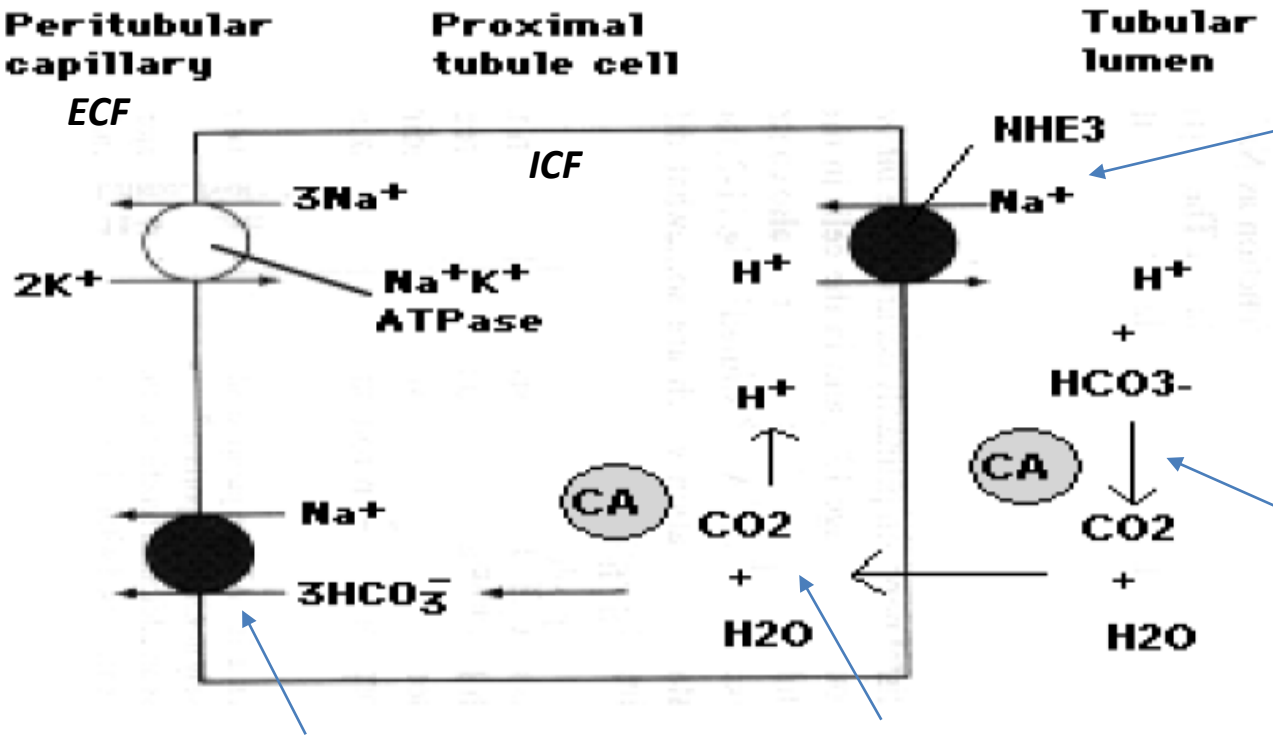
Kidney control of Acid-base balance

1. The Kidney reabsorbs HCO3- (in the Proximal Convoluted Tubule)

(Image credit: Dr. McLaughlin May 4th 2012 lecture)



1. Na+/H+ exchanger (NHE3):
-Found only in the PCT
-Reabsorbs 1 Na+ while secreting 1 H+ into tubule
-This is how HCO3- reabsorption is linked to Na+ reabsorption. HCO3- wasting (i.e. in vomiting) also means Na+ will be wasted, ↑ urine [Na+]

+

Angiotensin II
Stimulates NHE3 directly, to absorb more Na+ and water proximally

ICF pH:
Lower ICF pH = ↑ NHE3 activity (pump more H+ out of cell)

2. The secreted H+ binds to the HCO3- that was filtered into the tubule; an **extracellular Carbonic Anhydrase (CA)** converts them into water and CO2.
→As a gas, CO2 easily diffuses back into the cell.

3. In the cell, an intracellular Carbonic anhydrase converts CO2 and H2O back into HCO3- and H+
-The H+ is re-secreted back into the lumen by NHE3 to facilitate Na+ reabsorption

4. An HCO3/Na+ symporter reabsorbs both HCO3- and Na+ from the ICF into the peritubular capillary (back into the ECF)

Type 2 Renal Tubular Acidosis:

- Metabolic acidosis due to the failure to reabsorb HCO3- in the PCT
- Can be due to dysfunctional NHE3-antiporters, CA, or Na/HCO3-symporters. Results in a lower threshold for proximal HCO3- reabsorption (PCT can maximally reabsorb less HCO3-)
- Results in a high HCO3- fractional excretion (FE_{HCO3} > 15%): HCO3-wasting
- RTA type 2 can be isolated, or as part of Fanconi's syndrome (reduced PCT reabsorption of glucose, amino acids, uric acid, and phosphate, as well as bicarb)

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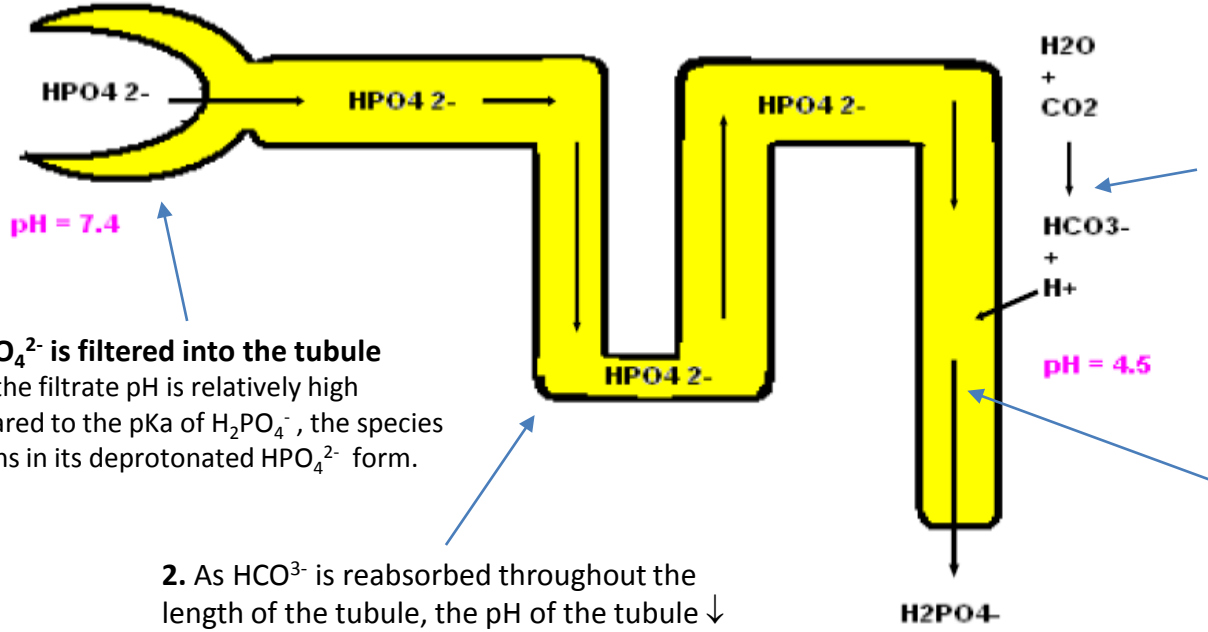
2. The Kidney secretes H+ as NaH_2PO_4 and NH_4Cl (and generates HCO3- for the ECF)

(Image credit: Dr. McLaughlin May 4th 2012 lecture)

Rationale:

→Metabolism in the body is constantly producing excess H+, so these H+ need to be excreted to prevent acidosis.



1. HPO_4^{2-} is filtered into the tubule

Since the filtrate pH is relatively high compared to the pKa of $H_2PO_4^-$, the species remains in its deprotonated HPO_4^{2-} form.

2. As HCO^{3-} is reabsorbed throughout the length of the tubule, the pH of the tubule ↓ the more distal to the bowman's capsule.

3. In the collecting duct, H+ is actively secreted into the tubule lumen, ↓ lumen pH:

- CO2 diffuses from the blood into the tubule epithelial cells
- Carbonic anhydrase in the tubule epithelium ICF converts the CO2 into HCO3- (reabsorbed) and H+ (secreted)

4. The Lower pH of the tubule lumen converts HPO_4^{2-} into $H_2PO_4^-$

- H+ is thus secreted as $H_2PO_4^-$
- Secretion of 1 H+ means the reabsorption/gain of 1 HCO_3^-

Acidosis can arise when this HCO3- regeneration/ reabsorption process fails! (Indirect loss of HCO3-):

→Occurs when H+ is not secreted as $H_2PO_4^-$, thus no HCO3- is reabsorbed.

→The H+ secreting capacity of this mechanism cannot increase! It's limited by the amt HPO_4^{2-} originally filtered!

→Another process is needed to ramp up H+ secretion in case the body produces excess H+

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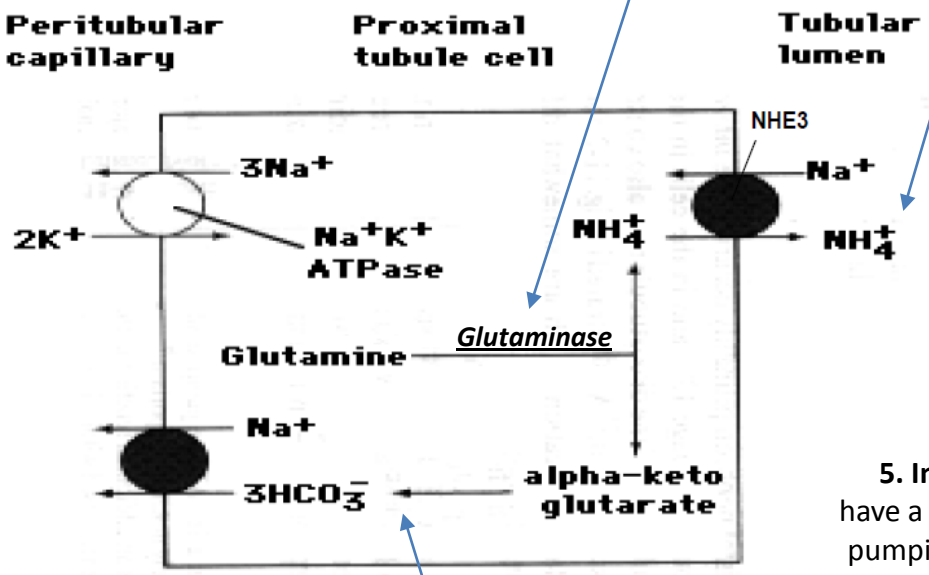
Rationale:
→Metabolism in the body is constantly producing excess H+, so these H+ need to be excreted to prevent acidosis.

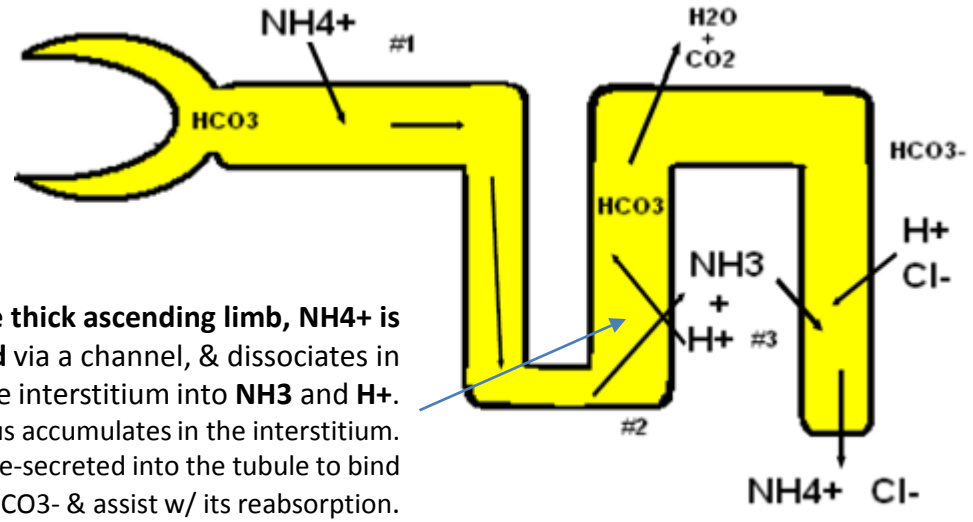
1. PCT cells contain *glutaminase* (activated by low pH)
→During ECF acidosis, more CO2 is delivered to the PCT cell, and converted into HCO3- and H+. The HCO3- is pumped out, the H+ remains to ↓ intracellular pH, activating glutaminase.



2. Glutaminase breakdown of 1 glutamine produces 1 **HCO3-**, which is reabsored to help counter ECF acidosis.

3. The glutaminase breakdown of glutamine also produces an **NH4+,** which is pumped into the tubule via NHE3

- Since it is charged, NH4+ cannot diffuse back into cells in its own; it traverses the length of the tubule until the LoH.

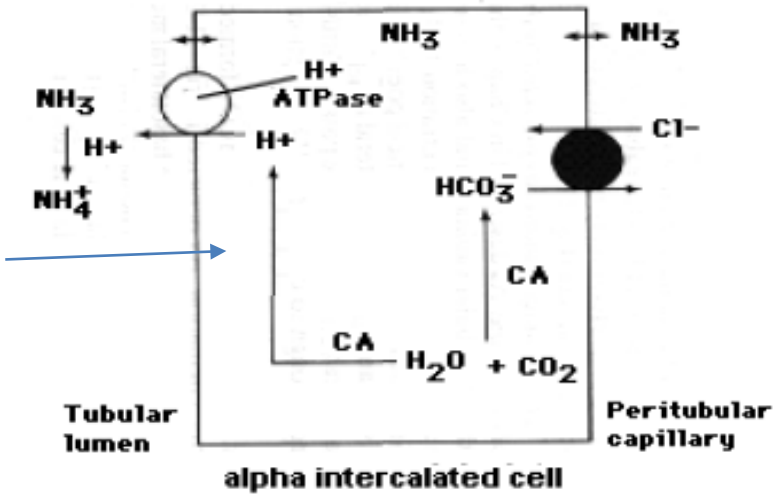


4. In the thick ascending limb, NH4+ is reabsorbed via a channel, & dissociates in the interstitium into **NH3** and **H+**.

- NH3 thus accumulates in the interstitium.
- The H+ is re-secreted into the tubule to bind HCO3- & assist w/ its reabsorption.

5. In the collecting duct, α-intercalated cells have a **proton-pump** on their apical membrane, pumping excess intracellular H+ into the tubule

- ECF H+ are brought to the CCD cells by CO2, coverted into H+ & HCO3- by Carbonic anhydrase.
- W/out NH3: H+ secreted w/ Cl-: very acidic (bad)!
- With NH3: acid is secreted as NH4+Cl-, much less dangerous to tubule.
- Secreting acids as NH4+ allows for fine-tuning of H+ secretion with virtually unlimited capacity.



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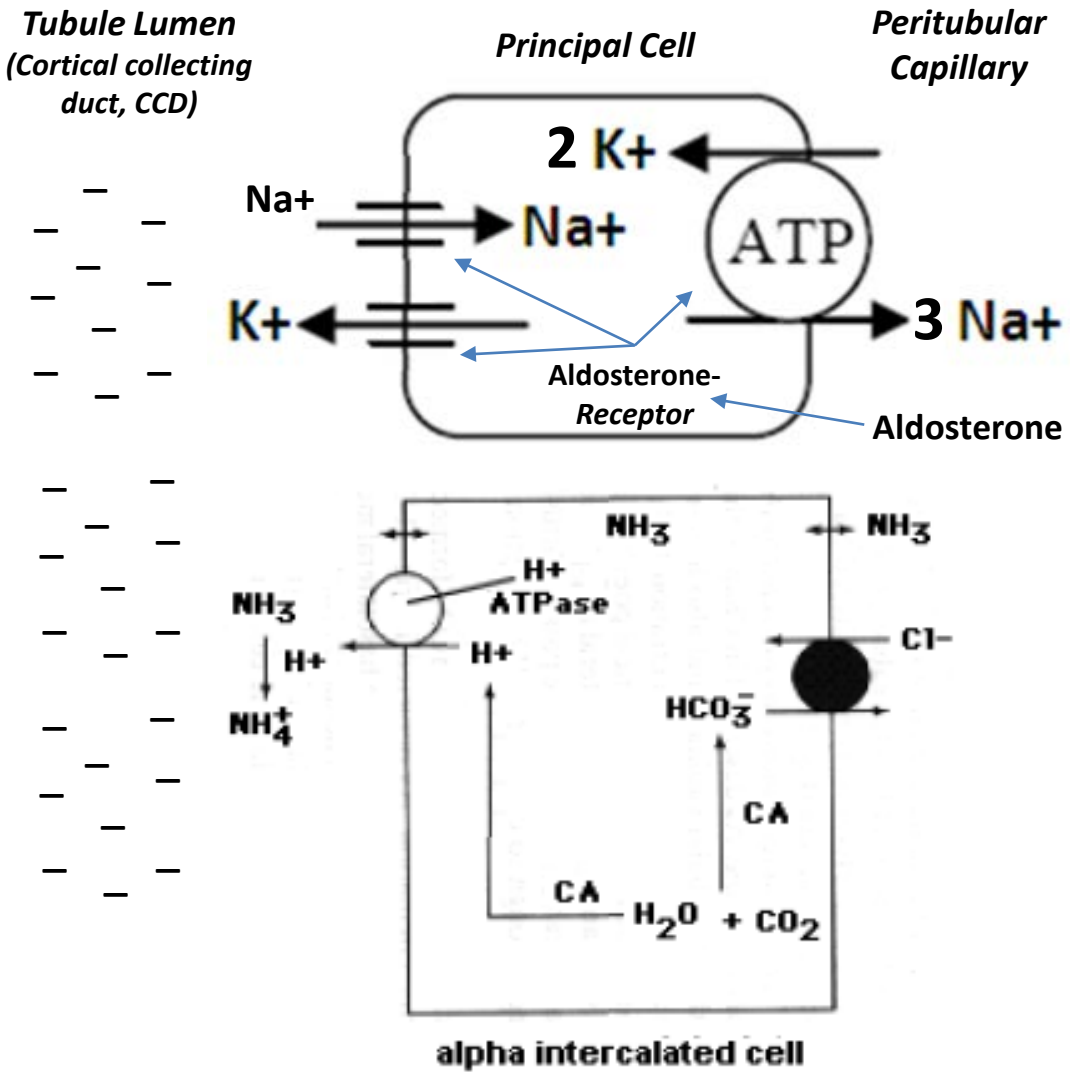

3 requirements for acid to be secreted as NH4+:

1. A functional proton-pump on the apical membrane of the Alpha-intercalated cell

→If this H+ pump fails, **Type 1 RTA**! → **High K+ secretion (↓ TTKG)** (Less H+ in tubule to counter-balance its negative charges, drawing out more K+)

2. Negative luminal charge, facilitating H+ export down its charge gradient.

→Negative luminal charge is created by a functional principal cell (Reabsorbing Na+ makes lumen relatively -ve)

→If principal cells fail (insensitive to aldosterone, etc) → lumen less negative, less H+ secreted → H+ builds up in ECF (acidosis) – **Type 4 RTA** → **Low K+ secretion (↑ TTKG)** (b/c of principal cell failure, for many reasons: less K+ channels in membrane, less Na+ reabsorbed, etc)

3. NH3 in the lumen

→A supply of NH3 is essential to bind to H+ and get rid of it as NH4+

→No NH3 can be due to 1) bad kidney damage to PCT, to glomeruli (↓ GFR), etc, 2) malnourished; no glutamine in diet.