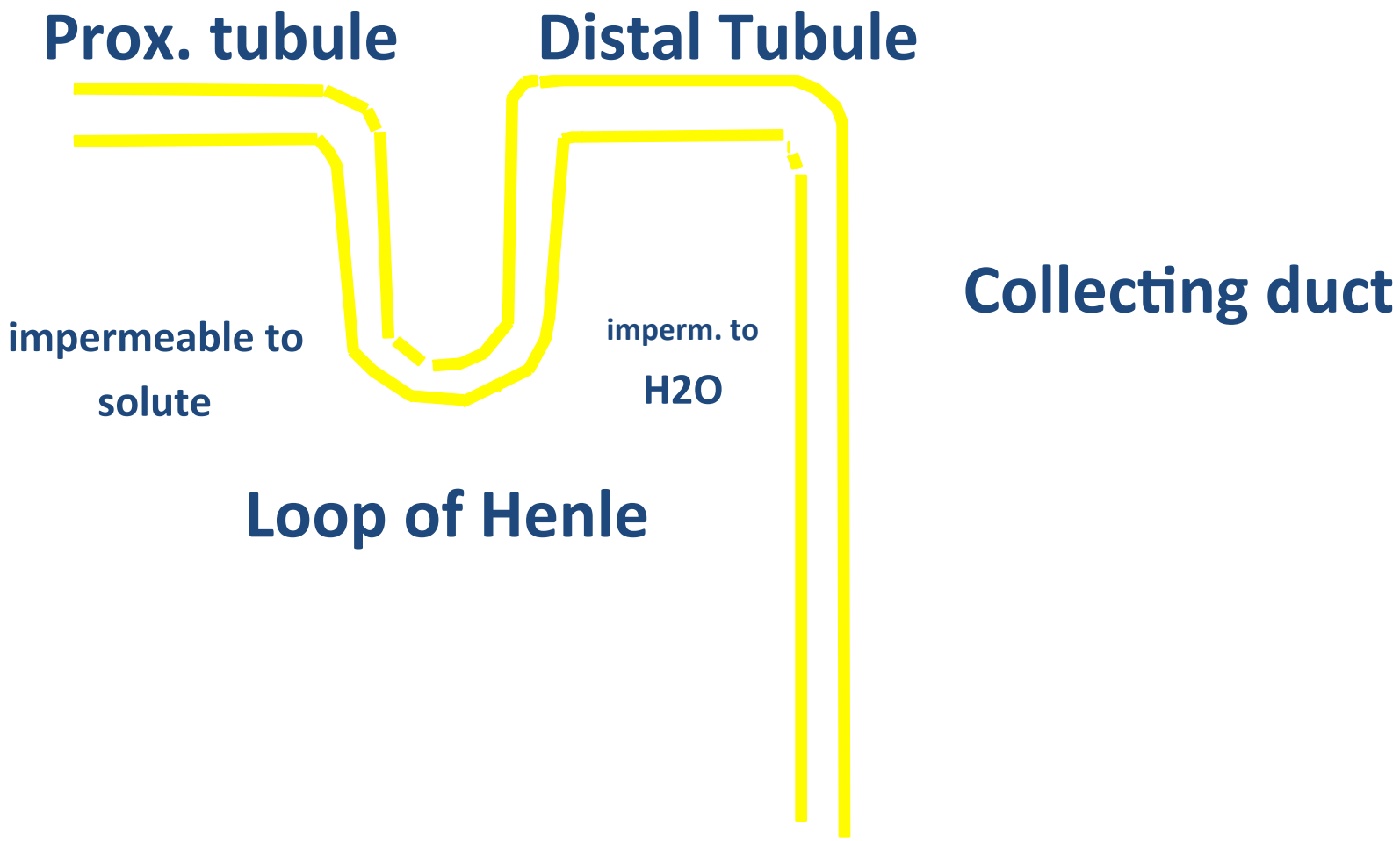

Renal Tubule Physiology

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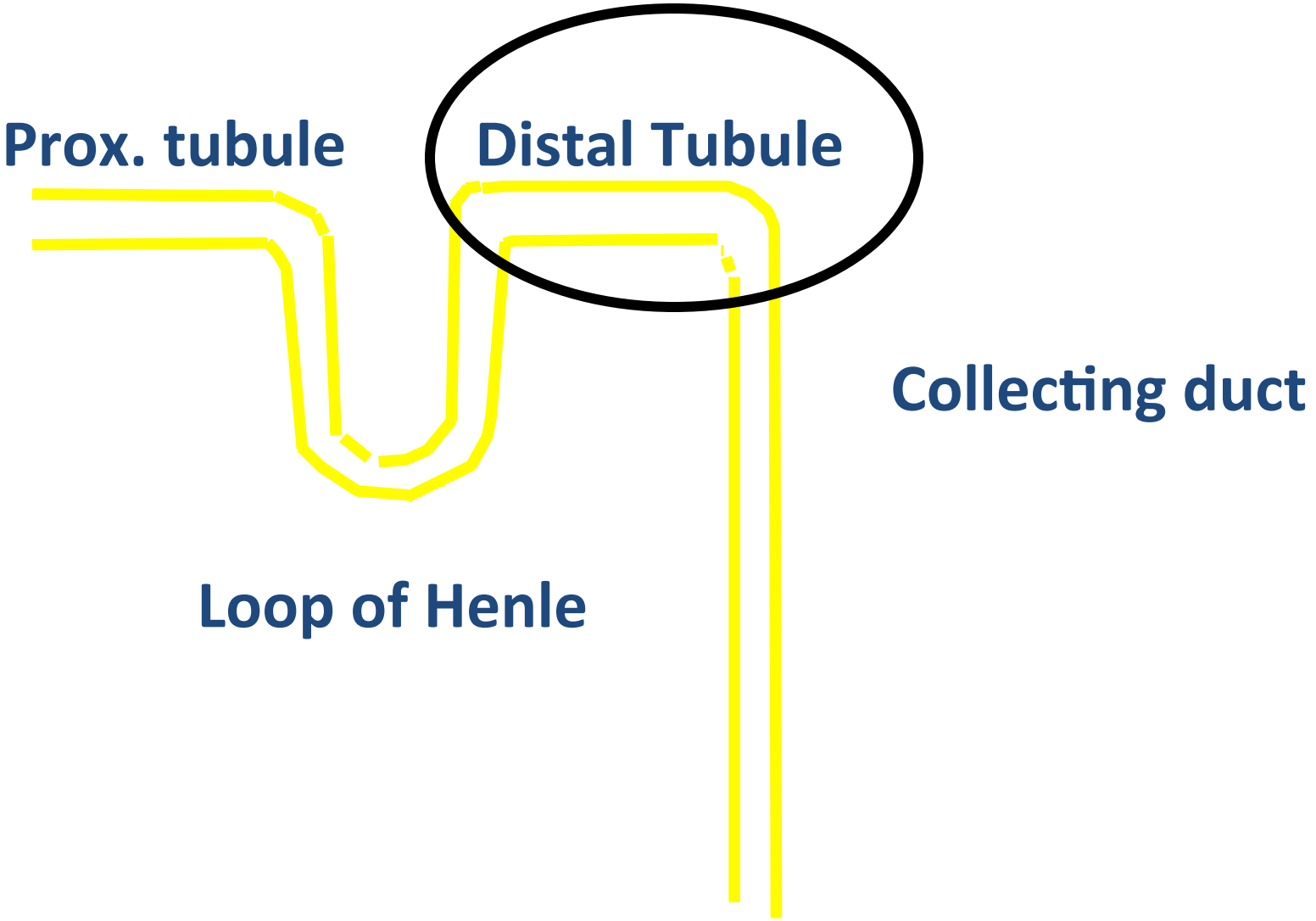

Renal Tubule Physiology

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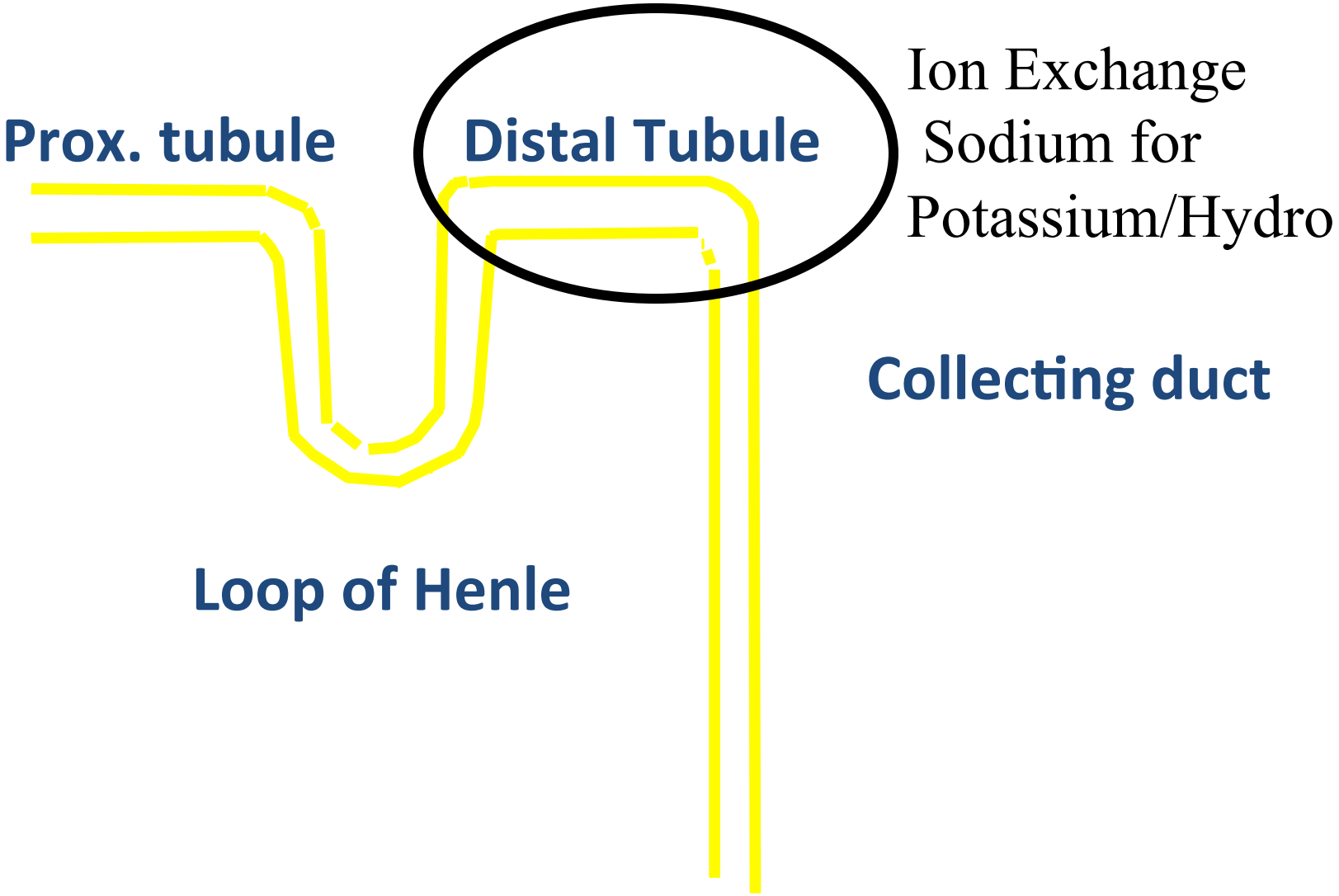

Renal Tubule Physiology

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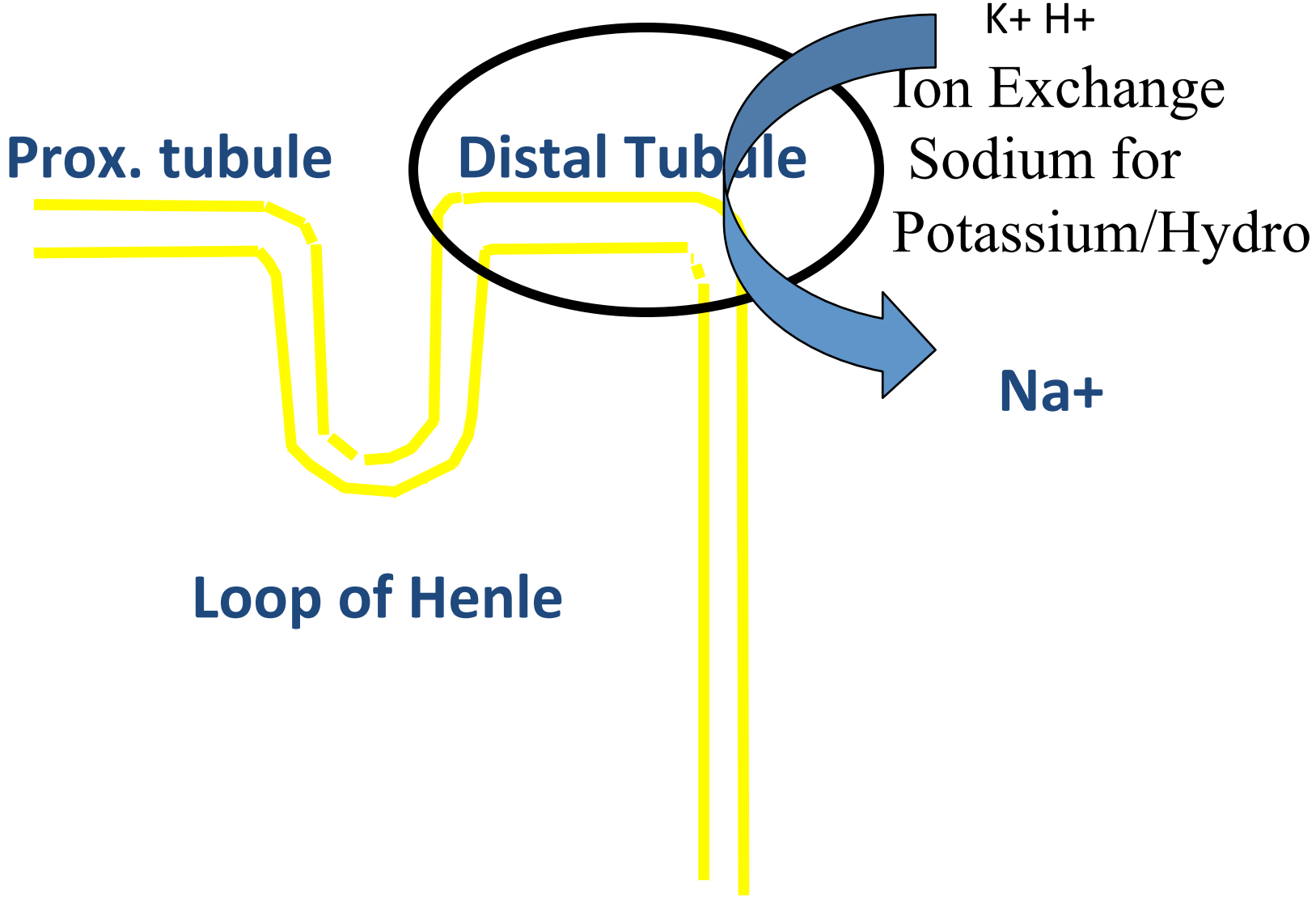

Renal Tubule Physiology

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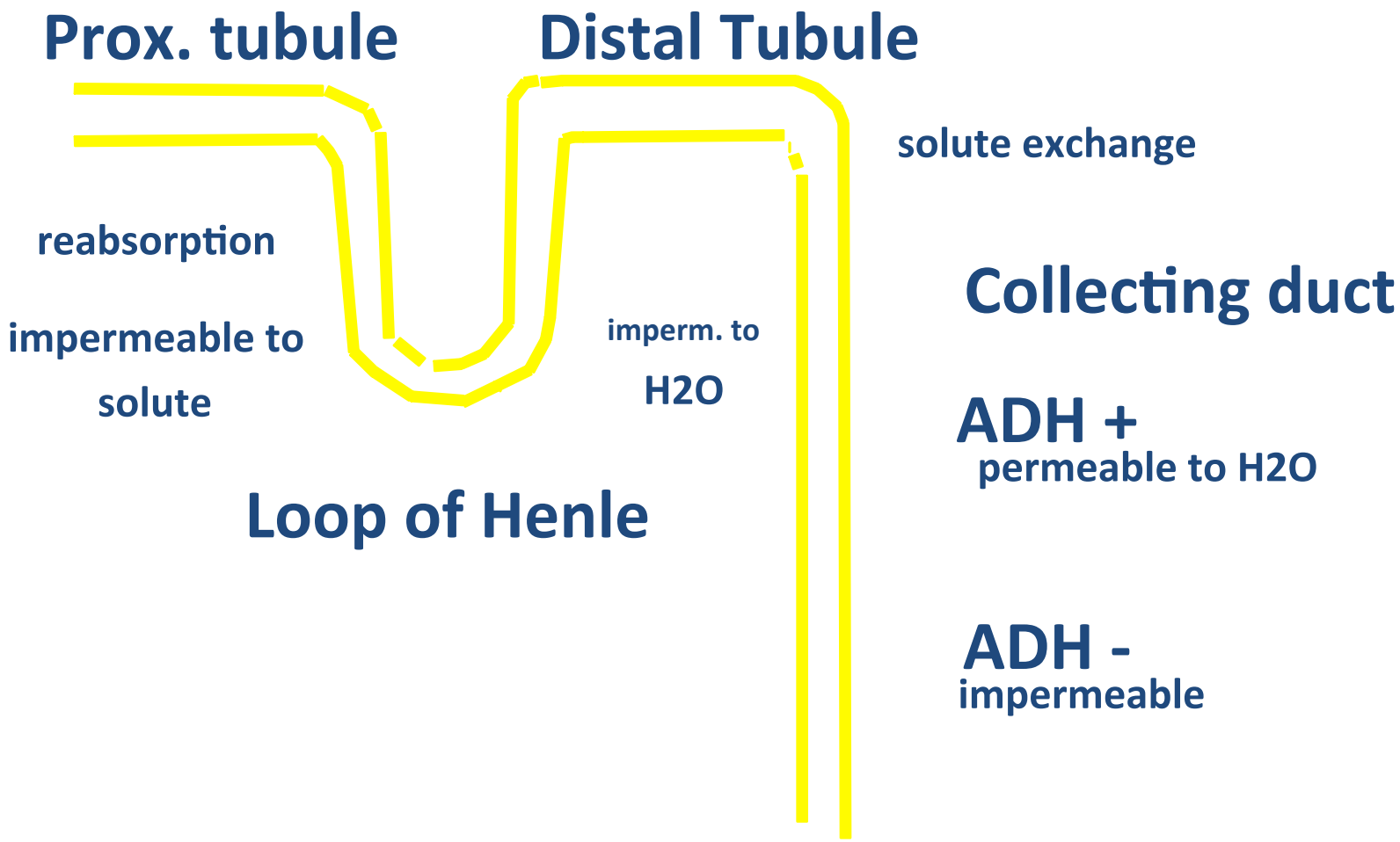

Interstitium

- The tissue in between the tubules
- Function:
- Ammoniagenesis
- Dependent on renin, aldosterone.
- NH_3 converted to NH_4Cl provides a huge sink for nontitratable acid

Disorders of ammoniagenesis occur in severe hypOkalemia and Diabetic Nephropathy.

RTA's

- Named according to order in which they were described, i.e. severity.
- Type I is worst showing up in children with failure to thrive, Ricketts, hypokalemia, stones
- Type II also shows up in children, but not as severe.
- Type III rare
- Type IV not described until diabetics lived long enough to develop renal comps.

Renal Tubular Acidosis

- Type I most severe, occurs in the Distal tubule, and is congenital problem with the transport proteins responsible for excretion of acid.
- Four types of Type I distal RTA:
  - Rate dependent (defective or decreased pump)
  - Secretory (absent proton pump),
  - Gradient dependent (Backleak of K)
  - Voltage dependent (defective K channels)
    - Seen in sickle cell, obstructive uropathy
    - Potassium channels affected by Amiloride, lithium
- Bicarb can go as low as 8
- HypOkalemia (hypERkalemia in voltage dependent)

Renal Tubular Acidosis

- Type II Proximal Tubular Acidosis
  - Less severe, immaturity of proximal tubule leads to bicarb loss.
  - Corrects during puberty
  - Bicarb usually 15 or greater
  - HypOkalemia
  - Large bicarb requirement
  - Stones, Failure to thrive.
  - 11 types associated with conditions such as myeloma, Fanconi's syndrome.

Type II Proximal RTA subtypes

- Hereditary
  - Fanconi syndrome
  - Wilson's dz, Cystinosis
  - Tyrosinemia, Pyruvate Carboxylase Deficiency
- Acquired
  - 1. Drugs (TCN, Gent, **Glue sniffer**, GMP)
  - 2. Heavy Metals
  - 3. Immunologic disease (sjogrens, **Myeloma**)
  - 4. Balkan nephropathy
  - 5. Nephrotic syndrome/ transplant dysfunction
  - 6. Osteoporosis
  - 7. PNH

Acquired Fanconi's Syndrome

- Features:
  - Glucosuria with normal serum glucose
  - Metabolic acidosis with bicarbonate wasting in urine
  - Phophaturia
  - Hypokalemia, hypouricemia, hypophosphatemia
- Most commonly due to drug toxicity

Thomas DeCato, Tenofovir induced Fanconi Synd. ACP Hospitalist Nov 2014. Pg 33

Acquired Fanconi's Syndrome

- Most commonly due to drug toxicity
  - Can appear after years of exposure
  - Can take weeks to months to resolve
  - Recovery may be incomplete
- Drugs that cause Fanconi syndrome:
  - Platinum and alkalating chemotherapy agents
  - Aminoglycosides
  - Valproic acid
  - Tenofovir and many other antiviral agents.

Renal Tubular Acidosis

- Type III
  - Small kindred of children born with Combo of type I distal RTA AND tubular immaturity of proximal tubule type II RTA. Have features of both, and the proximal tubule disorder corrects after puberty, leaving them with a true Type I distal RTA.

Renal Tubular Acidosis

- Type IV RTA
  - Also known as Hypoaldosteronism, Hyporeninism.
  - Problem with ammoniagenesis
  - Commonly seen in Diabetics, Sarcoidosis, Chronic Pyelonephritis, Gouty nephropathy, chronic rejection
  - Bicarb as low as 18, may be 22
  - HypERkalemia out of proportion to their renal dysfunction.

Type IV RTA subtypes

- Aldosterone Deficient
  - 1. Adrenal Insufficiency
  - 2. Hyporenin/hypoaldo (seen in Diabetics)
  - 3. Chloride shunt (Gordon's syndrome)
- Aldosterone Resistant
  - 4. PseudohypoAldosteronism
    - Will have HIGH levels of aldo: receptor is damaged
    - Pseudo-pseudo-hypoaldo patients have phenotype, but normal aldosterone function
  - 5. Early childhood type IV RTA from interstitial disease

Diagnosis

- First you must suspect RTA in patients with
  - Unexplained bone disease
  - Muscle weakness
  - Nephrocalcinosis
  - Glycosuria/aminoaciduria
  - Kidney stones
  - Non-Gap metabolic acidosis
  - Failure to thrive in children
  - Associated diseases (Diabetes, Gout, Myeloma)

Diagnosis of RTA

- Workup
  - Lytes and BUN/Creat
    - Measured bicarb < 15 is Type I RTA
    - Bicarb 15-18 is Type II proximal RTA
    - Bicarb > 18 with high K is Type IV RTA
  - Urine pH in basal state AND during bicarb supplementation
    - Urine pH > 7 means pt is spilling bicarbonate into urine (i.e Type II proximal RTA)
    - Urine pH > 6 in pt with severe acidosis probably means they are unable to excrete an acid load (Type I Distal RTA)
  - Urine pCO_2 (normal level = 32.7 +/- 3 mm/Hg)

Diagnosis of RTA

- Fractional Excretion of Bicarbonate
  - FE (HCO3) = $\frac{\text{U bicarb/P bicarb}}{\text{U creat/P creat}}$ X 100

RTA Type	FE HCO3
Distal	< 5 %
Proximal	> 15 %
Type III	5 – 15 %

Diagnosis of RTA

- Urinary Anion Gap – measure of ammonium production (NH4CL)
- UAG = (Na + K) – Cl
- Negative UAG (Cl >> Na + K) is due to:
  - GI loss of bicarb
  - Proximal Type II RTA
- Positive UAG (Cl < Na + K) is due to:
  - Distal Type I RTA
  - Or in an ALKALOSIS, loss of stomach HCl.

Diagnosis of RTA

- Caveats about urinary anion gap:
  - Invalid during DKA, lactic acidosis
  - Ingestion of salicylates or lithium use
  - Bartter's syndrome is a syndrome of urinary chloride wasting, associated with hypokalemia, metabolic alkalosis, low BP
    - Therefore UAG should be Negative (lots of chloride in urine)
    - Someone with Anorexia Nervosa /Bulemia should have a low urinary chloride due to GI loss)

Treatment of Distal RTA Emergencies

- 1. Hypokalemic paralysis
  - Supplement K with KCl, Kphos
  - Do NOT alkalinize until K near normal
  - May require up to 10 mEq/Kg per day!
- 2. Tetany
  - IV calcium, correct hypomagnesemia
- 3. Coma
  - Occurs in pts not taking their medicines
  - Severe acidosis with only mild hypERkalemia reflects **profound** total body potassium depletion

Treatment of RTA's

- Sholl's solution
- Bicitra
- Polycitra
- Polycitra K
- Sodium Bicarbonate
- Baking soda
- Calcium Carbonate
- Florinef, lasix, chronic kaexalate for Type IV's

Case 1

- 1. 45 y.o. female with HTN. C/O hand and feet tingling for 2 months. No injury, no repetitive motions, no prior hx. Not alcoholic, no new meds.
- Meds: Atenolol, Procardia XL, Premarin, Lopid, Cholestipol
- Fam Hx Nephrolithiasis in mother.
- Exam: BP 104/77, no edema.

Case 1

- Routine labwork showed:
  - Na K CL HCO3 AG
  - 138 4.0 105 19 14

  - Urine Lytes Na K CL AG pH
  - 40 30 50 +20 6.0

Case 1

- Type I distal RTA
  - Not spilling bicarb as the urine pH is < 7.0
  - Not able to excrete an acid load normally as the urine pH is over 5 in face of an acidosis.
  - Positive UAG.
  - Family history and late presentation suggests a mild form.
  - Probably a Rate Dependent type I distal RTA.

Case 2

- 50 y.o. male with chronic diarrhea after colectomy for Ulcerative colitis 2 years ago
- Frequent ER visits for volume depletion with ARF. Each time, BUN is > 40, creat > 2.5 which resolves with IVF.
- Stool up to 12 times a day.
- Meds: Paxil, synthroid, Sodium Chloride tabs
- Fam hx of Ulcerative Colitis, colon cancer.

Case 2

- Labwork shows:
  - Na K CL HCO3 AG
  - ER 129 3.9 95 20 14
  - After NS infusion:
  - 134 3.2 105 15
  - Urine lytes:
  - 20 10 60 UAG: - 30 pH 5.2

Case 2

- Initial non gap metabolic acidosis due to bicarb loss from diarrhea
- After normal saline infusion, acidosis worsened due to volume expansion acidosis.
- Negative UAG suggests GI bicarb loss.

Case 3

- 73 y.o. diabetic for years admitted for leg weakness and numbness. CT head negative, exam normal strength and sensation, EKG shows peaked T waves.
- Not on ACE, NSAID, or K supplements
- No Diarrhea, N/V.

Case 3

- Routine labwork showed:
  - Na K CL HCO3 AG
  - 135 6.8 105 19 11

  - Urine Lytes Na K CL AG pH
  - 30 20 50 0 5.0 to 5.5

Case 3

- Type IV RTA
- Longstanding diabetic
- Hyperkalemia out of proportion to renal dysfunction
- (relatively speaking) positive UAG means she is NOT excreting Ammonium chloride normally.

Case 4

- 25 y.o. female referred to you for eval of chronic hypOkalemia, and hypochloremic metabolic alkalosis. BP is low and aldosterone level is high. "Rule out Bartter's syndrome"

Case 4

- Routine labwork showed:
  - Na K CL HCO3 AG
  - 135 3.0 85 30 20

  - Urine Lytes Na K CL AG pH
  - 20 30 20 +30 5.0 to 5.5

Case 4

- This is not Bartter's syndrome:
- In Bartter's, the primary problem is chloride wasting from the urinary tubules.
- Results in contraction alkalosis, low K and low BP associated with high aldosterone level in response to chronic volume depletion.
- UAG will be markedly Negative due to increased chloride loss.

Case 4

- This is a case of Anorexia Nervosa with induced vomiting leading to the electrolyte abnormalities seen.
- Because of the hydrochloric acid loss from the vomiting, her urinary chloride is LOW and the UAG is positive.
- The metabolic alkalosis leads to renal tubular K wasting.

Type IV RTA
Differential Diagnosis

RTA/Type IV:Differential Diagnosis

	Serum Cortisol	Urine 17-OHS	Urine 17-KS	PRA	Serum Aldosterone	Response Mineralo-corticoids
1ry Aldo. Deficiency	Low	Low	Low	High	Low	YES
21-OH-lase Deficiency	Low	Low	High	Low	Low	YES
Hypoaldosteronism	Normal	Normal /High	Normal/ High	Normal/ High	Low	YES
PHA	Normal	Normal	Normal	++++	++++	NO
CRF	Normal	Normal	Normal	Low	High	NO
Spitzer's Syndrome	Normal	Normal	Normal	Low	Normal	NO

Contrasting Features of RTA

Finding	Type II [Proximal]	Type I [Distal]	Type IV [Low Buffer]	Voltage-Dependent
Growth Failure	Common	**Very Common**	Variable	Variable
Nephrocalcinosis	Rare	**Common**	Absent	Variable
Calculi	Rare	**Common**	Absent	Variable
Bone Disease	Frequent	Rare	Variable	Variable
Phosphaturia	**Common**	Rare	Rare	Rare
Glycosuria	**Common**	Absent	Absent	Rare
Aminoaciduria	**Common**	Absent	Absent	Rare
Uricosuria	**Common**	Absent	Absent	Rare
Fanconi Syndrome	**Common**	Absent	Absent	Absent
Serum Bicarbonate	Usually ≥ 15	Usually < 15	Usually ≥15	Variable
Serum Potassium	Low/Normal	Low/Normal	Normal-**High**	**High**
Severe K depletion	Uncommon	Common	Absent	Absent
BUN	Normal	Normal	± Increased	Variable §
Urine pH				
Random	Alkaline	Alkaline	Low	Alkaline
Morning	Usually < 6.0	Never <6.0	Commonly< 6.	Never < 6.0
Acid Load	< 5.3	Over 5.5	< 5.3	> 5.5
Corrected P HCO3	High	High	High	High
Urinary Bicarbonate:				
Severe Acidosis	Nil	Present	Present	Present
Corrected P HCO3	++++ Increased	+ Increased	± Increased	± Increased
Tm HCO3	Low	Normal	Mildly Low	Normal
FE [HCO3]	> 15 %	< 5 %	< 5 %	< 5 %
[U-B] pCO2	> 20 mm Hg	< 15 mm Hg	< 15 mm Hg	< 15 mm Hg
Urinary Citrate	Normal	Low	Variable	Low
Urinary TA & NH_4:				
Severe Acidosis	May be normal	Decreased	Decreased NH_4	Decreased
Corrected HCO3*	Decreased	Decreased	Variable	Decreased
Ease of Bicarbonate Replacement	Resistant [7-10 mEq/ kg/day]	Sensitive [<2-6 mEq/ kg/day]	Sensitive	Sensitive
Daily K Requirement	Increases with Correction	Decreases with Correction	Variable	Variable
Aldosterone	Normal	Normal	Deficient/ Resistant	Normal

J.F. Pascual, M.D./1990

Type III RTA: FE [HCO3] = > 5%, but < 15 %

RTA:

Proximal: 7 sub-types
Distal: 4 sub-types
Type IV: 5 sub-types

Distal (Type I)

1. Rate Dependent
   - -Defective on ↓ Proton Pump
2. Secretory
   - - absent proton Pump
3. Gradient (back leak)
4. Voltage Dependent:
   - - Defective K+ Channels
   - -Amiloride, lithium
   - - SS

Proximal (Type II)

Hereditary:

- Fanconi's Syn.
- Wilson"s
- Cysinosis
- Tyrosinemia
- Pyruvate Carboxylase Def.

Acquired:

1. Drugs:
   - TCN, Gent, Glue, GMP
2. Heavy Metals
3. Immunologic Dz:
   - SLE, Sjorgen's, Myeloma
   - Transplant
4. Bulkan's Nephropathy
5. Nephrotic Syndrome
6. Osteoporosis
7. PNH (Uretro-neosigmoidostomy)

Type IV

↓ Ammonia genesis

Aldo Deficient:

1. 1 Adrenal cortex deficiency
2. Hyporenin,hypoAldo,InterstitialD
3. Chloride shunt

Aldo Resistant:

4. Pseudo hypoAldo
5. Early childhood type IV
   - Interstitial Dz