Hashemite University
H • U • M
Medical School Committee

Scientific Team
الفريق العلمي

PHYSIOLOGY

Lecture : 6

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Renal clearance & Introduction to acid base balance

بسم الله الرحمن الرحيم.

السلايدات باللون **الأسود**، الشرح باللون الأزرق

❖ Clearance

• "Clearance" describes the rate at which substances are removed (cleared) from the plasma.

• Renal clearance of a substance is the volume of plasma completely cleared of a substance per min by the kidneys.

من اسمه "clear" معناها تنظيف، يعني البلازما فيها مادة/مواد معينة احنا بدنا نشوف حجم البلازما اللي رح ينظف من المواد هاي (كم ملي بالدقيقة).

To illustrate the clearance principle, consider the following example: If the plasma passing through the kidneys contains 1 milligram of a substance in each milliliter and if 1 milligram of this substance is also excreted into the urine each minute, then 1 ml/min of the plasma is "cleared" of the substance.

The higher the renal clearance, the more plasma that is cleared of the substance.

➢ Clearance Technique

Renal clearance of substance is calculated from the urinary excretion rate of that substance divided by its plasma concentration.

Cs x Ps = Us x V

$$Cs = \frac{Us \times V}{Ps} = \frac{\text{urine excretion rate}}{\text{Plasma conc}}$$

Where:

Cs = clearance of substance S

Ps = plasma conc. of substance S

Us = urine conc. of substance S

V = urine flow rate

➢ Osmolar Clearance

osmolar clearance (Cosm)= total clearance of solutes from the blood

= Volume of plasma cleared of solutes each minute

هون الclearance بكون لكل الsolutes اللي بالبلازما مش لمادة وحدة بس

$$C_{osm} = \frac{U_{osm} \times V}{P_{osm}}$$

Where:

Uosm = urine osmolarity

V = urine flow rate

P = plasma osmolarity

example

If plasma osmolarity is 300 mOsm/L, urine osmolarity is 600 mOsm/L, and urine flow rate is 1 ml/min. Calculate the volume of plasma cleared of solutes each minute?

plasma osmolarity = 300 mOsm / L

urine osmolarity = 600 mOsm /L

urine flow rate = 1 ml/min

$$C_{osm} = \frac{U_{osm} \times V}{P_{osm}}$$

$$C_{osm} = \frac{600 \times 1/1000}{300}$$

=0.002 L/min

=2 ml of plasma are being cleared of solute each minute

"Free" Water Clearance (CH2O)

Free-water clearance (CH2O) = rate of solute-free water excretion

This tells us if water is being reabsorbed or secreted by the kidneys (basically, anything that's happening after water is filtered into the bowman's space). That's helpful because it tells us if there's a problem in distal convoluted tubule and distal collecting ducts which have aquaporins that only absorb water.

It is calculated as the difference between water excretion (urine flow rate) and osmolar clearance.

$$C_{H_2O} = V - C_{osm} = V - \frac{(U_{osm} \times \dot{V})}{P_{osm}}$$

If: Uosm < Posm, CH2O = + indicating water is being removed

If: Uosm > Posm, CH2O = - indicating water conservation

If the free water clearance value is positive this means that free water is being secreted and the urine is hypo-osmolar compared to plasma (meaning the urine is less concentrated). This happens when we drink a lot if water and the body wants to get red of some of it or if the kidneys aren't responding to ADH

-If the value is negative this means that free water is being reabsorbed and the urine is hyperosmolar compared to plasma (urine is more concentrated). This happens when we're dehydrated or if we're releasing an inappropriate amount of ADH.

Question

Given the following data, calculate "free water" clearance :

urine flow rate = 6.0 ml/min
urine osmolarity = 150 mOsm /L
plasma osmolarity = 300 mOsm / L

→ Is free water clearance in this example positive or negative ?

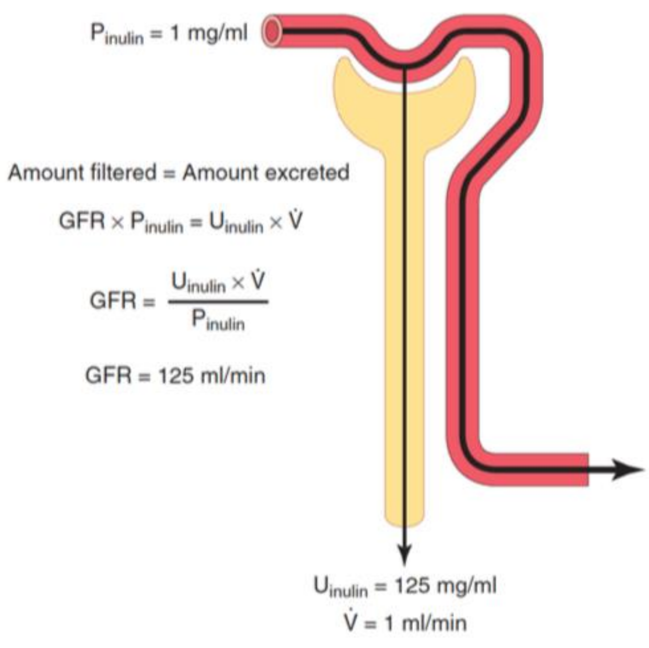
$$C_{H_2O} = V - \frac{U_{osm} \times V}{P_{osm}} = 6.0 - \frac{(150 \times 6)}{300}$$

$$= 6.0 - 3.0$$

$$= +3.0 \text{ ml / min (positive)}$$

➢ Use of Clearance to Measure GFR

For a substance that is freely filtered, but not reabsorbed or secreted (inulin, 125 I-iothalamate, creatinine), renal clearance is equal to GFR



The figure shows the renal handling of inulin. In the example, the plasma concentration is 1 mg/ml, urine concentration is 125 mg/ml, and urine flow rate is 1 ml/min. Therefore 125mg/min of inulin passes into the urine. Then, inulin clearance is calculated as the urine excretion rate of inulin divided by the plasma concentration = 125 ml/min.

Thus, 125 milliliters of plasma flowing through the kidneys must be filtered to deliver the inulin that appears in urine.

كونه حكينا انه الinulin مش المادة الوحيدة اللي بنقدر منها انه نقيس الGFR، فخلينا نحكي عن الcreatinine :

➢ **Creatinine clearance and plasma creatinine concentration can be used to estimate GFR**

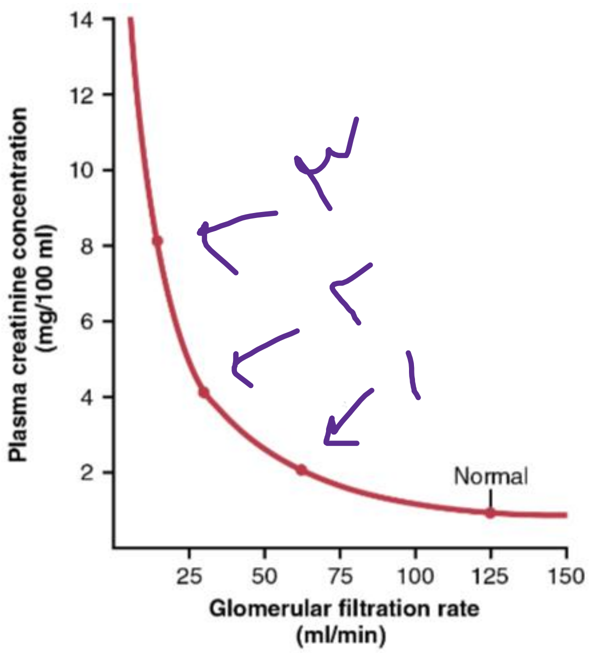
• cleared from the body fluids almost entirely by glomerular filtration

• not require intravenous infusion (endogenous substance)

• is not a perfect marker of GFR because a small amount of it is secreted by the tubules —> amount of creatinine excreted > amount filtered أكبر بشوي

• a slight error in measuring plasma creatinine

Plasma creatinine can be used to estimate changes in GFR



Normal GFR = 125 ml/min …normal levels of creatinine in blood range from 0.9-1.3

The figure shows the relationship between GFR and plasma creatinine concentration under steady-state conditions. Decreasing GFR by 50 percent will increase plasma creatinine to twice normal if creatinine production by the body remains constant —> الحالة الأولى

If GFR falls to falls to one-forth normal, plasma creatinine would increase to about four times norma —> الحالة الثانية, and a decrease of GFR to one-eight normal would raise plasma creatinine to eight times normal —> الحالة الثالثة.

➢ Use of Clearance to Estimate Renal Plasma Flow

Theoretically, if a substance is completely cleared from the plasma, its clearance rate would equal renal plasma flow (RPF)

Let's remember the definition of renal plasma flow: RPF is the volume of blood delivered to the kidneys per unit time.

وكونه الGFR بتشكل بس 20% من الRPF، عشان أعرف أقيسه بدي مادة يتم التخلص منها بشكل كامل (100%) ، وهاد بكون عن طريق الGFR&Secretion.

Paraminohippuric acid (PAH) is 90% filtered and secreted and is almost completely cleared from the renal plasma

-The amount of PAH in the plasma of the renal artery is about equal to the amount of PAH excreted in the urine. Therefore, the renal plasma flow can be calculated from the clearance of PAH.

amount of substance delivered to kidneys in blood= amount excreted in urine

(RPF x Ps) = (Us xV)

RPF = Us xV/ Ps=Cs

Cx = renal plasma flow

To calculate actual RPF , one must correct for incomplete extraction of PAH

There is no known substance that is completely cleared by the kidneys

ما في مادة الclearance تبعها ممكن يوصل ل١٠٠%، عشان نكون دقيقين بحساب الRPF في معادلة ثانية اله اللي هي الtotal renal plasma flow= PAH clearance/PAH extraction ratio

The percentage of PAH removed from the blood is known as the extraction ration of PAH and averages about 90 percent in normal kidney.

The calculation of RPF can be demonstrated by the following example (in the figure below): Assume that the plasma concentration of PAH is 0.01 mg/ml, urine concentration is 5.85 mg/ml, and urine flow rate is 1 ml/min. PAH clearance can be calculated from the rate of urinary PAH excretion (5.85 mg/m x 1 ml/min) divided by the plasma PAH concentration (0.01 mg/m). Thus clearance of PAH calculates to be 585 ml/min.
If the extraction ratio for PAH is 90 Percent, the actual RPF can be calculated by dividing 585 ml/min by 0.9, yielding a value of 650 ml/min. Thus, total RPF can be calculated as:
Total renal plasma flow= PAH clearance/PAH extraction ratio

The extraction ratio (E_{PAH}) is calculated as the difference between the renal arterial PAH (A_{PAH}) and the renal venous PAH (V_{PAH}) concentrations, divided by the renal arterial PAH concentration.

هسا هاد الشرح كله عشان نفهم العنوان وانه في معادلة ثانية لحساب الRPF بدقة، لكن المطلوب منا نعرف انه من معادلة حساب الE_{PAH} قدرنا نعرف انه الFiltration& secretion لل PAH يساوي 90%

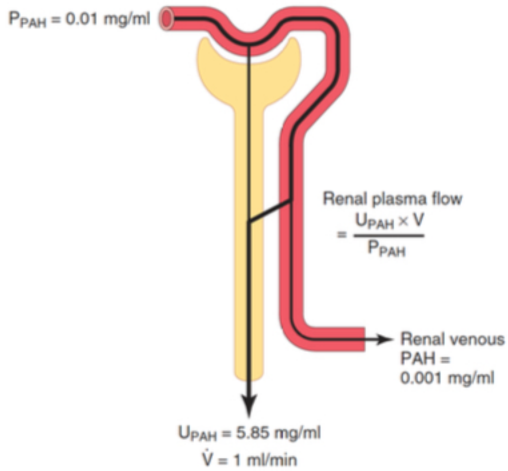
To calculate <u>actual</u> RPF , one must correct for incomplete extraction of PAH

$$E_{PAH} = \frac{A_{PAH} - V_{PAH}}{A_{PAH}}$$

$$= \frac{0.01 - 0.001}{0.01} = 0.9$$

normally, $E_{PAH} = 0.9$

i.e., PAH is 90% extracted



- **Filtration fraction is calculated from GFR divided by RPF**

To calculate the filtration fraction, which is the fraction of plasma that filters through through the glomerular membrane, we need to know first RPF & GFR

RPF =PAH clearance

GFR =inulin clearance

If the RPF is 650 ml/min and the GFR is 125 ml/min, the filtration fraction (FF) is calculated as

FF = GFR/RPF = 125/650 = 0.19

- **Calculation of Tubular Reabsorption**

If the rates of glomerular filtration and renal excretion of a substance are known, one can calculate whether there is a net reabsorption or a net secretion of that substance by the renal tubules.

if the rate of excretion of the substance (Us x V) < the filtered load of

the substance (GFR x Ps), then some of the substance must have been reabsorbed from the renal tubules.

if the excretion rate of the substance > filtered load, then the rate of excretion= sum of the rate of glomerular filtration plus tubular secretion.

- Calculation of Tubular Reabsorption

Reabsorption = Filtration - Excretion

Filt s = GFR x Ps

Excret s = Us x V

Example: Urine flow rate = 1 ml/min

Urine concentration of sodium (UNa) = 70 mEq/L = 70µEq/ml

Plasma sodium concentration = 140 mEq/L

= 140 µ Eq/ml

GFR (inulin clearance) = 100 ml/min

- Calculate:

1-Filtered sodium load

2- Urinary sodium excretion

3- Tubular reabsorption

- The answer:

1-filtered sodium load= GFR x P_{Na}

=100 ml/min x 140 µ Eq/ml = 14,000 µ Eq/min.

2- Urinary sodium excretion =U_{Na} x urine flow rate=70 x1 =70 µ Eq/min.

3- tubular reabsorption of Na= filtered load - urinary excretion 14,000 µ Eq/min − 70 µ Eq/min = 13,930 µ Eq/min.

❖ Acid-Base Regulation

➢ Introduction

Acid base balance —> to keep acid base state in ECF constant for optimal function of cells.

Multiple acid-base buffering mechanisms are involved in maintaining normal H+ concentrations in both the extracellular and intracellular fluid:

1-blood 2-cells 3-lungs 4-kidneys

في mechanisms بالجسم بتقاوم التغير بال+H وبتحافظ على نسبته داخل الخلية وخارجها

➢ Acid-Base Fundamentals

• An Acid = a molecule that can release H+ in a solution (proton donor).

- H2CO3 (carbonic acid)
- HCl (hydrochloric acid)

• A base = a molecule that accepts H+ in a solution.

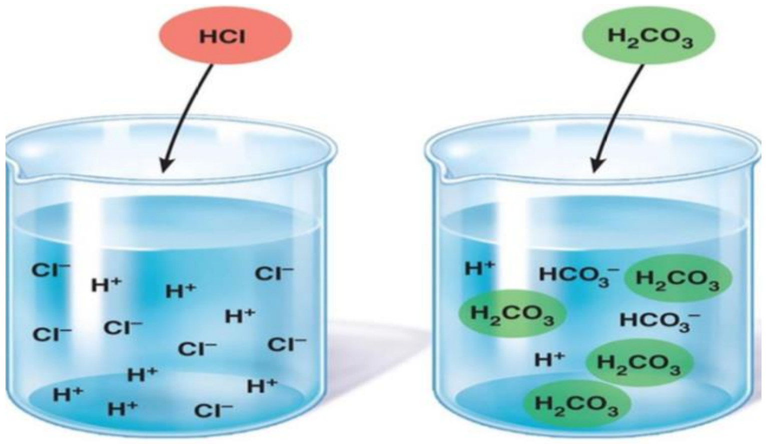
- Bicarbonate ions (HCO3-).
- Hydrogen phosphate (HPO4-2)
- Proteins in body function as bases because some of amino acids that make up proteins have net negative charges that readily accept H+.

المركبات الحمضية بتعطي ال+H وبتكون إما حموض قوية (strong acids) تفككها عن الهيدروجين بكون بنسبة ١٠٠% فبتنفصل بسرعة أو حموض ضعيفة (weak acids) نسبة التفكك تبعها عن الهيدروجين ١٪

أما المركبات القاعدية فهي مستقبلة لل+H وبتكون إما قواعد قوية (strong bases) ارتباطها بالهيدروجين بكون قوي أو قواعد ضعيفة (weak bases) ارتباطها بالهيدروجين ضعيف

➢ Strong vs weak Acid/Base

- Strong acids dissociate rapidly and release large amounts of H+ in solution
- Weak acids dissociate incompletely and less strongly releasing small amounts of H+ in solution



- A strong base is one that reacts rapidly and strongly with H+ —> quickly removing H+ from a solution.

  Example is OH− + H+ —> H2O

- weak base e.g HCO3− because it binds with H+ much more weakly than does OH−.

- Most acids and bases in ECF that are involved in normal acid-base regulation are weak acids and bases.

Alkalosis= excess removal of H+ from the body fluids

Acidosis= excess addition of H+

- [H+] & the pH

• [H+] is precisely regulated at 0.00004 mEq/L (important for enzyme functions)

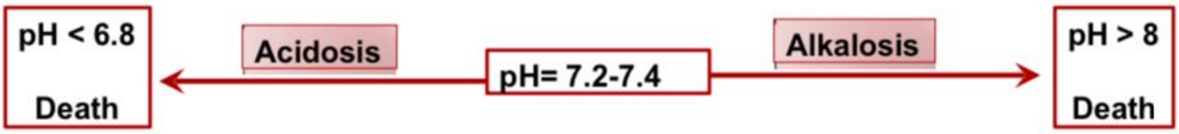
H+ concentration in ECF is very low = 0.00004 mEq/L

• H+ ion concentrations are expressed as pH.

• pH=-Log[H+] <—— العلاقة بين أيون الهيدروجين ودرجة الحموضة بهاي المعادلة

- If the [H+] increase → pH will decrease (more acidic)
- If the [H+] decrease → pH will increase (more alkaline)

Normally pH= 7.2-7.44



If pH < 7.2 —> acidosis

If pH > 7.4 —> alkalosis

PH = 6.8-8 ‹‹‹ if pH less than 6.8 or more than 8 will lead to death.

Table 31-1 pH and H^+ Concentration of Body Fluids

	H^+ Concentration (mEq/L)	pH
Extracellular fluid		
Arterial blood	4.0×10^{-5}	7.40
Venous blood	4.5×10^{-5}	7.35
Interstitial fluid	4.5×10^{-5}	7.35
Intracellular fluid	1×10^{-3} to 4×10^{-5}	6.0-7.4
Urine	3×10^{-2} to 1×10^{-5}	4.5-8.0
Gastric HCl	160	0.8

Intracellular pH usually is< plasma because the metabolism of the cells produces acid especially (H_2CO_3).

Hypoxia and poor blood flow to tissues —> acid accumulation and ↓intracellular pH.

➢ Acid Production by the Body

• The body produces large amounts of acids on daily basis as by products of metabolism.

• Metabolism of dietary proteins.

• Anaerobic metabolism of carbs and fat.

• Acids in the body are of two kinds:

1. Volatile (CO_2)

2. Non-volatile “fixed” (sulfuric acid, lactic acid)

الmetabolism بجسمنا لا ينتج غير acids

الكربوهيدرات بتنتج 12-20 thousand mmol/day من الcarbonic acid وهو عبارة عن volatile acid لانه عن طريق الcarbonic anhydrase بتحول لـH_2O و CO_2 اللي بطلع بالتنفس

بينما الprotein & lipid فيهم phosphorus & sulfur فبعطوا phosphoric acid & sulfuric acid اللي هم عبارة عن fixed acids بتم التخلص منهم عن طريق الkidney

والanaerobic metabolism of carbohydrates بنتج lactic acid واللي هو fixed acid

The Body’s defense against changes in [H+]

Three main systems:

1. Body fluid buffers (chemical buffers).

اللي بعمله انه بحول الstrong acid لـweak acid أو الstrong base لـweak base بس ما بلغيهم

(Just minimize the change in pH)

مثلا lactic acid (حمض قوي) بتحد مع $NaHCO_3$، بعطي sodium lactate و H_2CO_3 (حمض ضعيف)

Works within seconds (bind acid/base).

2. Lungs

Works within minutes (eliminate CO_2).

3. Kidneys

Works within hours-days (EXCRETE ACID/BASE).

The most powerful of the three.

زي ما حكينا قبل انه الاحماض نوعين: volatile (بتتخلص منها الlungs) و fixed (بتتخلص منها الkidneys)

أهم خط دفاع هو الثالث (الkidneys)، دايما أهم اشي هو الأبطأ

➢ Chemical Buffer Systems in the Body

• There are 3 chemical buffers in the body;

1. The Bicarbonate buffer system.

2. The phosphate buffer system.

3. Proteins.

• They are the 1st line of defense against changes in pH i.e. [H+], act within seconds.

• Some are more powerful extracellularly and others are more powerful intracellularly.

➢ The Bicarbonate Buffer System

• The main ECF buffer system.

• Composed of:

  - A weak acid (H2CO3).
  - Its conjugated base (NaHCO3).

الشغلتين اللي بأثروا بالpH هم الacids & bases ، فالbuffer system لازم يتكون من شغلة بتجابه الacid وشغلة بتجابه الbase —> منحتاج حامض ضعيف مع ملح قاعدي

The buffer system is composed of 2 components (weak acid & its conjugated base), these components can be formed in the body by this reactions:

1. ***H_2CO_3 forms in the body by the reaction of CO_2 & H_2O***

$$CO_2 + H_2O \underset{}{\overset{\text{Carbonic anhydrase}}{\rightleftharpoons}} H_2CO_3$$

2. ***H_2CO_3 ionizes weakly to form small amounts of H^+ & HCO_3^-***

$$H_2CO_3 \rightleftharpoons H^+ \ \& \ HCO_3^-$$

3. ***The second component is $NaHCO_3$ which dissociates to form Na^+ & HCO_3^-***

$$NaHCO_3 \rightleftharpoons Na^+ \ \& \ HCO_3^-$$

الacid بجابهه بالملح القاعدي والbase بجابه بweak acid

Putting it all together;

$$CO_2 + H_2O \rightleftharpoons H_2CO_3 \rightleftharpoons H^+ + \underbrace{HCO_3^-}_{+\,Na^+}$$

Adding ACID (HCl)

$(HCl \rightarrow H^+ + Cl^-)$

$$+HCO_3^- \rightarrow \underset{\text{Weak acid}}{H_2CO_3} \rightarrow \overset{\text{lung}}{CO_2} + H_2O$$

Adding base (NaOH)

$$CO_2 + H_2O \longrightarrow \underset{+\,NaOH}{H_2CO_3} \longrightarrow \uparrow \underset{+\,Na}{HCO_3^-} + H^+$$

- **the henderson hasselbalch equation**

What is the HHE?

• It is an equation that enables the calculation of pH of a solution.

$$pH = pK + log \frac{HCO3^-}{0.03\ X\ PCo_2}$$

في اثبات للقانون بالصفحة الجاية

K = dissociation constant, pK = 6.1 0.03 = solubility of CO2

$$CO_2 + H_2O \underset{}{\overset{CA}{\rightleftharpoons}} H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$$

$$pH = pK + \log \frac{[HCO3^-]}{0.03\ X\ PCO2}$$

pK = dissociation constant= 6.1

0.03 = solubility of CO_2

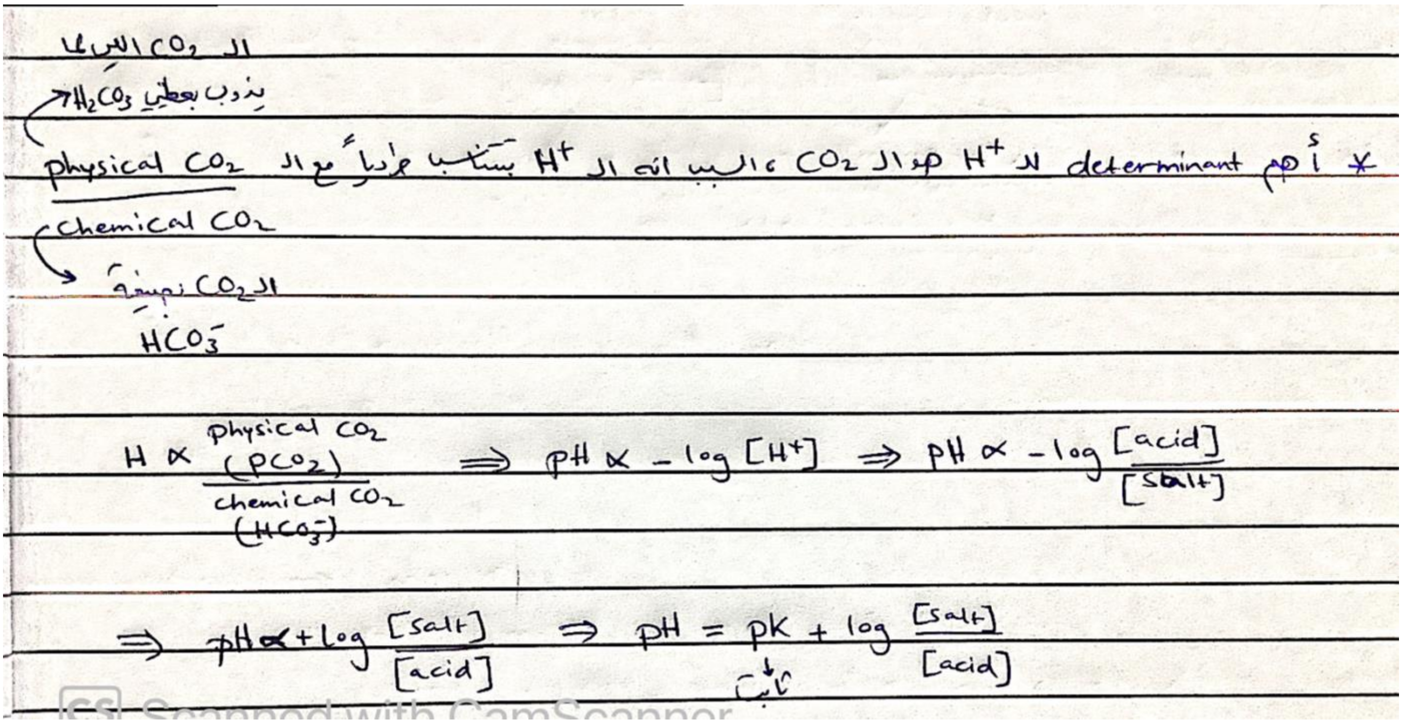
- ***What do we understand from this equation?***

1. pH α $\frac{HCO3^-}{PCO2}$ — HCO3⁻: Regulated by kidneys; PCO2: Regulated by lungs

Each element of the buffer system is regulated

- ↑↑ HCO_3^- will ↑↑ pH
- ↑↑ PCO2 will ↓↓ pH

إثبات القانون للي بحب يشوفه:


ال CO_2 الي بلا

يذوب بعطيني H_2CO_3

* أهم determinant لل H^+ هو ال CO_2 ، السبب انه ال H^+ بيتناسب طردياً مع ال physical CO_2

chemical CO_2

ال CO_2 نسميه: HCO_3^-

$$H \propto \frac{\text{physical } CO_2\ (PCO_2)}{\text{chemical } CO_2\ (HCO_3^-)} \Rightarrow pH \propto -\log[H^+] \Rightarrow pH \propto -\log\frac{[acid]}{[salt]}$$

$$\Rightarrow pH \propto +\log\frac{[salt]}{[acid]} \Rightarrow pH = pK + \log\frac{[salt]}{[acid]}$$

ثابت

➢ Other Buffering Systems

The phosphate buffer:

- Plays a major role in buffering intracellular & renal tubular fluid.
- Composed of;
  - $H_2PO_4^-$ (dihydrogen phosphate/ACID) كونه في ٢ ايون من الهيدروجين بكون هو الاسيد
  - HPO_4^{-2} (Hydrogen phosphate/BASE)

When a strong acid such as HCL is added to a mixture of these two substances, the hydrogen is accepted by the base HPO_4^{-2} and converted to $H_2PO_4^-$.

When a strong base, such as NaOH, is added to the buffer system, the OH- is buffered by the $H_2PO_4^-$ to form additional amounts of HPO_4^{-2} + H_2O

Proteins: PLENTIFUL (high concentration)

- Contributes to buffering inside cells—> H^+ /HCO_3^- diffusion to the cell.
  - E.g. Hb.

In red blood cells, hemoglobin (Hb) is an important buffer

$H^+ + Hb \longrightarrow HHb$

- Summary of Body’s Buffering Systems

• Buffer systems do not work independently in body fluids but actually work together.

• A change in the balance in one buffer system, changes the balance of the other systems.

• Buffers do not reverse the pH change, they only limit it.

• Buffers do not correct changes in $[H^+]$ or $[HCO_3^-]$, they only limit the effect of change on body pH until their concentration is properly adjusted by either the lungs or the kidney.

"قويّ التوكل لا يُهزم، ومُلِحّ الدعاء لن يُخذل."

Good luck Hope..