Urogenital system

Physiology

Sheet Slide

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Acid-Base balance

Throughout this lecture, we will come across another important function of the kidney, which is regulating the concentration of extracellular hydrogen ions (H^+), through what is usually referred to as ***Acid-Base balance***.

General statements regarding Ph and H^+ concentration:

- H+ concentration In the plasma is 40nM/L ($4*10^{-8}$), which can be expressed using Logarithms as → log 4 + log 10^{-8} ***(log(x*y)= log x +log y)*** …

- Log 4 =0.6, while log 10^{-8} = -8 ***($log10^X = X$)*** → thus; **log $4*10^{-8}$ = 0.6-8** which equals -7.4; the minus signs are often not welcomed, so we **define the concentration of H+ as -Log,** the capital letter "P" is used instead of the three letters of -Log.

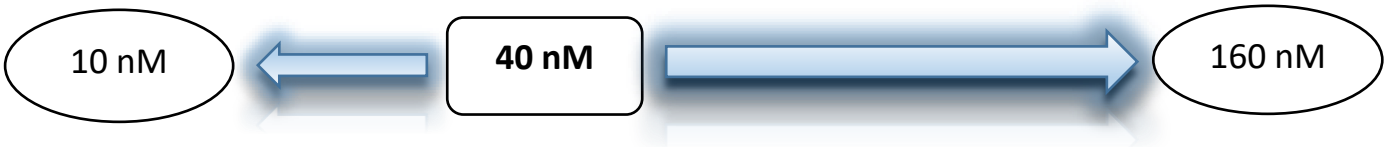
- We conclude that → "Ph" is the -Log of [H+] (moles/liter), the same applies for any other ion, i.e. PCa= -Log [$Ca+^2$].

- Any ion in our body has a normal range which it varies within. [K^+] has a range of (3.5-5.5), [Na^+] has a range of (135-145) and all are in millimoles/liter (mmol/L). While [H+] range is relatively wide (10-160) **nanomoles/liter. Thus, the Ph varies between (6.8-8).** (which correspond to (1/4) x and 4x respectively, where x is the normal concentration of H+)

This fact suggests that:

1- Our body can ***hardly*** tolerate a Ph at the two extremes (6.8 and 8); yet it is not in a good shape unless the Ph is between **(7.35-7.45)**. However, if the Ph dropped below 6.8 or rose above 8, it is very unlikely to survive.

2- **Our body can handle acidosis much easier than alkalosis**. Remember that 40 nanomolar is the normal concentration of H+ in plasma, and that corresponds to a Ph of merely **7.4**. On the other hand, the *extreme acidic* state is 160 nanomolar (120 nanomolar away from the normal), while the *extreme alkalotic* state is 10 nanomolar (30 nanomolar difference).



- A Ph Below 7.35 is acidosis, while a Ph above 7.45 is alkalosis, and these two values are our reference all the way along this chapter.

- The normal Ph range is important for the normal protein function, ions disturbances and function of different enzymes.

Having said that, how does our body control acids and what are the mechanisms of which?

- The body of a normal human being generates **300 liters of CO_2 per day** (which corresponds to 10 moles of CO_2); joined with water it can affect the Ph of the plasma as it forms **carbonic acid (H_2CO_3)**. However, the lungs can readily get rid of this form of acids, known as "**Volatile Acids"**, through normal respiration**.**

- Another form of acids is also produced, which the lung can't take care of, known as **"Fixed Acids".** Each single kilogram in a human being mass produces 1 millimolar of fixed acids **(H^+)** in the form of $HP0_4^-$, H_2SO_4 , lactic acid, glutamic acid and many others. Assuming that a normal individual has a mass of 80 kg, **80 millimoles of fixed acids are daily produced**.

- So, we conclude that our body possesses acids in two forms, **volatile (10 Moles)** and **Fixed 80 millimoles.**

- The major threat to our plasma Ph is not CO_2, rather it is the 80 millimoles of H^+ produced each day, which can drag the Ph to low levels. These 80 millimoles are concentrated in **14 Liters of extracellular fluid** (H^+ can hardly enter the cells). 5.5 millimoles in

each liter contribute to a Ph of around 2.5, which is not by any means compatible with life.

How can our body handle these 80 millimoles?

Answering this question is our main concern in this lecture.

What if:

- **All of this H^+ was added to HCO_3^- ?** to form carbonic acid H_2CO_3, which further dissociates to H_2O and **CO_2**, the lung then proceeds further by exhaling all the CO_2.

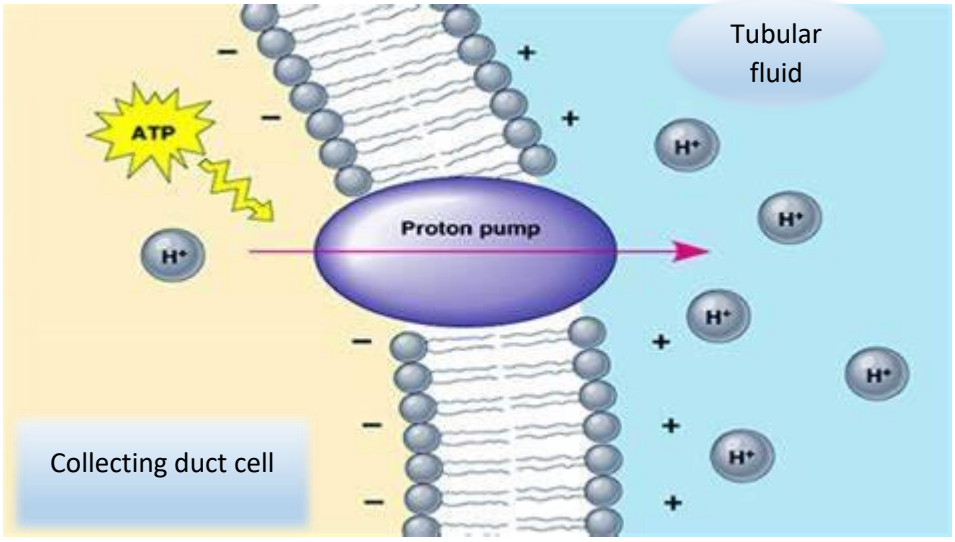
This solution seems logical, yet it is not reliable. Our storage of bicarbonate (HCO_3^-) is limited and scarce, 24 millimole/L; thus, the total amount of HCO_3^- never exceeds 24mM/L*14L= 336 mM, which aids in the formation of CO_2 only for a couple of days. This mechanism is not applicable.

- **All of this H+ was excreted in urine?**

Let us have a closer look at the **collecting duct cell**, which represents the last modifier that can change tubular fluid contents before it becomes urine. **Hydrogen pump** at the apical membrane of the **collecting duct cell** can pump hydrogen actively towards the lumen (primary active transport) with a capacity to generate 900-1,000 folds difference in gradient. That seems acceptable?

Well, let us see *for how many millimoles does this difference correspond to*. The Ph within collecting duct cells is around 7, generating a 1,000 folds difference will shift the Ph within the lumen to merely 4-4.5, by a simple calculation we conclude that a Ph of 4.5 only contains 0.1 millimolar of H^+. This amount is not significant at all to be considered as a mechanism of H^+ clearance.

This mechanism is not applicable too.



The conclusion: These 80 millimoles of H+ must be dealt with, the only way our body can do so is by providing HCO_3^- in sufficient amount; forming H_2CO_3 which dissociates to water & CO2, that is further exhaled.

Let us have a closer look at HCO_3^- and set general statements regarding its filtration and reabsorption.

- ***HCO_3^-*** is freely filtered to Bowman's space; it's a relatively small molecule.

- The amount of ***HCO_3^-*** that enters Bowman's space (Filtered Load) = GFR*[***HCO_3^-***] $_{plasma}$ = 180*24= 4320 millimole/day.

- *Note: the doctor used the unit milliequivalent for $HCO3^-$; a certain amount of univalent ions provides the same amount of equivalents while the same amount of divalent ions provides twice the amount of equivalents. For example, 1* ***mmol*** *(0.001 mol) of Na^+ equals 1* ***meq****, while 1* ***mmol*** *of Ca^{++} equals 2* ***meq****. Conclusion: for bicarbonate; mmol = milliequivalent (meq).*

- Our body can't tolerate any loss of HCO_3^- in urine, we need every single molecule; to join H+ forming carbonic acid (H_2CO_3).

- **So, the kidney's main function is to reabsorb every single molecule of HCO_3^- 4320 mM/day?? But is that enough?**

Apparently, it is not, we still need the kidney to produce an extra 80 mM of HCO_3^- within its renal vein, unless it does that, the body can't neutralize the fixed acids represented by **80 mM of H^+.**

***Note: clearance of HCO^- is negative*.**

- **The kidney has two main functions regarding** HCO_3^- :

  1- To reabsorb every single molecule of the filtered load.
  2- To produce an extra 80 mM.

Let us discuss the reabsorption first.

The reabsorption process in steps:

- Within the cell of the **proximal tubule,** CO_2 exists. →
- When it is combined with water it forms H_2CO_3 →
- & with the presence of **carbonic anhydrase,** HCO_3^- is formed and reabsorbed to the peritubular capillary through the basolateral membrane →
- H+, on the other hand, is secreted to the lumen of the proximal tubule, to join HCO_3^- and form H_2CO_3 →
- the later dissociates to water and CO_2 by the action of carbonic anhydrase →
- CO_2 re-enters the cell to contribute to the cycle all over again.

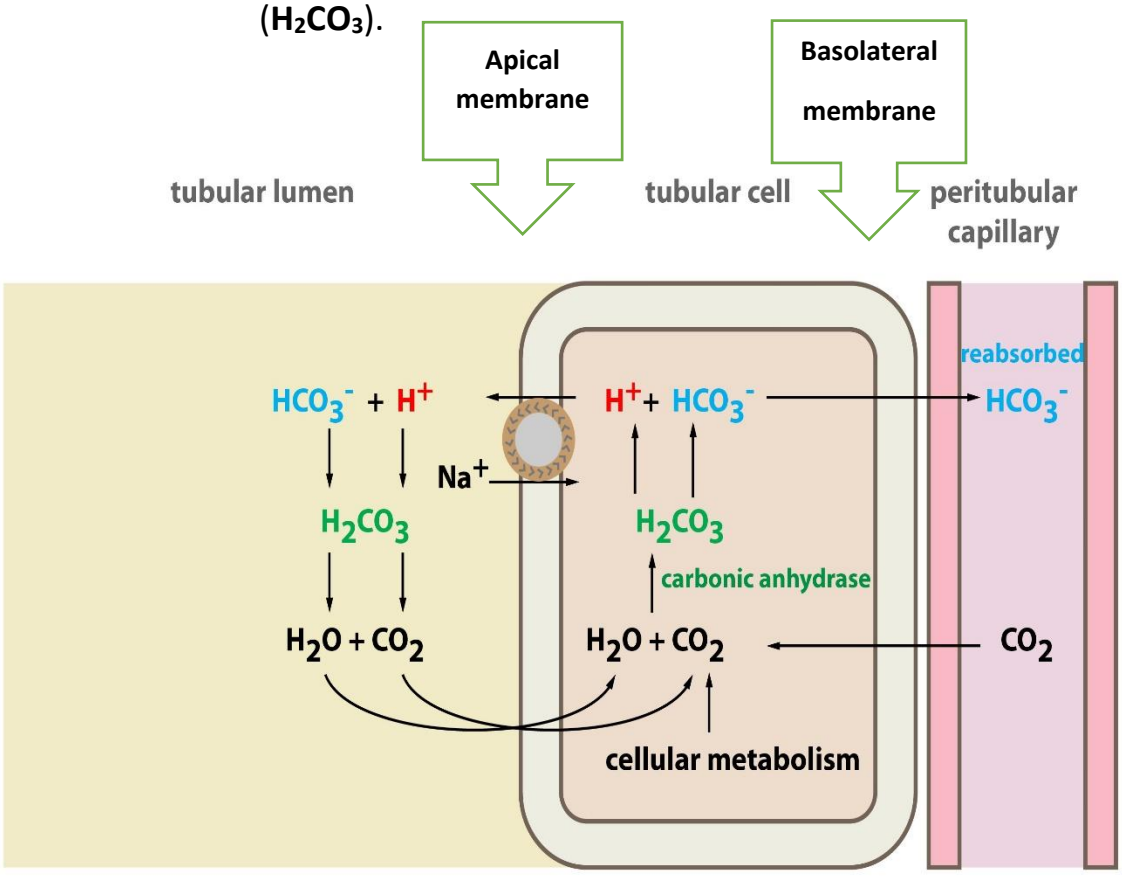
Additional notes:

- HCO_3^- can't cross the apical membrane; due to its charge.

- CO_2 exists within cells because of many factors. The filtered load, blood and metabolism of the cell itself, all contribute to CO_2 continuous availability.

- It takes ***only one atom of H^+*** to reabsorb all of the filtered load of HCO_3^- which means that the hydrogen ion generated within the cell of the **proximal tubule**, will go back and forth through the apical membrane until no longer bicarbonate is there, thus there is no net secretion of H+ *till now*.

  Notice that this is **not a direct re-absorption of HCO_3^-,** rather it depends on the formation and dissociation of carbonic acid (**H_2CO_3**).



We are done with the re-absorption of bicarbonate. Now we will move to bicarbonate gain.

The goal is: a net gain of 80mM bicarbonate.

The moment bicarbonate is depleted within the tubular fluid, any further secretion of H+ is a bicarbonate gain. How?

By the same mechanism of CO_2 combination with water and dissociation of H_2CO_3 to H^+ and HCO_3^- . Every time H^+ is secreted into the lumen of the tubule, HCO_3^- is reabsorbed by the peritubular capillaries through the basolateral membrane.

So, why not keep secreting H+ towards the lumen?

H^+ is secreted towards the lumen using a secondary active transporter, Na^+ enters the cell & H^+ is pumped towards the lumen, ***as it is depicted in the drawing above***. The problem with secondary active transporters is there **modest capacity to generate a concentration gradient across membranes**. Na^+/H^+ counter-transporter is capable of only 5 folds difference in gradient. When this transporter stops, no further production of HCO_3^- can take place.

How to overcome this obstacle?

If the excess H+ within the lumen is buffered, the pump works soundly and smoothly. We need 80mM of buffers, this amount guaranties 80mM of bicarbonate production.

Role of buffers:

- However, **only 25mM of buffers** will neutralize H^+, as the concentration of buffers is not excess.

- These **25mM are constant** & can't be increased, regardless of the body's inner environment, *more details in the last topic*.

- The **most common** buffer to exist in the tubular fluid is HPO_4^{-2}, when combined with H+ it is then $H_2PO_4^-$.

Q: How many millimoles of buffers do we possess?

A: Filtered Load $_{HPO4^-}$= 1.2mM * 180 = 225mM/day

90% is reabsorbed under the effect of Parathyroid hormone, so we are only left with 10%, which corresponds to 25mM in their base form, HPO_4^-.

→ 25mM of HPO_4^- means **25mM of H+ is neutralized**, and much more important, **25mM of HCO_3^- is being produced** and reabsorbed by the peritubular capillaries through the basolateral membrane.

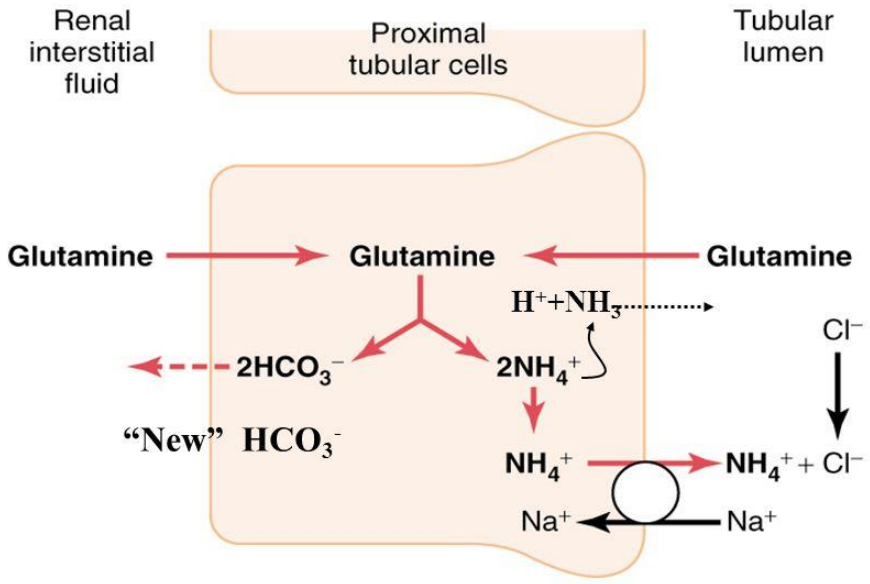
And that's all what buffers are capable of.

Role of Glutamate & Glutaminase:

The remaining 55mM of HCO_3^- is produced in a quite bizarre way. The cells of the proximal tubule benefit from the catabolism of glutamine, an amino acid, via glutaminase to yield 2 HCO_3^- and 2 NH_4^+.

55mM of NH_4^+ production means 55mM HCO_3^- gain.

Production and Secretion of NH_4^+ and HCO_3^- by Proximal, Thick Loop of Henle,and Distal Tubules



Note: glutamine can reach the cells of the proximal tubule using many different routes, through the blood is the most common.

<u>Now, and using all the previous mechanisms, the kidney has reabsorbed 4320mM of HCO_3^- and gained new 80mM.</u>

Calculate Bicarbonate gain in the urine

- So far, we've stated that a normal healthy individual, produces 1mM of fixed acids per Kg. 80 Kg mass, means 80mM of H+, which further needs 80mM of HCO_3^- to neutralize.

- How can we make sure that this individual has normal concentration of Bicarbonate?

Examining a urine sample

Bicarbonate gain = Titratable acids + NH_4Cl – HCO_3^- (if present)

- Remember that around 25mM of H+ was buffered using HPO_4^-. However, many other buffers also played a part in this process i.e. citrate, lactate; yet it is not feasible to calculate every single buffer alone, so all of these buffers were referred to as **Titratable Acids**.

- These acids when found in urine are **Tittered** using NaOH, how many millimoles of NaOH added indicates how many millimoles of H+ were buffered; and thus, how many millimoles of HCO_3^- were produced.

- Ph of the urine is around 6-6.5, while the ultrafiltrate had a Ph of 7.4. you keep ***titrating*** the acids by adding NaOH, until it is back to its normal 7.4.

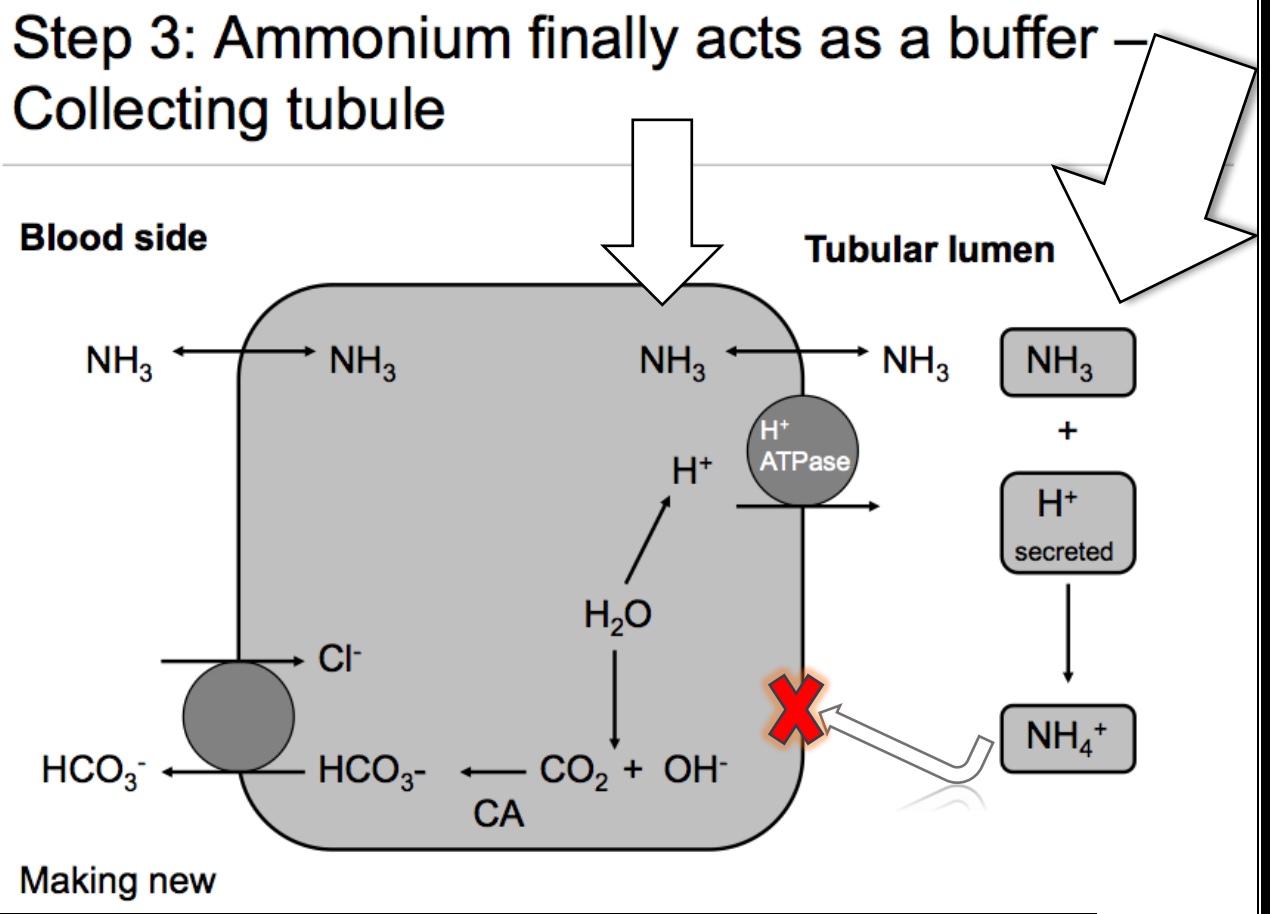
- **Bicarbonate gain is nothing but the sum of both the role of buffers and glutamate.**

Remember that glutamate role was represented by how many millimoles of NH_4^+ is there. NH_4^+ is often combined with an anion.

- **But does NH_4^+ have another resource other than glutamate ?**

- **NH_4^+ is *mainly* produced through the catabolism of glutamate. However, the other *minor* percentage of NH_4^+ is due to "Ammonia" that is added to hydrogen ion in the distal part of the tubule, $NH_3 + H+ \rightarrow NH_4^+$.**

NH_3 can readily cross the membrane, while NH_4^+ can't; it is a charged molecule, so it* is *trapped* →This process is called ammonia trapping.



Kidney injury and diabetic ketoacidosis

This is the final topic we are going through in this lecture.

You should bear in mind that kidney contribution to any physiologic process is often slow and needs time to exert its effect.

- Normal healthy kidney can produce up to **500 mM of NH_4^+ are produced each day**. As a result, the normal body can handle and regulate different foods and drinks with various Ph's.

If the diet was more alkalotic → no need for this huge amount of bicarbonate, so the urine will have high concentrations of HCO_3^-.

If the diet was more acidic → Bicarbonate gain will increase, and HCO_3^- is totally reabsorbed.

- But in an injured kidney, or in a diabetic ketoacidosis patient. The kidney role in physiologic regulation subsides; as takes long time to show a significant contribution, so the neural and hormonal processes take the part in homeostasis.

The generalization is: kidneys don't show efficient or significant role to overcome any physiological disturbance in **<u>acute</u>** injuries. These injuries **develop abruptly**; thus, the kidneys won't respond until it's too late.

- In order to manage an acidotic state, the body's production of HCO_3^- should increase. As stated previously, the role of buffers can't exceed these 25mM, it is the production of **NH_4^+ that mainly contributes to overcome and acidotic state.**

- The ability to produce HCO_3^- in huge amounts and through different mechanisms may explain why our body is more capable to manage acidotic rather than alkalotic states.

Love is wise … Hatred is Foolish