AB balance; *úvod do patofy-siologických aspektů*

AB balance; introduction into pathophysiological aspects

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Co je acidobazická rovnováha?

- rovnováha mezi acidifikujícími a alkalizujícími vlivy
- nerovnováha znamená, že se:
  - změnily se poměry kyselin a bází,
  - změnilo se pH organismu (neplatí obecně),
  - narušily regulační mechanismy,
  - postupně uplatňují kompensující mechanizmy

What is AB balance/dysbalance

- balance between factors induced acidosis or alkalosis
- dysbalance is due to:
  - changes of both acids and bases,
  - change of pH in organism (however, it is not in every cases)
  - regulatory machanismis are affected
  - compensatory mechanisms of different organs

AB balance

Recall:
General aspects of buffers:

$A \rightleftarrows H^+ + B$
Acid (A) is able
to release (resp. accept) proton (H^+)
Base (B) is able

a) $H_2CO_3 \rightleftarrows H^+ + HCO_3^-$
b) $HBuff \rightleftarrows H^+ + Buff^-$

acid $H^+ + HCO_3^- \rightarrow H_2CO_3$

base $OH^- + H_2CO_3 \rightarrow HCO_3^- + H_2O$

Koncentrace vodíkového kationtu (H^+)

- Ionty se v krvi vyskytují v řádu mmol/l = 10^{-3} mol/l
- $[H^+]$ = 40 x 10^{-9} mol/l = **40 nmol/l** (rozmezí: 36 - 44 nmol/l)
- pH = **7,40** (rozmezí 7,44 - 7,36)
- hodnoty slučitelné se životem 20 - 160 nmol/l = pH - **7,70 - 6,80**)
- $H_2CO_3 \rightarrow H^+ + HCO_3^-$ nejdůležitější pufr

Concentration of H - protons

- Blood concentration of different ionts is in order of mmol/l = 10^{-3} mol/l
- $[H^+]$ = 40 x 10^{-9} mol/l = 40 nmol/l (range: 36 - 44 nmol/l)
- pH = 7,40 (between 7,44 - 7,36)
- Values for surviving (20 - 160 nmol/l, = pH - 7,70 - 6,80)
- $H_2CO_3 \rightarrow H^+ + HCO_3^-$ the most important buffer

AB balance

Production:

a) H^+ from respiration of tissues (as H_2CO_3) - about 20 000 mmol/day

b) H^+ from non- volatile acids (as H_2SO_4 or H_3PO_4 …) - about 30-80 mmol/day

Buffers - total capacity 2400 mmol

Elimination - lung

capacity 20 000 mmol/day

- kidney

capacity 30-80 mmol/day

Hendersonova – Hasselbach rovnice *(další úvahy)*

- $pH = pK + \log ([HCO_3^-] / [H_2CO_3])$

- pK kyseliny uhličité není konstantou, kolísá kolem hodnoty 6,1
- **$[H_2CO_3] = \alpha * pCO_2$**

  α je koeficient solubility oxidu uhličitého (0,03 $mol^{-1}l^{-1}torr^{-1}$, ¨tj 0,225 $mol^{-1}l^{-1}kPa^{-1}$

Hendersonova – Hasselbach equilibrium *(remarks)*

- $pH = pK + \log ([HCO_3^-] / [H_2CO_3])$

- pK H_2CO_3 is not constant - but around value 6,1
- **$[H_2CO_3] = \alpha * pCO_2$**

α coefficient of solubility CO2 (0,03 mol^{-1} l^{-1} $torr^{-1}$, corresponding 0,225 mol^{-1} l^{-1} kPa^{-1}

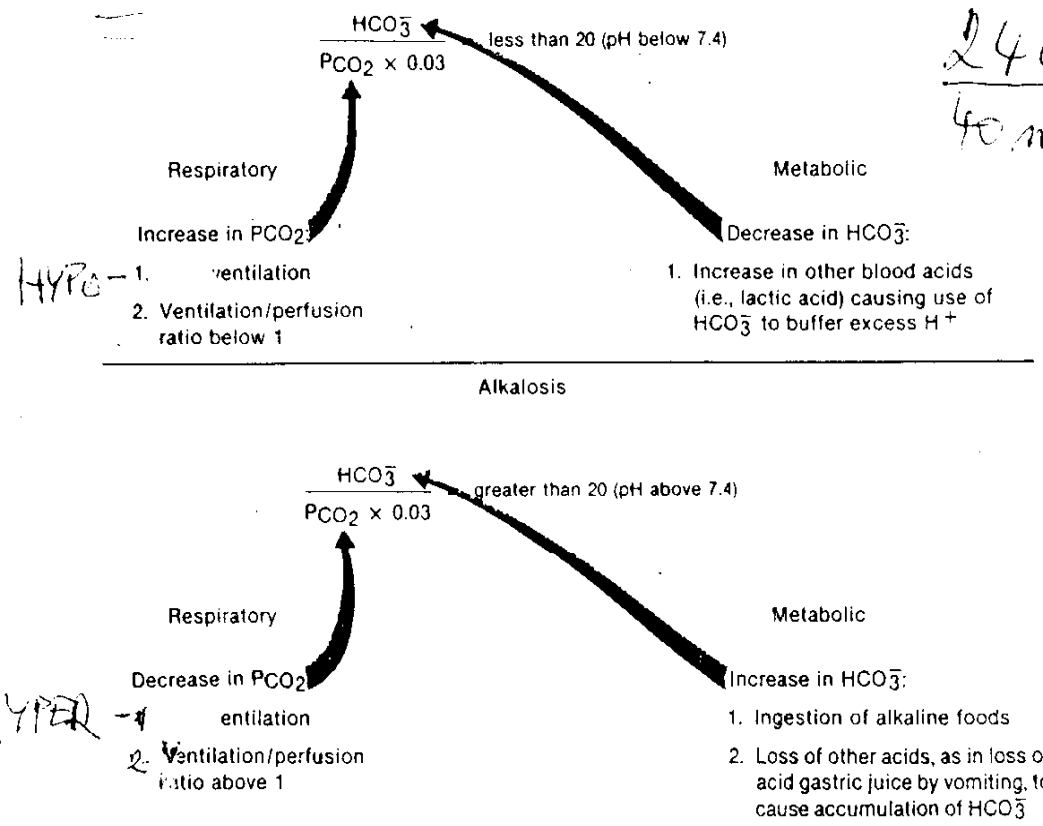
AB balance

- **<u>Buffer systems</u>:**
  - bicarbonate, ($[HCO_3^-]/[H_2CO_3]$),$[H_2CO_3] = \alpha * pCO_2$ >50% (plasma 35%, ERY = 18%,)
  - Hb ~ 35% ,
  - proteins,
  - phoshate (minor effect in blood, important in kidney)
- **<u>Metabolic pathways</u>:** (where H^+ are *either* producing / *or* consuming / *or* neutral chemical reactions)

- **<u>Regulatory mechanisms:</u>**
  - ***respiration:*** *<u>lung</u>* (hypo-/hyperventilation)
  - ***non respiration:*** *kidney* (bicarbonate, phoshate, NH_4 - ions), *GIT* (acid gastric, alkaline pancreatic fluids), *liver* (*acidosis:* ↑ NH_4 ions in urine, ↓ formation of urea in liver due to effect of pH on inhibitory mechanism of enzyme: *carbamoyl synthase*, *alcalosis:* vice versa)

$$pH = pK_A + \frac{A^-}{HA}$$ Henderson-Hasselbalch

$$\frac{M}{R} =$$



$$\frac{24 \text{ mEq/L}}{40 \text{ mm Hg} \times 0.03} = \frac{24}{5.3 \times 0.} = 22.5$$

AB balance

- Acidosis x alkalosis
- *Metabolic* (MAC or MAL) x *respiratory* (RAC or RAL)
- Combination of both factors

Arterial

pH = 7.37 - 7.43

H^+ = 37 - 43 nmol

pCO_2 = 36 - 44mmHg *kapnie*

muži 4,7 - 6.0 kPa

ženy (děti) 4,3 - 5,7 kPa

HCO_3^- = 22 - 26mmol/l *bazemie*

muži 23,6 -27,6 mmol/l

ženy (děti)21,8- 27,2 mmol/l

Venous

pH = 7.32 - 7.38

H^+ = 42 - 48 nmol

pCO_2 = 42 - 50 mmHg

HCO_3^- = 23 - 27 mol/l

New AB aspects is derived from basal „non- dependent“ variable (nezávisle proměnné)

pCO_2 **(partial pressure of CO_2**

SID **(strong ion difference)**

A_{tot} **(albuminát, fosfát)**

Základní proměnné
Basal dependent variable

Stewart &

Fencl:

- pCO_2
- SID
- Atot

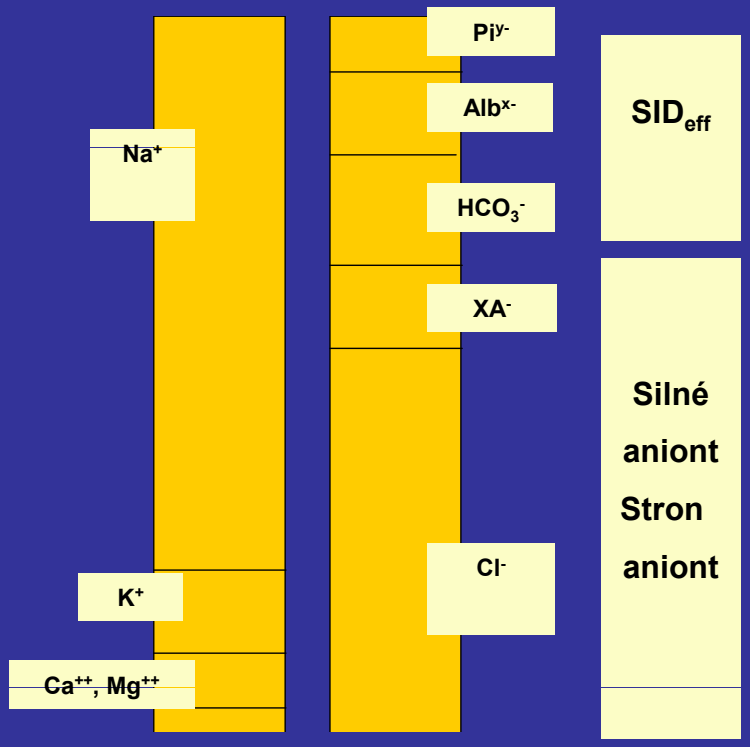
Astrup &

Siggaard-Andersen:

- pH
- pCO_2
- base excess
- HCO_3^-

SID, strong ion difference

$SID_{eff} = [HCO_3] + [Alb^{x-}] + [Pi^{y-}]$



Relevant AB parameters:

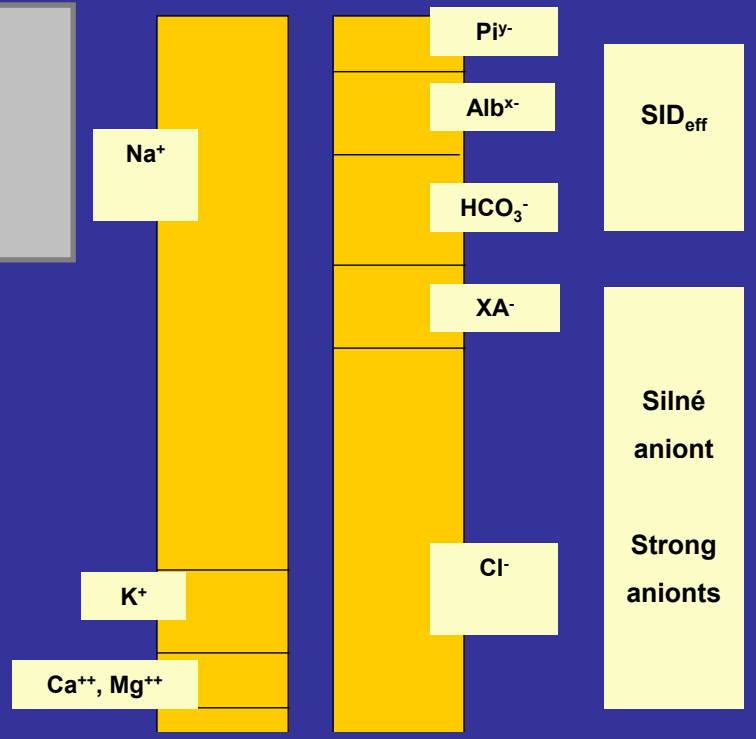
- **pH, physiological 7,36 - 7,44**
- **pCO_2, -"- 4,9 - 5,7 kPa** *kapnia*
- **HCO_3^-, -"- 22 - 26 mmol/l** bazemia
- **BE(ECT), -"- -2,5 až +2,5 mmol/l**
- **Non – estimated anionts**
  6 - 10 mmol/l
- **SID_{eff}, -"- 38 - 40 mmol/l**
- **Cl_{corr}, -"- 104 - 108 mmol/l**

Base excess function of both HCO^{3-} and non-bicarbonate buffers

albuminate

phosphate

bicarbonate is function of non-dependent factors (SID, albumin, phoshate)



Astrup & Siggaard-Andersen:

Base excess

(pH, pCO_2, HCO^{3-})

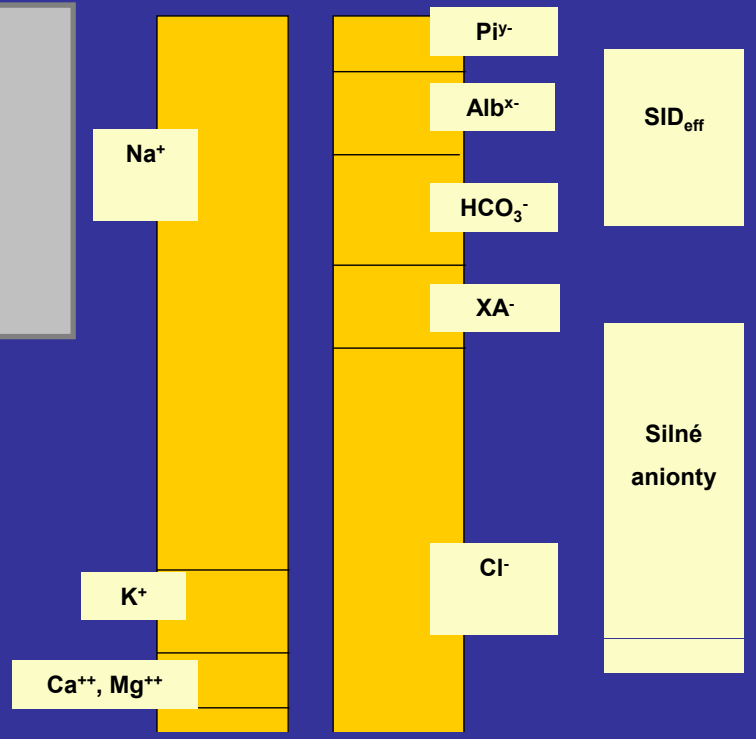
Albuminate

phosphate

Stewart & Fencl

HCO3-

(SID, albuminate, phosphate



Respiratory acidosis (hypercapnie)

- relativní pokles alveolární ventilace k produkovanému množství oxidu uhličitého
- může se jednat o primární nebo sekundární fyziologický proces (hypoventilace)

- *Abnormal process: relative decrease alveolar ventilation to production of CO_2*
- *Either primary or secondary procedure*
- pCO2 ~ produkce *(production)* CO_2 / alveolarní ventilace *(alveolar ventilation) - hypoventilation*

Respiratory alkalosis (hypocapnia)

- abnormální proces, při kterém je relativní vzestup alveolární ventilace k produko-vanému množství oxidu uhličitého
- může se jednat o primární nebo sekundární fyziologický proces – hyperventilace

- *Abnormal procedure – relative elevation alveolar ventilation to produce amount of CO2*
- *Either primary or secondary procedure*
- pCO2 ~ (produkce *(production)* CO_2 / alveolární ventilace *(alveolar ventilation) – hyperventilation*

Metabolická acidóza

- abnormální proces charakterizovaný primárním **vzestupem silných kyselin** nebo **ztrátou HCO_3^-** z extracelulární tekutiny
- abnormální proces charakterizovaný primárním **vzestupem silných kyselin** nebo **ztrátou silných kationtů** (hyponatremie) z extracelulární tekutiny

- *abnormal procedure – primary elevation of **strong acid** or **lost HCO_3^-** from extracellular fluid*
- *abnormal procedure primary elevation of **strong acid** or lost of **strong cations** (hyponatremia) from extracellular fluid*

Metabolická alkalóza

- abnormální proces charakterizovaný primárním **vzestupem silných bazí** (nebo ztrátou silných kyselin) nebo **vzestupem** HCO_3^- v krvi
- abnormální proces charakterizovaný primární **ztrátou silných kyselin** nebo primárním **vzestupem silných kationtů (hypernatremia) v** krvi
- *abnormal procedure – primary elevation of **strong bases** (lost of strong acid) or elevation of* HCO_3^- *from extracellular fluid*
- *abnormal procedure primary lost of **strong acid** or **elevation of strong cations** (hypernatremia) in blood.*

- **Další poznámky k AB rovnováze**
  Further notes to AB balance

➢ Další obrázky jsou podrobněji vysvětlující k AB – rovnováze (látka byla diskutována v rámci biochemie a fysiologie - 2 ročník)

❖ *Next slide are explanatory remarks to AB balance (details see lectures: biochemistry and physiology - 2 year of study).*

AB – balance

RECAL:

Acid – compound (ion) with tendency lost (release) proton (H^+) ton,

Base - "- -"- with tendency accepted proton

Different acids according to proton theory
Different base according to proton theory

AB balance

Concentration of many ions in blood is in range of 10^{-3} (mmol), however, H^+ is in range of 10^{-9} (nmol)

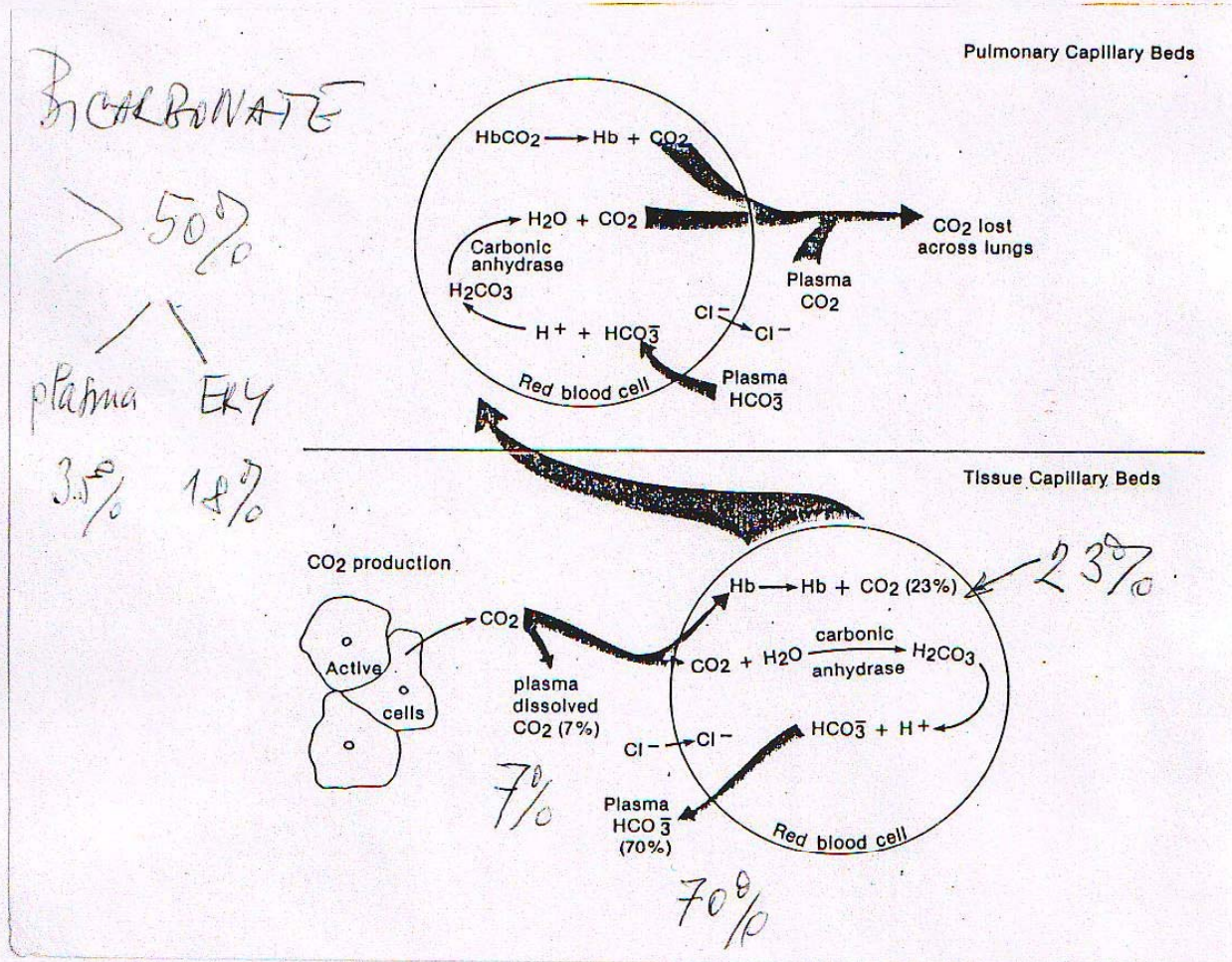
pH of blood = 7,40 ± 0,04

Origin of proton (H^+) is from metabolic pathways

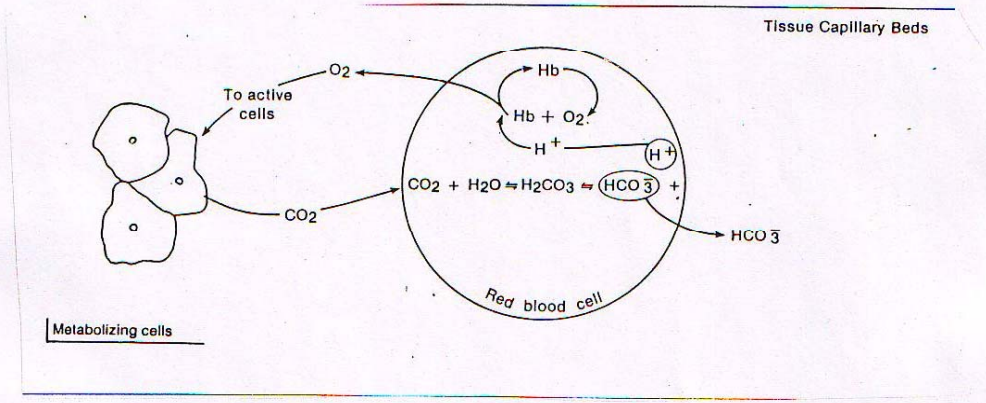
Metabolism

non- volatile *(netěkavé)*		*volative* *(těkavé)*
	a c i d s	
PO_4^{3-}		HCO_3^-
SO_4^{2-}		
dailly production:		
about 70 mmol		25 000 mmol

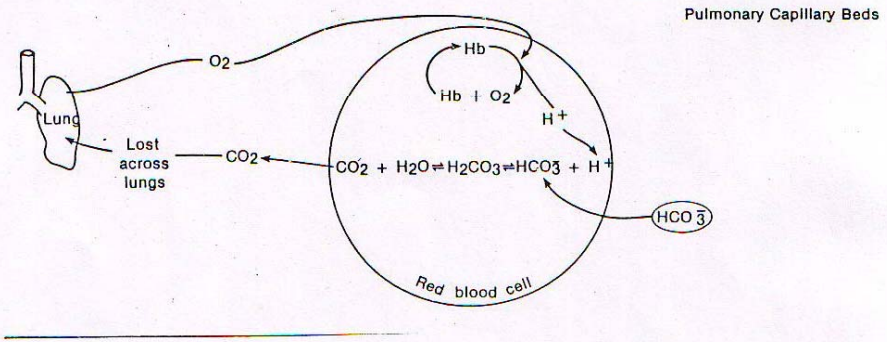
BUFFERING SYSTEMS



BUFFERING SYSTEMS



Hb
35%



Hb as buffer (both HHb and after binding of oxygen - $HHbO_2$ are acids – pK 7,71 and 7,15 - stronger is, therefore $HHbO_2$)

$$HHB + O_2 \rightarrow HHbO_2 \rightarrow H^+ + HbO_2^-$$

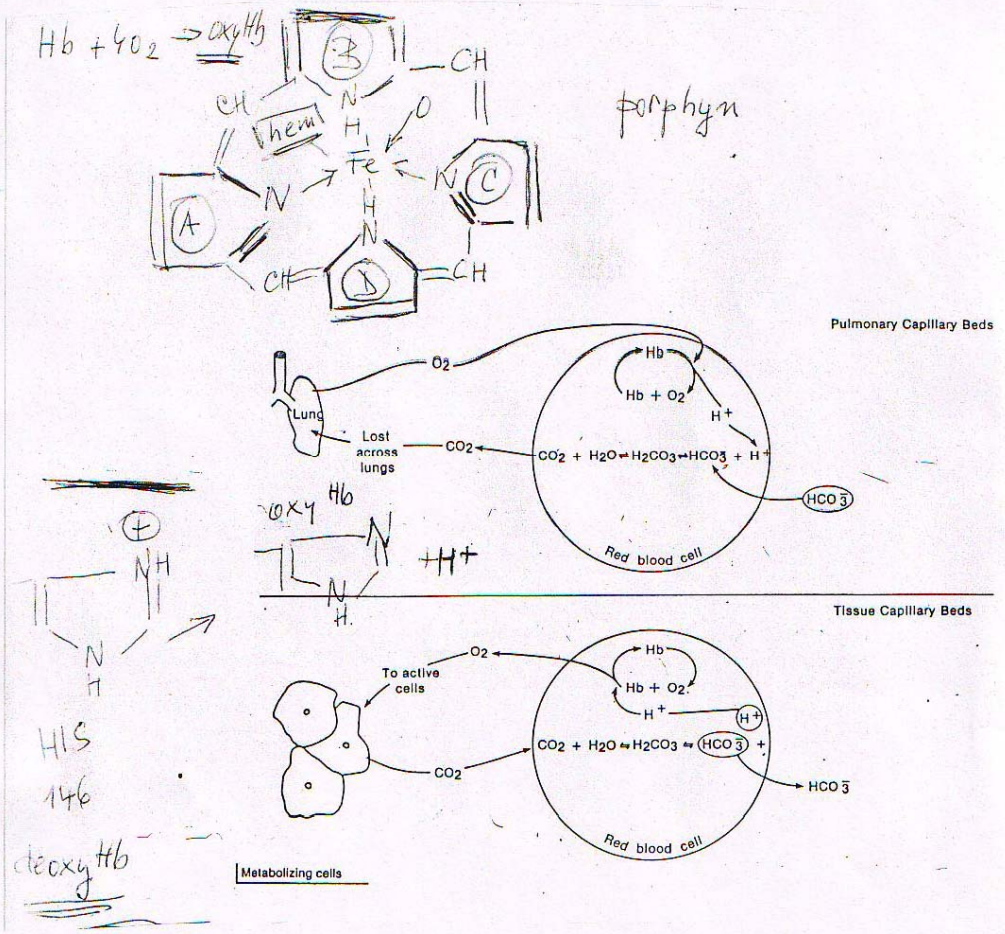
$$H^+ + HbO_2^- \rightarrow HHb + O_2$$

$$Hb\text{- }BPG + 4\ O_2 \rightarrow Hb(O_2)_4 + BPG$$

is composed from *four subunits:* $\alpha_2\beta_2$; each subunit is formed by globin + hem (pyrrol structure – with central atom Fe^{2+} - has six binding position: four of then to each pyrrol, fifth to globin – via histidin and sixth to oxygen)

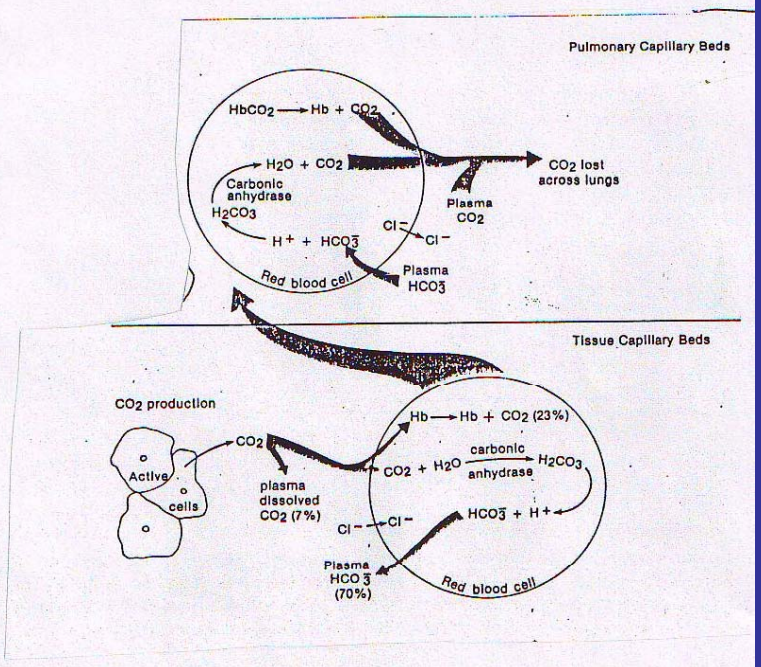
TRANSPORT OF OXYGEN

Hb + $4O_2$ oxyHb



TRANSPORT OF CO_2

a) bicarbonate mechanism



b) carbamate mechanism

$$R\text{–}NH_2 + CO_2 = R\text{–}NH\text{–}COO^-$$

$(\alpha - NH_2)$

3

CO_2 BINDS TO THE TERMINAL AMINO GROUPS OF HEMOGLOBIN AND LOWER ITS OXYGEN AFFINITY

Most of CO_2 is transported as bicarbonate by the action of carbonic anhydrase

$$CO_2 + H_2O = HCO_3 + H^+$$

Much of H protons generated by this reaction is takne up deoxyhemoglobin as part of the Bohr effect

In addition, CO_2 is carried by Hb in the form of carbamate (reversible reaction of CO_2 with alfa- amino groups of hemoglobin

$$R\text{-}NH_2 + CO_2 = R\text{-}NHCOO^- + H^+$$

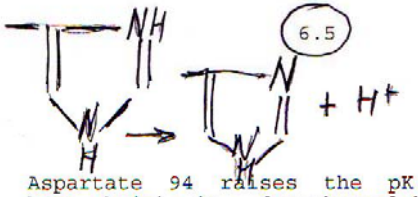
$\alpha\text{-}NH_2$ ... carbamate

MECHANISM OF THE BOHR EFFECT

The affinity of some sites for H protons must be increased as a consequence of transition (deoxy-Hb to oxy-Hb)

His 146

Acid ---> Base + H^+ pK 6.5

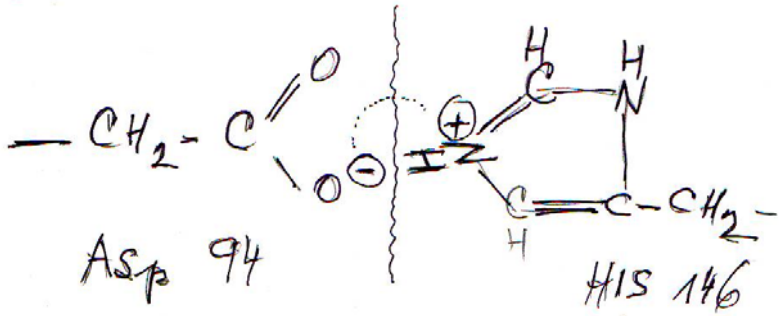


Asp 94

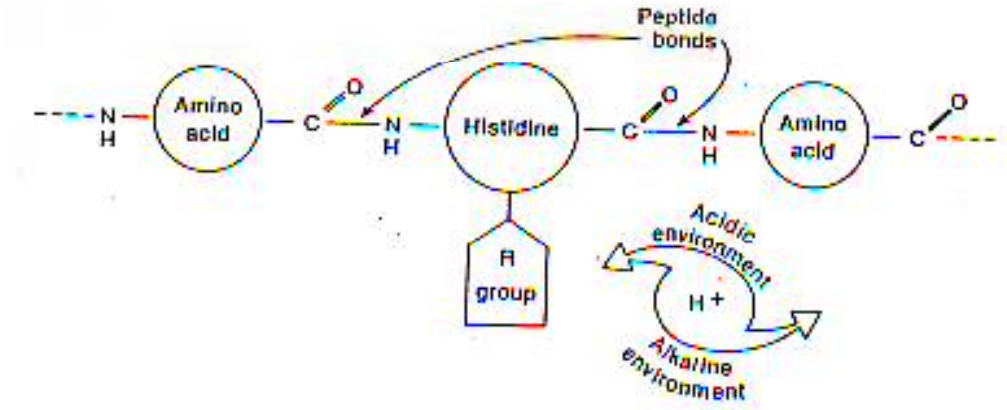
Acid ---> Base + H^+ pK

$-COOH \rightarrow COO^- + H^+$ 4.4

Aspartate 94 raises the pK of histidine 146 (on each beta-chain) in deoxyhemoglobin. The proximity of the negative charge on aspartate 94 favors protonation of histidine 146 in deoxy-Hb. In oxy-Hb, his (146) rotates freely, whereas, in deoxy-Hb this terminal residue participates in a number of interactions



Aminoacids are able to buffer pH due to different AA: dissociation of both **NH_2** **and** **COOH groups**



AB - BALANCE

1) buffer systems

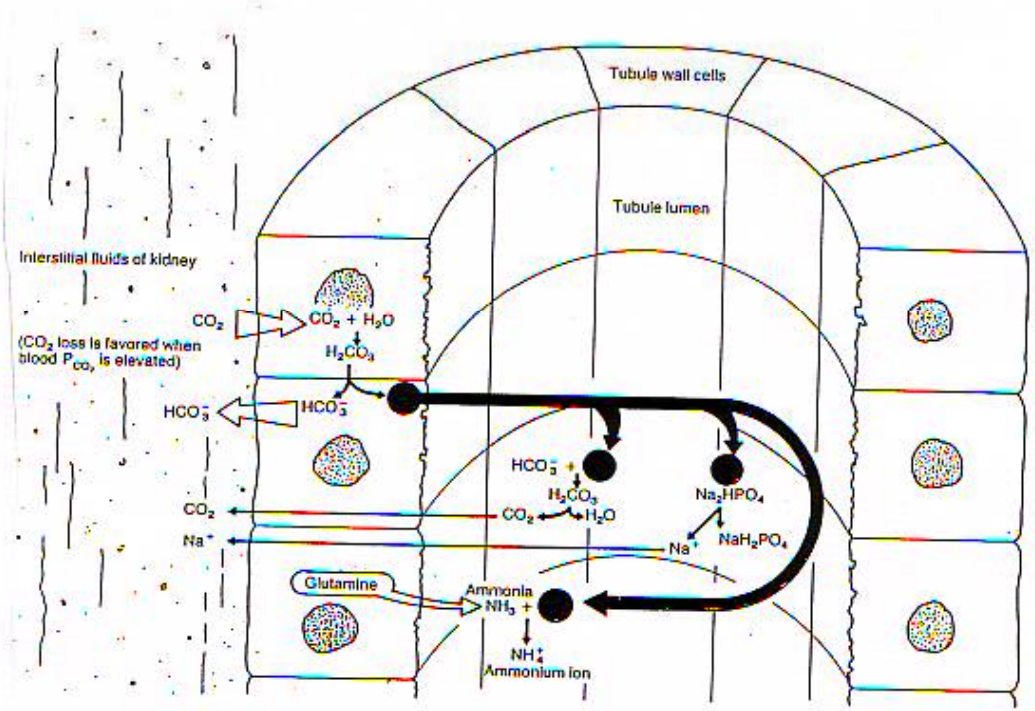
a) HCO_3^-
b) Hb
c) proteins
d) phosphate

2) metabolic pathways

proton-production	*proton-consumption*	*proton-neutral*
glucose - lactate	*lactate - glucogenesis*	*glucose - Krebs cycle*
lipolysis - FA + glyc. $+H^+$	*lactate - $CO_2 + H_2O$*	*lipogenesis from glucose*
ketogenesis - acetoac./ $+3H^+$	*AA - urea + CO_2 + H_2O*	*glutamin from lactate*
diH_2 AA - urea + H	*diCOOH AA - urea $+CO_2$ + H_2O*	
urea from NH_4		

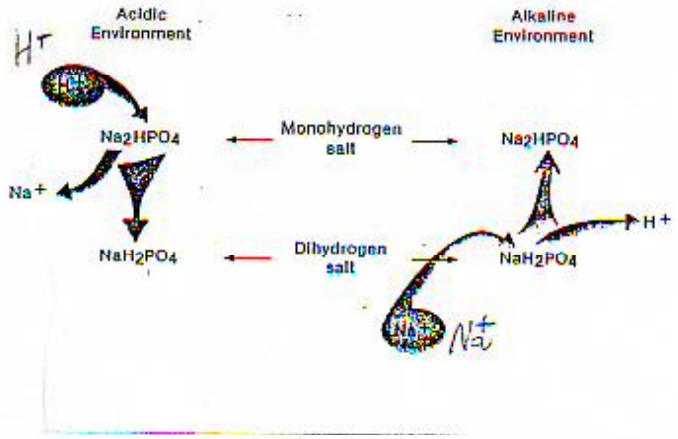
BUFFERING SYSTEMS (kidney)

a) bicarbonate



BUFFERING SYSTEMS (kidney)

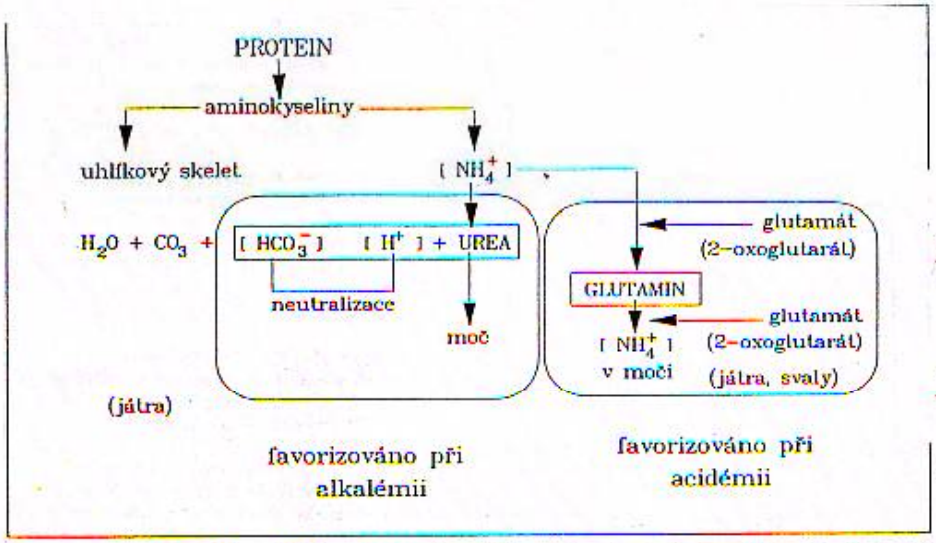
b) phosphate



b) ammonium ion

NH_3 (ammonia is derived from glutamine) **+ H^+ ----------> ---> NH_4^+** (ammonium ion)

100 g of protein ----------> urea + HCO_3^-
(metabolism of proteins….)



Obr. 3. Přesmyk detoxikace [NH_4^+] cestou tvorby močoviny na tvorbu glutaminu v játrech (a obráceně) v závislosti na pH-krve

elevation of H (pH from 7.4 to 7.1)

in urine e l e v a t i o n of ammonium
in blood d e c r e a s e of ammonium
lower ureagenesis in liver due to inhibition of carbamoylphosphate synthese

decrease of H (pH from 7.4 to 7.8)

in urine d e c r e a s e of ammonium
in blood e l e v a t i o n of ammonium
higher ureagenesis in liver due to activation of carbamoylphosphate synthese

3) regulatory systems

a) respiration
b) non-respiration
   1) liver
   2) kidney (acidification of urine)
   3) stomach and pancreas
      (secretion H^+/HCO_3^-)

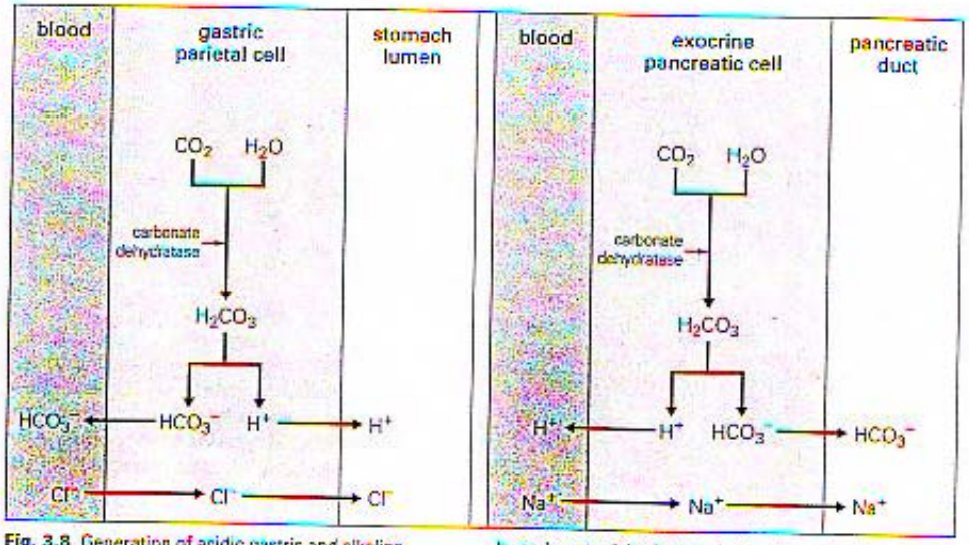


Fig. 3.8 Generation of acidic gastric and alkaline pancreatic secretions. Hydrogen and bicarbonate ions are generated from carbon dioxide and water, catalyzed by carbonate dehydratase. In the stomach, the hydrogen ions are secreted while bicarbonate is retained. The reverse process occurs in the pancreas.

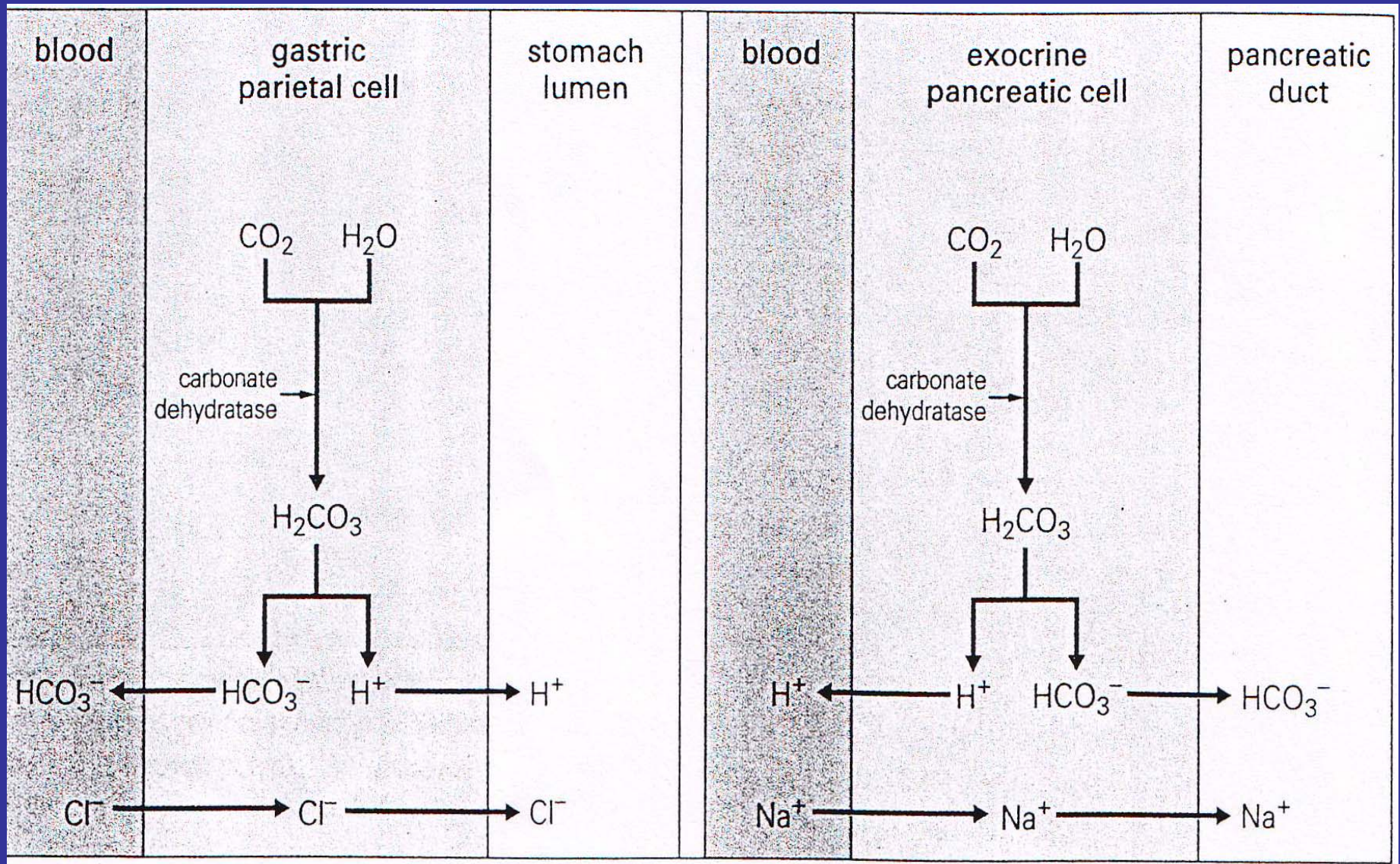


Fig. 3.8 Generation of acidic gastric and alkaline pancreatic secretions. Hydrogen and bicarbonate ions are generated from carbon dioxide and water, catalyzed by carbonate dehydratase. In the stomach, the hydrogen ions are secreted while bicarbonate is retained. The reverse process occurs in the pancreas.

pK klinicky významných kyselin

clinical important acids

- HCl (pK 0),
- H_3PO_4 (2.00),
- acetoacetat (3.58),
- lactic acid (3.86)
- β -hydroxybutyrate (4.39),
- H_2CO_3 (6.10).

Henderson had introduced dissociation constant (K_a - ratio between dissociated $[H^+]$, $[A^-]$ and non- dissociated $[HA]$ fraction of appropriate acid

$$K_a = \frac{[H^+] + [A^-]}{[HA]}$$

Hasselbach transformed this formula into negative log formulation (to be compatible with value for pH)

$$[H^+] = \frac{[HA]}{[A^-]}$$

$$pH = pK_a + \log [A^-] / [HA]$$