REVISE NEPHROLOGY

Revise Nephrology 2023

Disorders of Potassium

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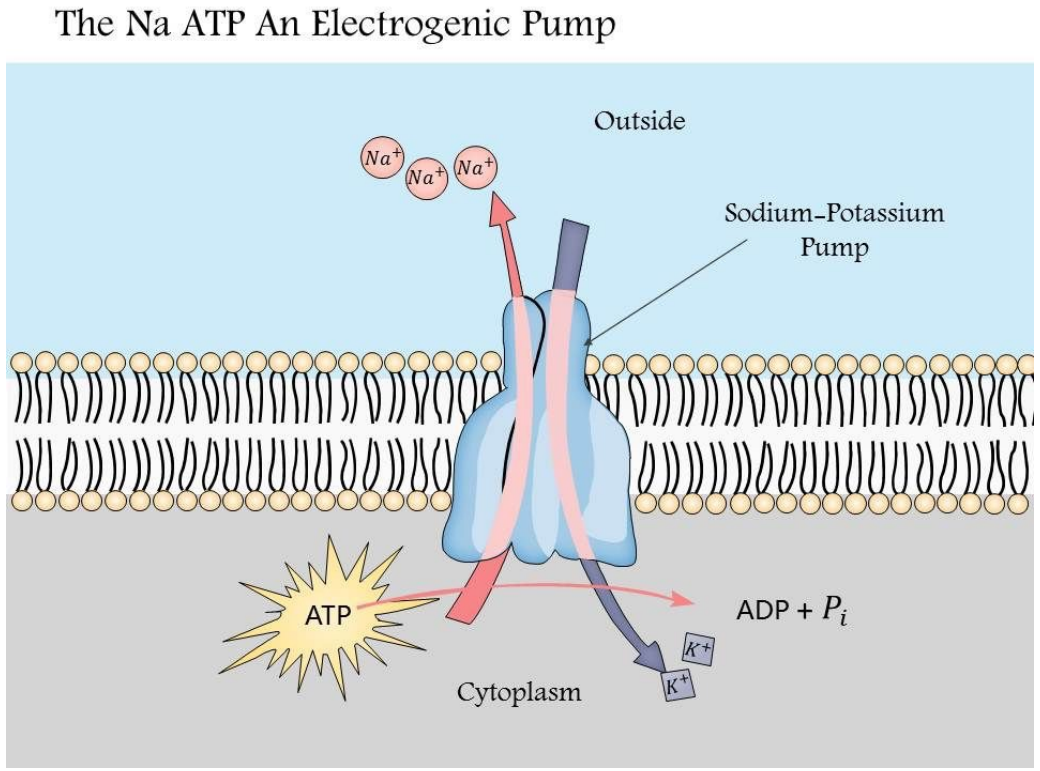
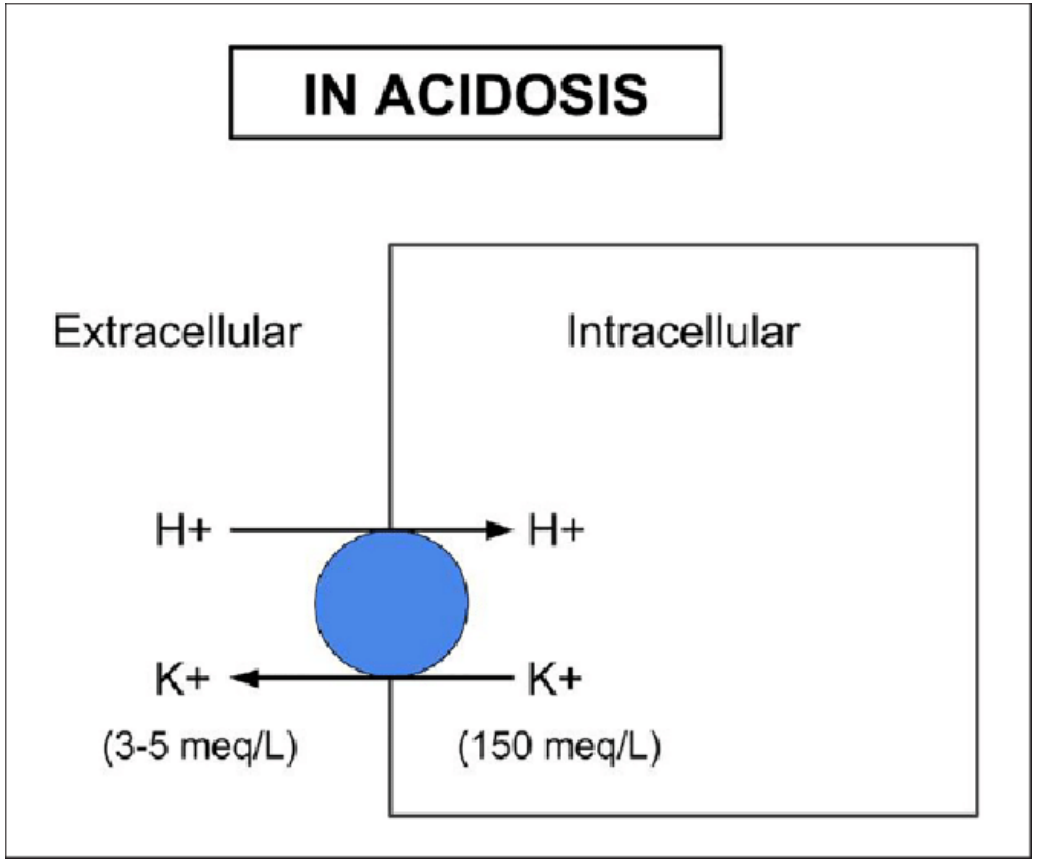
Few key points to ponder before we proceed..

- Disorders of the **renal tubules** can lead to both metabolic acidosis/alkalosis and hypokalaemia/hyperkalemia
- K and H often move together- hyperkalemia predisposes to metabolic acidosis and vice versa……similarly metabolic alkalosis predisposes to hypokalemia
- BUT- hypokalemia can be associated with either **alkalosis or acidosis**
- The renal tubular cells are rich in K and low in Na due to the action of the basolateral Na-K-ATPase



Na-K-ATPase pumps

3 Na out and pulls 2 K into cells



Cellular shifts between H and K

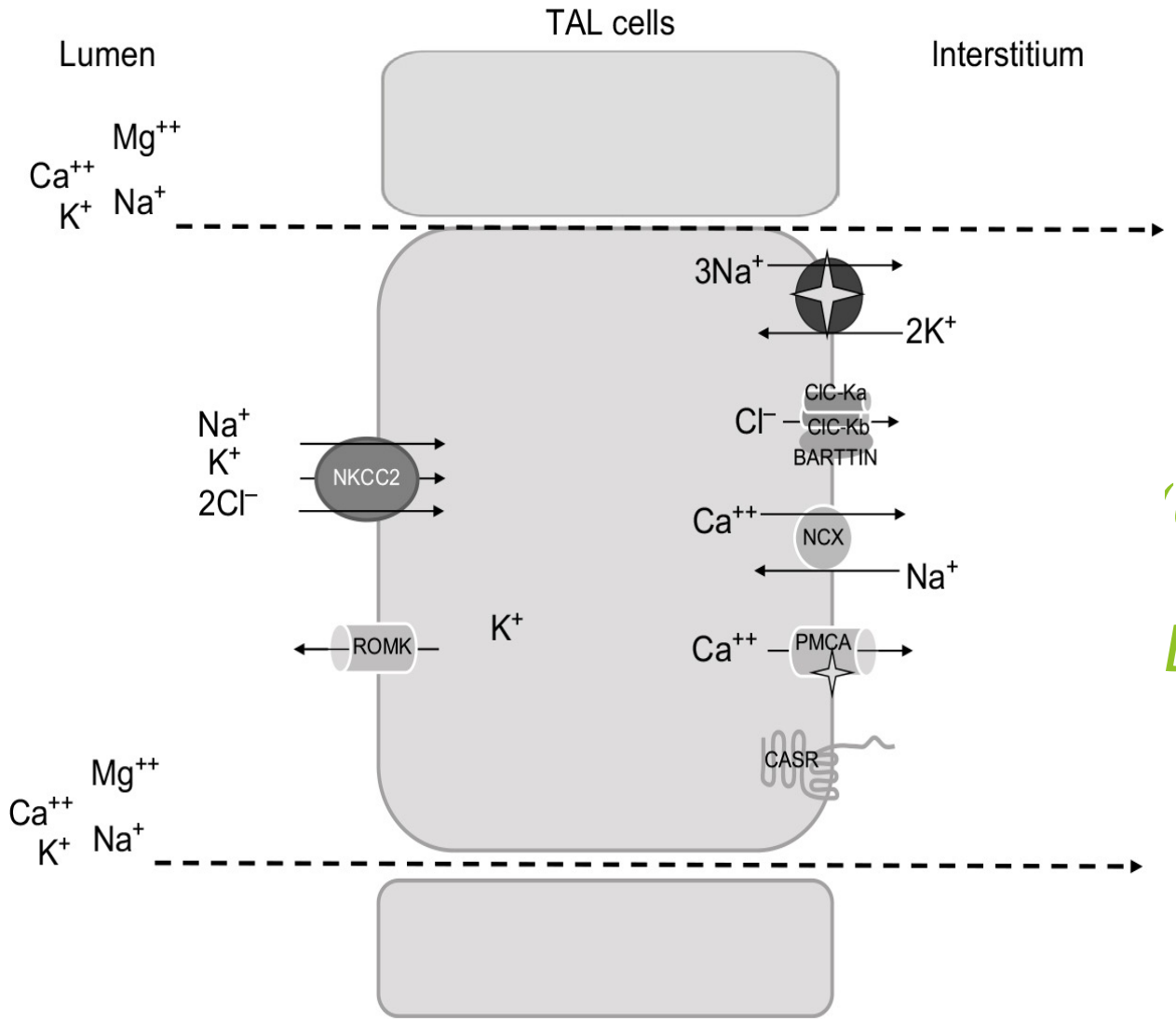
With a GFR of 125 ml/min, why don't we make 180 L urine everyday?

Because:

- Tubular cells are hungry for water?
- Tubular cells are hungry for Na?
- Tubular cells are hungry for K?
- ADH causes most of the water reabsorption?

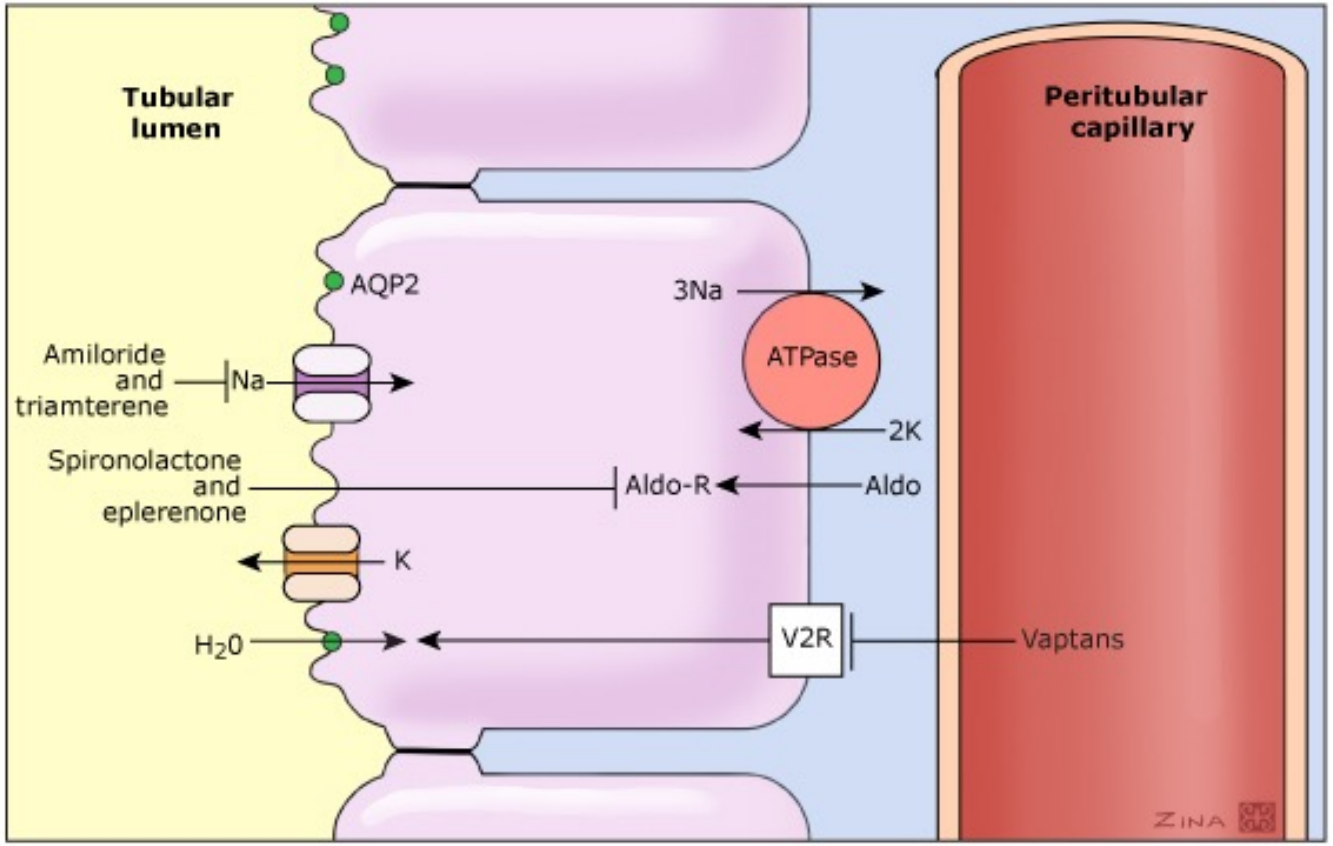
Remember water follows sodium

Tubular cells reabsorb Na and water passively follows the Na



Na uptake in the TAL of loop of Henle

'downregulated on frusemide and in Bartter syndrome)



Aldosterone

- Absorption of Na
- Excretion of K
- Water passively absorbed with the Na
- *Indirect* excretion of H

Aldosterone

- Aldosterone helps to reabsorb Na by the principal cells of the collecting duct
- Aldosterone helps to excrete K directly by the same principal cells
- Aldosterone helps to excrete H indirectly by the alpha intercalated cells of the collecting duct
- Net results of aldosterone action:

  - directly reabsorb Na (and water passively)

  - directly excrete K

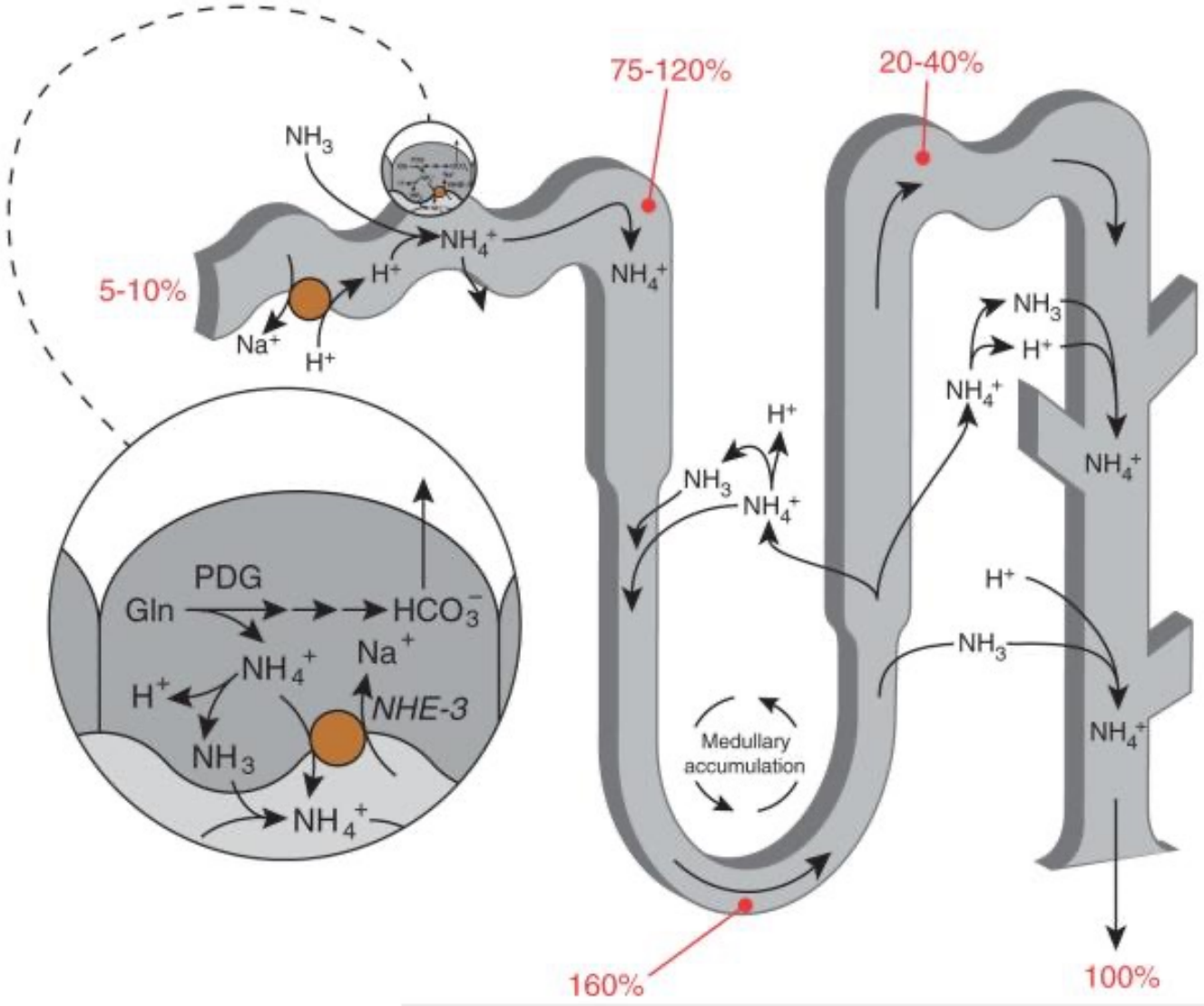
  - indirectly excrete H

H in the urine needs buffer

- Hyperkalaemia decreases renal ammonia generation:
  - H+ in the urine needs buffers otherwise urine would quickly become saturated
  - Chief buffer is ammonia which becomes ammonium after accepting the H^+ {$NH3 + H^+ \leftrightarrow NH4^+$}
  - Ammonia is derived from breakdown of glutamine by glutaminase in the PCT cells
  - **Hyperkalemia decreases glutaminase activity and therefore decreases ammonia production**

- In the CD, the basolateral Na-K-ATPase can also function as an Na-NH_4 exchanger, permitting uptake of NH_4 from the interstitium and subsequent secretion into the urine
- K competes with NH_4 for this exchanger, and therefore hyperkalaemia impairs the capacity of the pump to carry ammonium into the cell

Renal ammonia metabolism
Gln-Glutamine; PDG-Phosphate Dependent Glutaminase

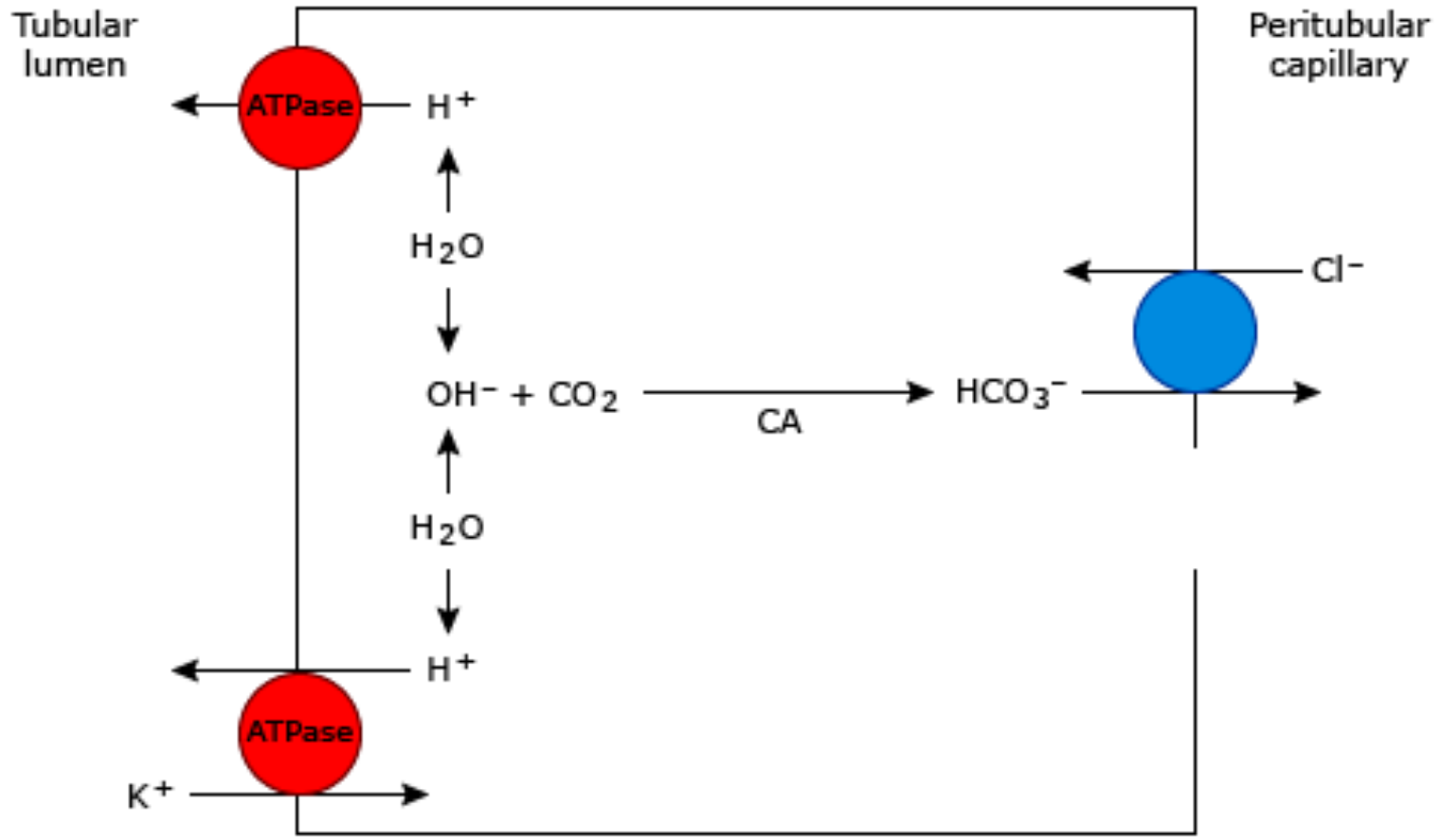


Summing up the K and H relation…….

- **Hyperkalaemia leads to metabolic acidosis by three mechanisms-**
  - Excess K^+ enters the cell and in exchange H^+ comes out of cells
  - K^+ competes with H^+ for secretion by the collecting duct in exchange for Na^+
  - Hyperkalaemia by decreasing renal ammonia production inhibits H^+ excretion in urine (ammonia is the chief buffer for urinary H^+)
- **Metabolic acidosis leads to hyperkalaemia by-**
  - Excess H^+ enters the cell and in exchange K^+ comes out of cells
  - H^+ competes with K^+ for secretion in exchange for Na^+

Note: hypokalaemia causes alkalosis by augmenting the H-K-ATPase pumps which reabsorb K^+ and secrete H^+ in the type A intercalated cells in CD

10 to 15% HCO3 reabsorbed (with K) along with H secretion in the type A intercalated cells in CD



Hypokalaemia associated with metabolic alkalosis

High BP (will cover these in the secondary HTN talk)

- Primary hyperaldosteronism (Commonest condition in this group)
- Liddle syndrome
- Chronic liquorice ingestion
- Apparent mineralocorticoid excess
- Familial Hyperaldosteronism (including Glucocorticoid –remediable hyperaldosteronism)

Low-normal BP

- Bartter syndrome
- Gitelman syndrome (milder disease and commoner in adult population)

K and metabolic acidosis

- Hypokalaemia with normal anion gap metabolic acidosis
  - Renal tubular acidosis type 1 (distal RTA)
  - Renal tubular acidosis type 2 (proximal RTA)
  - *Beware of chronic diarrhoea*

- Hyperkalaemia with normal anion gap metabolic acidosis
  - Renal tubular acidosis type 4 (type 4 RTA)

Primary aldosteronism (PA)

- 5-13% of all patients with hypertension have PA
- Aldosterone producing adenoma (35%) or bilateral idiopathic hyperplasia (>60%)
- Suspect in HTN and metabolic alkalosis with hypo or normokalemia (K normal but on the lower side) OR in HTN with adrenal incidentaloma
- Initial test: Plasma aldosterone to renin ratio (PAC/PRA) of >30 suggestive
- Confirmatory tests show non-suppressibility of aldosterone production after IV saline infusion (2 L over 4 hours) or heavy oral salt loading (1 g salt tablets tds x 3 days)
- CT adrenal and adrenal vein sampling

Liddle Syndrome (Pseudohyperaldosteronism)

- Rare autosomal dominant condition
- Presents in young age with HTN and hypokalemic metabolic alkalosis
- Mutation in the ENAC channel (Na^+ reabsorbing channel in the collecting duct) renders it resistant to normal degradation- look at diagram on slide no.8
- Characteristically associated with low plasma renin and aldosterone
- Therapy consists of Na^+ restriction and K^+ supplementation and Triamterene or Amiloride (why not spironolactone??)

Apparent mineralocorticoid excess (AME) and Chronic Liquorice Ingestion

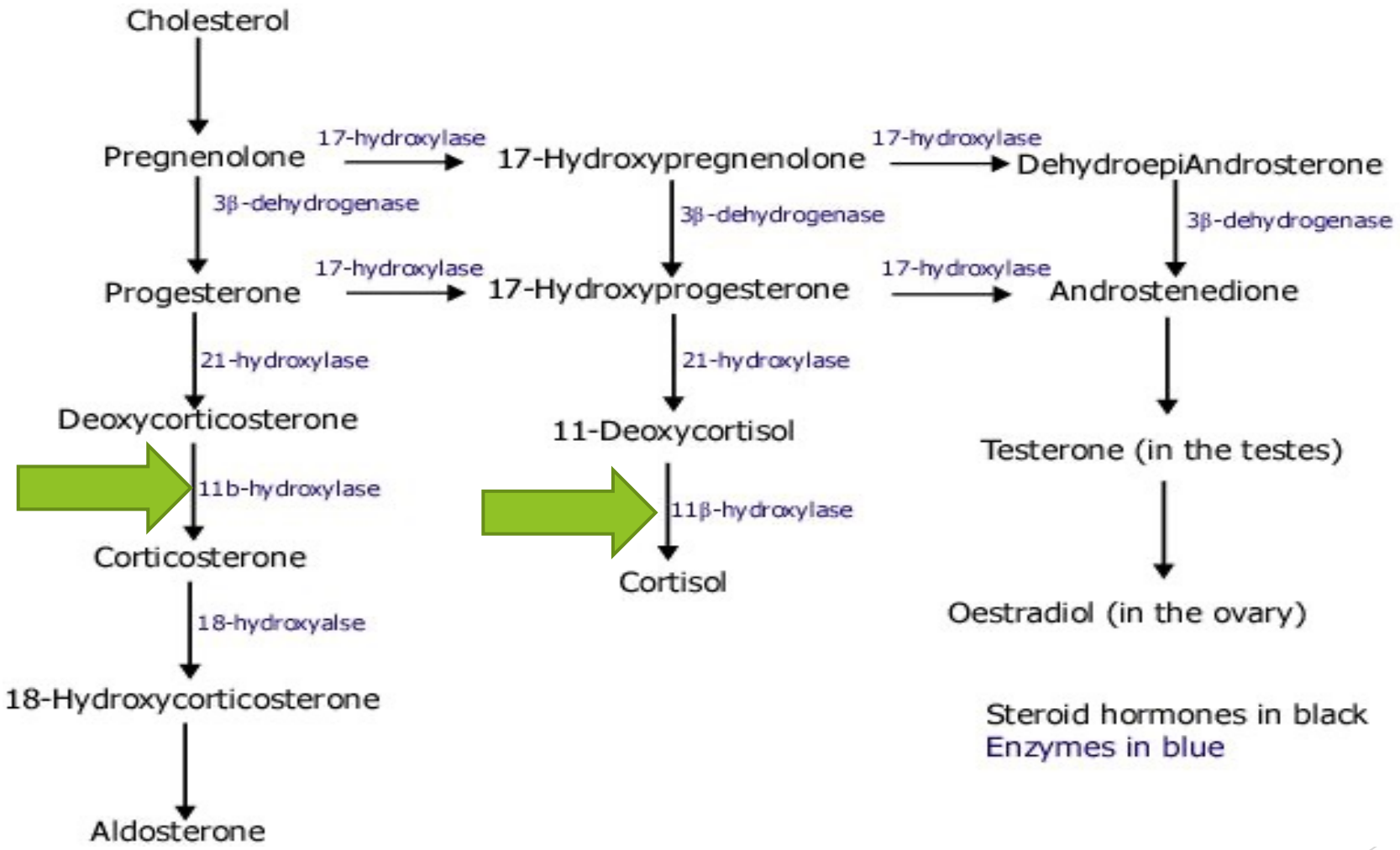
- Cortisol binds avidly to the renal aldosterone receptor and the plasma cortisol concentration is 100-fold > plasma aldosterone concentration
- In kidney, 11-beta-hydroxysteroid dehydrogenase enzyme type 2 isoform (11-beta-HSD2) converts cortisol into the inactive cortisone
- **AME:** defective 11-beta-HSD2 causes high renal concentration of cortisol which leads to excess stimulation of aldosterone receptor
- Autosomal recessive and presents in childhood with HTN, low K and metabolic alkalosis
- Both plasma aldosterone and renin low while urinary free cortisone levels are very low or undetectable
- Genetic testing available
- *Liquorice inhibits 11-beta-HSD2 and so causes an acquitted AME like condition*

Familial Aldosteronism

- FH type I or **glucocorticoid-remediable aldosteronism (GRA)** due to a *CYP11B1*/*CYP11B2* chimeric gene
- FH type II: This is the largest group and has autosomal dominant inheritance. Is clinically indistinguishable from sporadic primary aldosteronism. While the exact mutation not known, it is suspected to have linkage to chromosome 7p22
- FH type III: Caused by germline mutations in the potassium channel subunit KCNJ5, patients usually present early with massive adrenal hyperplasia.
- FH type IV caused by germline mutations in the *CACNA1H* gene, which encodes the alpha subunit of an L-type voltage-gated calcium channel (Cav3.2). While CT may show cortical adenoma, bilateral hyperplasia, or normal-appearing adrenal glands, adrenal venous sampling shows bilateral aldosterone hypersecretion

Glucocorticoid-remediable aldosteronism (GRA)

- While both cortisol and aldosterone are synthesised in the adrenal cortex, only cortisol is under the control of ACTH
- 11B- hydroxylase involved in the pathways of both cortisol and aldosterone synthesis (isoenzymes B-1 in cortisol synthesis and B-2 in aldosterone synthesis) has 95% homology between the two isoenzymes
- Unequal meiotic crossovers in chromosome 8 produces a hybrid 11B-hydroxylase enzyme which is involved in both cortisol and aldosterone synthesis and therefore, both cortisol and aldosterone production are controlled by ACTH
- Genetic testing diagnostic


Cholesterol
Pregnenolone
17-hydroxylase
17-Hydroxypregnenolone
17-hydroxylase
DehydroepiAndrosterone
3β-dehydrogenase
3β-dehydrogenase
3β-dehydrogenase
Progesterone
17-hydroxylase
17-Hydroxyprogesterone
17-hydroxylase
Androstenedione
21-hydroxylase
21-hydroxylase
Deoxycorticosterone
11-Deoxycortisol
Testerone (in the testes)
11b-hydroxylase
11β-hydroxylase
Corticosterone
Cortisol
Oestradiol (in the ovary)
18-hydroxyalse
18-Hydroxycorticosterone
Aldosterone
Steroid hormones in black
Enzymes in blue

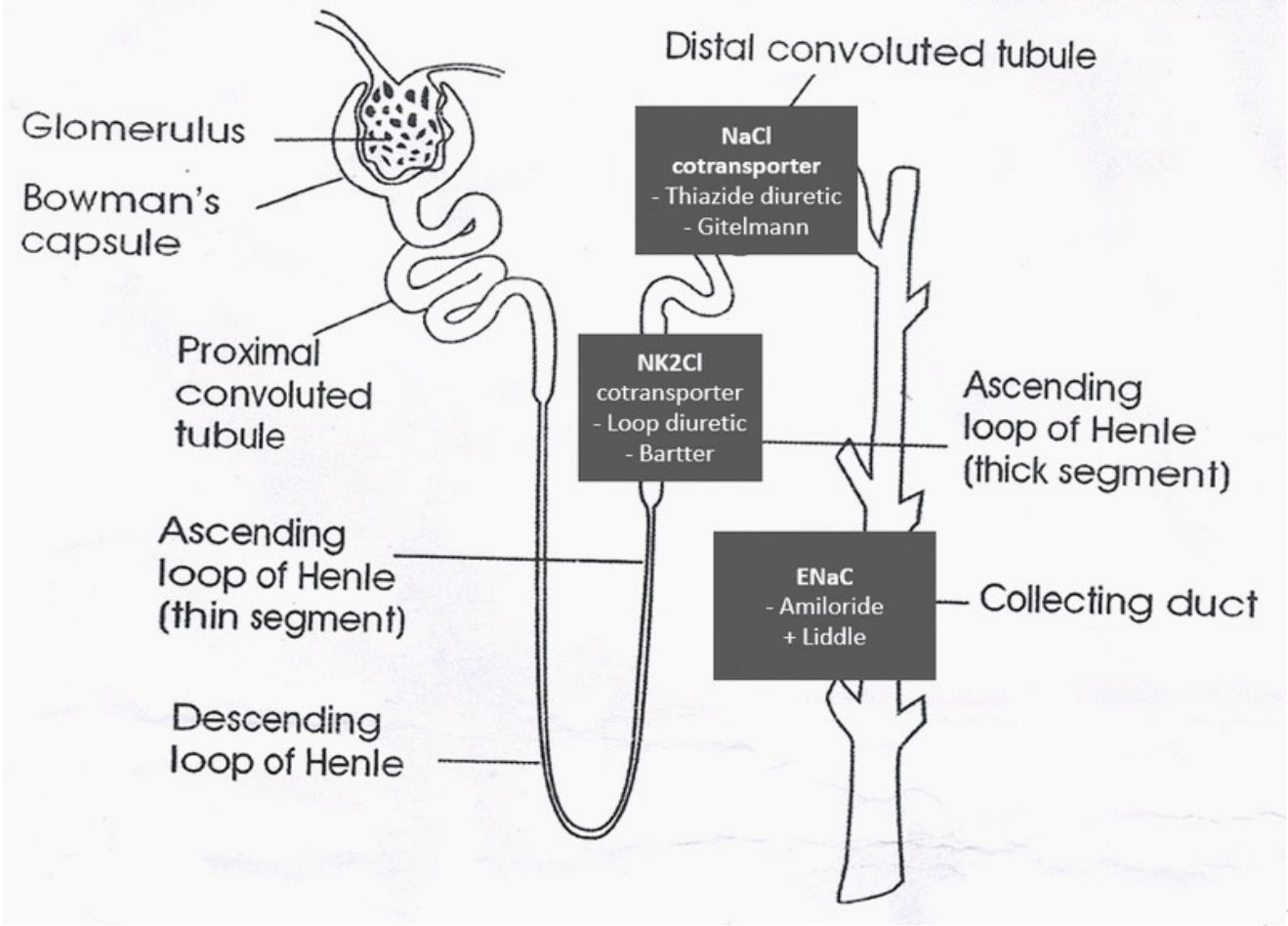
Bartter and Gitelman syndromes

- Bartter syndrome usually presents in perinatal period or childhood
- Gitelman syndrome is mostly a disorder of adulthood with hypomagnesaemia a striking feature
- Prevalence of Gitelman syndrome is 1 in 40,000 compared with 1 in 1,000,000 for Bartter syndrome
- Having Bartter and Gitelman syndromes is the same as being born on loop and thiazide diuretics respectively
    - 5 types of Bartter syndrome depending on the protein mutation involved-

Na-K-2Cl - type 1, ROMK- type 2, ClC-kb type 3, barttin- type 4, upregulation of CaSR- type 5 and loss of function of ClC-kb type and ClC-ka type

- Bartter-like syndrome can be secondary to aminoglycoside use
- Volume contraction in both conditions leads to RAAS activation and the secondary aldosteronism leads to urinary loss of K and H

Diagrammatic representation of Bartter, Gitelman and Liddle syndromes



Bartter and Gitelman Syndromes

Bartter Syndrome

- Defect in Na^+ reabsorption in the TAL of loop of Henle
- Usually presents in perinatal period or childhood
- Normal to increased urinary Ca
- Increased renal vasodilatory prostaglandins
- Treatment: NSAIDs, K supplementation and K-sparing diuretic e.g. spironolactone
- Type III classically grow to adulthood and may develop CKD due to nephrocalcinosis and NSAIDs use
- Often growth and mental retardation

Gitelman Syndrome

- Defect in thiazide-sensitive Na^+-Cl^- cotransporter in DCT
- Mostly a disorder of adulthood
- Low urinary Ca
- Hypomagnesaemia: high urinary Mg loss due to down regulation of Mg^+ channel TRPM6
- Treatment: K-sparing diuretic and Mg and K supplementation
- No growth or mental retardation

What can mimic Gitelman or Bartter syndromes?

- **Surreptitious self-induced vomiting**
  - Urinary Cl^- is characteristically low as hypovolemia leads to increased Na^+ reabsorption with the accompanying Cl^- reabsorption
  - Often scarring on the dorsum of the hand and dental erosions
- **Surreptitious diuretic use**
  - Variable urinary Cl^- levels depending on the timing of diuretic use
  - Urine diuretic screen may be helpful

Renal tubular acidosis (RTA)

- Group of disorders characterized by normal anion gap metabolic acidosis with either hypokalemia or hyperkalemia and relatively well preserved GFR
- **Normal anion gap metabolic acidosis with hypokalemia:**

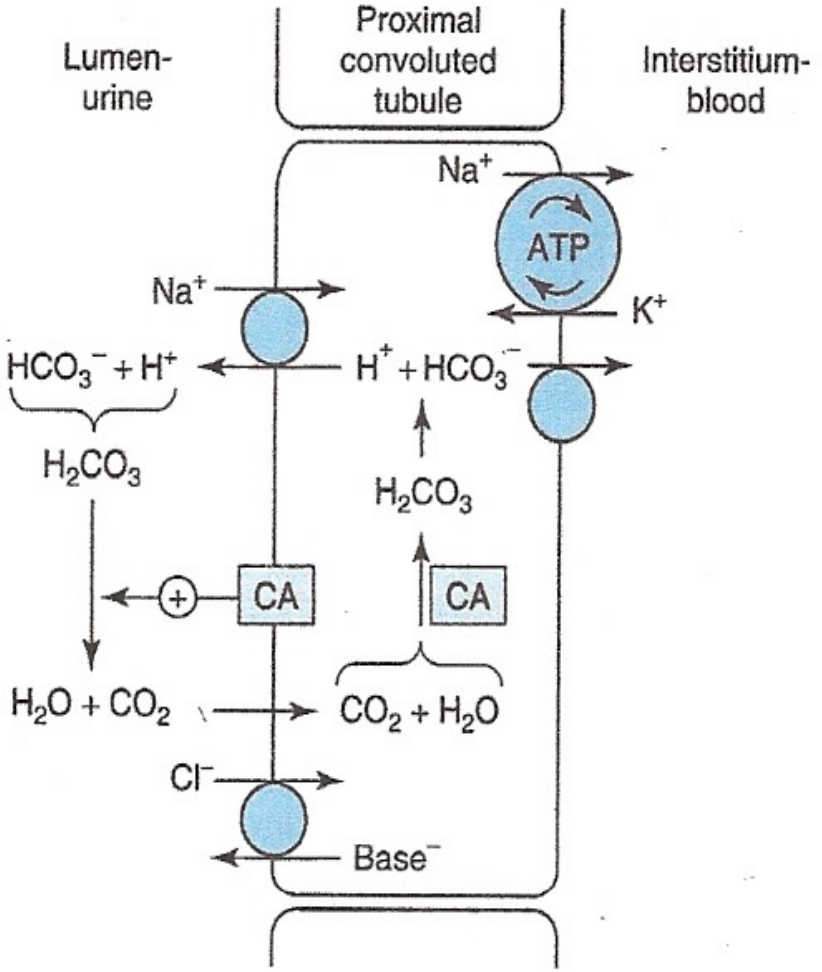
  - Proximal RTA (type 2) caused by reduced ability to reabsorb bicarbonate (HCO_3) in the proximal tubules

  - Distal RTA (type 1) caused by defects in distal H ion excretion

- **Normal anion gap metabolic acidosis with hyperkalemia:**

  -Type 4 RTA is due to either aldosterone deficiency or tubular resistance to the action of aldosterone and is the commonest among RTAs

PCT- Role of Carbonic Anhydrase (CA)



Proximal RTA (Type 2 RTA)

- Isolated defect in proximal HCO3 reabsorption or with impaired reabsorption of phosphate, glucose, uric acid, and amino acids (Fanconi syndrome)
- Urinary pH usually <5.5 due to compensatory increased H secretion by distal tubules
- Can be caused by myeloma due to tubular toxicity of the light chains
- Other causes include carbonic anhydrase inhibitors acetazolamide and topiramate, tenofovir, Wilson's disease, Cystinosis, Lowe syndrome, outdated tetracycline and lead or mercury poisoning
- **Fanconi syndrome often suspected in normal anion gap metabolic acidosis with hypokalaemia , glycosuria AND low plasma phosphate and uric acid levels**

Distal RTA (Type 1 RTA)

- Type 1 RTA is caused by inability of the distal tubules to secrete H
- Characterised by urinary pH >5.5 due to lack of H in urine THUS differentiating from type 2 RTA
- Causes: **Sjogren's syndrome**, SLE, hypergammaglobulinemic states, primary biliary cirrhosis, autoimmune hepatitis, chronic obstructive uropathy, renal transplantation and glue sniffing
- Drugs causing RTA type 1: lithium, ibuprofen, ifosfamide (chemo agent) and amphotericin
- Genetic associations: Marfan syndrome and Ehler Danlos syndrome

My patient has diarrhea……

- Metabolic acidosis and hypokalaemia in diarrhea due to

  -Faecal loss of bicarbonate rich pancreatic secretions

  - Intravascular depletion and RAAS activation
- *How do I differentiate from RTA?*

Urine anion gap (UAG)

- UAG = Urine(Na + K − Cl)
- UAG is positive in healthy individuals
- With metabolic acidosis from any cause, the kidney will appropriately respond by excreting a heavy load of H *(except in type1 RTA where H excretion is characteristically defective)*
- NH3 in urine accepts H to form NH4 which combines with the negatively charge Cl to form NH4Cl
- **UAG is positive in type 1 RTA (lack of H and hence low NH4Cl) and negative in metabolic acidosis due to any cause including diarrhea (excess H and hence high NH4Cl)**

Bones and stones in RTA

- Metabolic acidosis causes bones to release calcium phosphate as buffer (causing progressive osteomalacia and osteopenia over time)
- Kidneys try to eliminate the excess Ca
- Normally urinary citrate binds Ca and keeps it soluble
- In type 1 RTA, the proximal reabsorption of citrate is enhanced
- Low urinary citrate and high urinary pH in type 1 RTA predisposes to Ca stones

Treatment of types 1 and 2 RTA

- Alkali and potassium replacement
- Higher doses of alkali needed in type 2 RTA
- Potassium citrate useful in patients with hypokalemia or stones
- Patients with severe or symptomatic hypokalemia should be given potassium prior to or concomitantly with sodium bicarbonate therapy

Recap of type 1 and 2 RTAs

Type 1 RTA (distal RTA)	Type 2 RTA (Proximal RTA)
Inability to secrete H+	Inability to reabsorb HCO3
Urine pH >5.5 (low H+ in urine)	Urine pH <5.5 (compensatory increase in distal tubular H^+ secretion)
Nephrolithiasis and nephrocalcinosis	No renal stones
No Fanconi syndrome	May have Fanconi syndrome:glycosuria,phosphaturia, uric aciduria and aminoaciduria
Treat with alkali and K+ replacement	Same treatment but often need bigger doses of alkali

Type 4 RTA

- Normal anion gap metabolic acidosis and hyperkalaemia
- Hyporeninemic hypoaldosteronism as well as diminished tubular response to aldosterone
- Common in diabetics especially those with diabetic nephropathy
- Caused by ACEI, ARBs, K-sparing diuretics, Calcineurin inhibitors (cyclosporine and tacrolimus), NSAIDs, heparin, trimethoprim
- May be seen in chronic interstitial nephritis of any cause or sickle cell disease
- Synthetic mineralocorticoid such as fludrocortisone may be effective
- In patients with hypertension or fluid overload, thiazide or loop diuretic may help

Hyperkalemia

- Hyperkalemia is a rare occurrence in normal individuals
- Persistent hyperkalaemia requires **impaired urinary potassium excretion**
- Following changes in the principal cells of the collecting duct increase the efficiency of K excretion in response to increased K intake
  - *Increased Na-K-ATPase activity, which enhances basolateral K uptake, thereby increasing the size of the K secretory pool*
  - *Increase in the density and activity of K secretory channels in the renal tubules*

Pseudo-hyperkalemia

- Mechanical trauma during venepuncture
- Repeated and excessive fist clenching during blood drawing
- Thrombocytosis
- Very high white blood cell counts due to leukemia or lymphoma

Causes of hyperkalemia

- Insulin deficiency in uncontrolled diabetes mellitus
- Acute on chronic kidney disease
- Drugs: ACE-I, ARB, CNI, heparin, trimethoprim ,and nonselective beta-blockers (remember-beta1 receptors cause renin release and beta 2 activity drives K into cells)
- Type IV RTA
- Increased tissue catabolism e.g. in cytotoxic or radiation therapy or trauma
- Hyperkalemic periodic paralysis
- Digitalis overdose by inhibition of the Na-K-ATPase pump
- Red cell transfusion due to leakage of K out of cells during storage

Manifestations of hyperkalemia

- Ascending muscle weakness
- Cardiac manifestations and ECG changes :

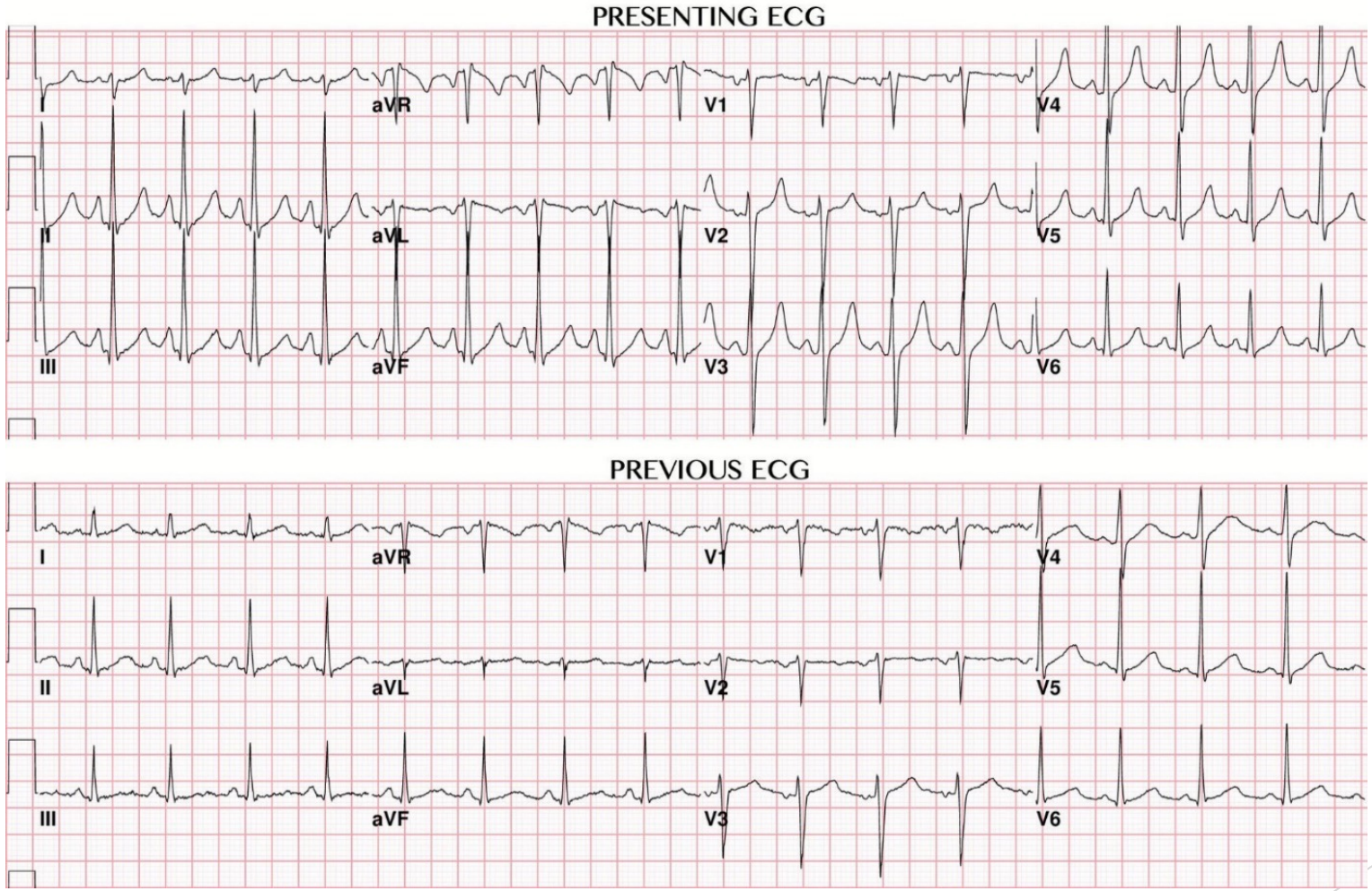
  -Tall peaked T waves with shortened QT interval

  - Followed by progressive lengthening of the PR interval and QRS duration and absent p wave

  - Finally, QRS widens further to a sine wave pattern

  - Cardiac conduction abnormalities and cardiac arrhythmias e.g. bradycardia, sinus arrest, VT, VF and asystole
- Hyperkalemia can cause metabolic acidosis

ECG changes with high K



Treatment of Hyperkalemia

Hyperkalemic emergency: muscle weakness or paralysis and cardiac conduction defects need cardiac monitoring and repeat testing of K every 1-2 hours

- Administration of calcium chloride or gluconate (10 mL of a 10 percent solution) to antagonize the membrane actions of high K (cardio-protective) can be repeated every 30 to 60 minutes
- IV insulin with glucose to drive extracellular K into cells
- Salbutamol nebuliser
- Ensure ceasing all drugs that can cause raised K- (ACEI, ARB, CNI, heparin, trimethoprim and NSAID)

Above treatment often needs to be repeated multiple times

Additive effect in treatment of Hyperkalemia

- Used but of doubtful value in acute setting: Cation exchangers Patiromer (veltassa), and Sodium polystyrene sulfonate (resonium) which bind K in the GIT
- Loop diuretics with/without saline hydration
- IV sodium bicarbonate as correction of acidosis can lead to lower K
- Haemodialysis if conservative management fail

Albert Einstein

I have no special talent. I am only passionately curious.

Thank you