Acid Base Balance II

Seminar No. 10

- Chapter 21, II. part -

Three ways of CO_2 transport in blood (scheme, p. 121)

1. **cca 85 % in the form of HCO_3^-**

   it is formed in ery by the action of carbonic anhydrase, then is transported to plasma, exchange for chloride is needed to maintain **electroneutrality** in ery

2. **cca 10 % in the form of unstable carbamates**

3. **cca 5 % of physically dissolved CO_2**

Q.

How is CO_2 formed in tissues?

The production of CO_2 in tissues

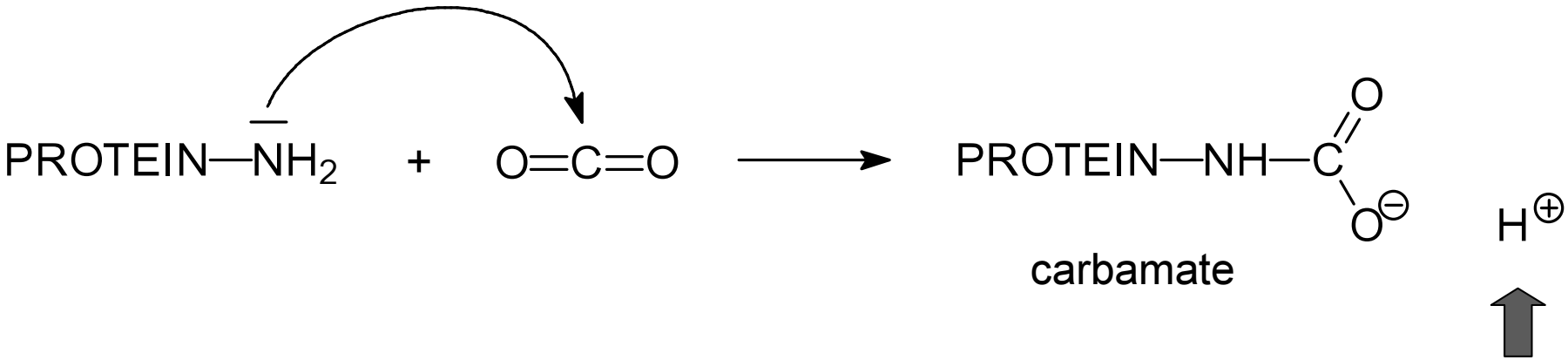
- CO_2 is produced in **decarboxylation** reactions
- **oxidative decarboxylation of pyruvate → acetyl-CoA**
- **two decarboxylations in CAC (isocitrate, 2-oxoglutarate)**
- decarboxylation of aminoacids → biogenous amines
- non-enzymatic decarboxylation of acetoacetate → aceton
- catabolism of pyrimidine bases

  (cytosine, uracil → CO_2 + NH_3 + β-alanine)
- catabolism of glycine → CO_2 + NH_3 + methylen-THF

Q.

Write the reaction of carbamate formation.

A.



- the nitrogen atom of N-terminal adds to carbon atom of CO_2
- released proton is buffered by the protein itself
- in lungs, carbamates are non-enzymatically hydrolyzed and CO_2 is exhaled

Kidney functions in acid-base balance

- **<u>kidneys excrete acid species:</u>**

  ammonium cation NH_4^+

  dihydrogenphosphate anion $H_2PO_4^-$

  (uric acid and some other ...)

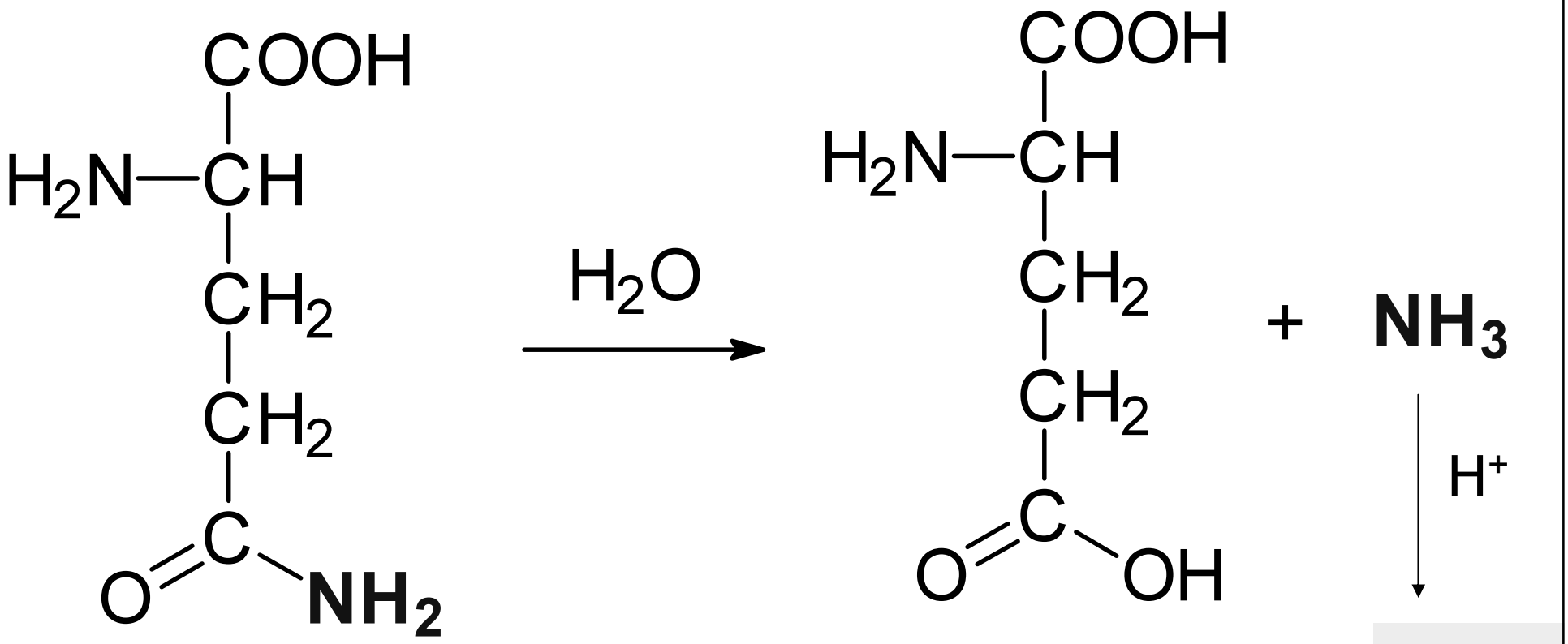
- **<u>kidneys resorb basic species:</u>**

  the main buffer base = hydrogencarbonate anion HCO_3^-

Q.

How is NH_4^+ formed in the kidney?

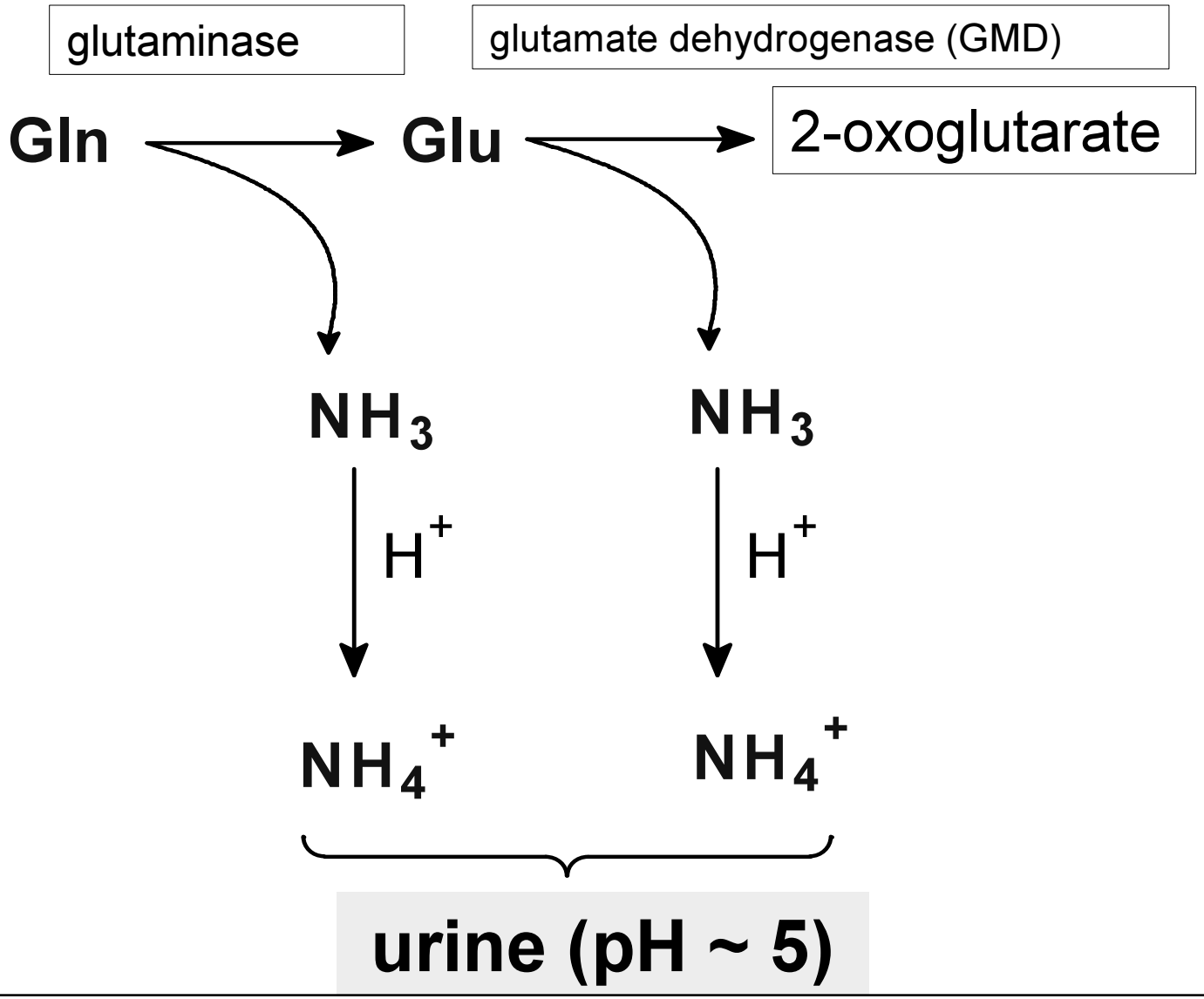
Glutaminase catalyses the hydrolysis of amide group in glutamine



glutamine

glutamate

Glutamine deamination in tubular cells occurs stepwise



Q.

What is pH range of urine?

A.

the pH of urine

usual range: 5 – 6

extremes: 4.5 – 8.0

Q.

What are the three main acid species in urine?

A.

Acid	Type	pK_A	Daily excretion
NH_4^+	cation	9.25	~ 50 mmol/d
$H_2PO_4^-$	anion	6.80	~ 30 mmol/d
Uric acid	neutral	5.40	~ 2 mmol/d

Q.

What is the ratio of HPO_4^{2-} / $H_2PO_4^-$ in urine with pH = 4.8?

A. Calculation from H.-H. equation

$4.8 = 6.8 + \log x$

$\log x = -2$

$x = 10^{-2} = 0.01 \Rightarrow$ **$[HPO_4^{2-}] : [H_2PO_4^-] = 1 : 100$**

under normal conditions (in mild acidic urine)
the essentially prevailing species is dihydrogenphosphate

Q.

What is the consequence of the reversed ratio?

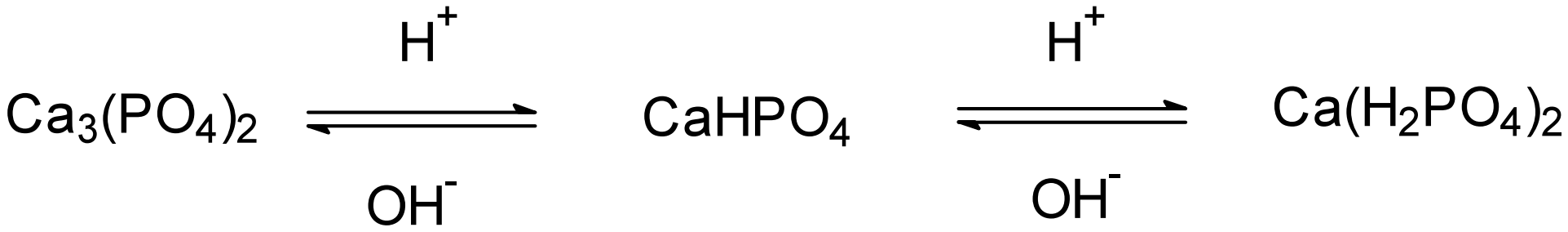
$HPO_4^{2-} / H_2PO_4^{-} > 1$

A.

formation of urine concrements

calcium hydrogenphosphate $CaHPO_4$ is **<u>insoluble</u>**

Solubility of calcium phosphates



insoluble **insoluble** **soluble**

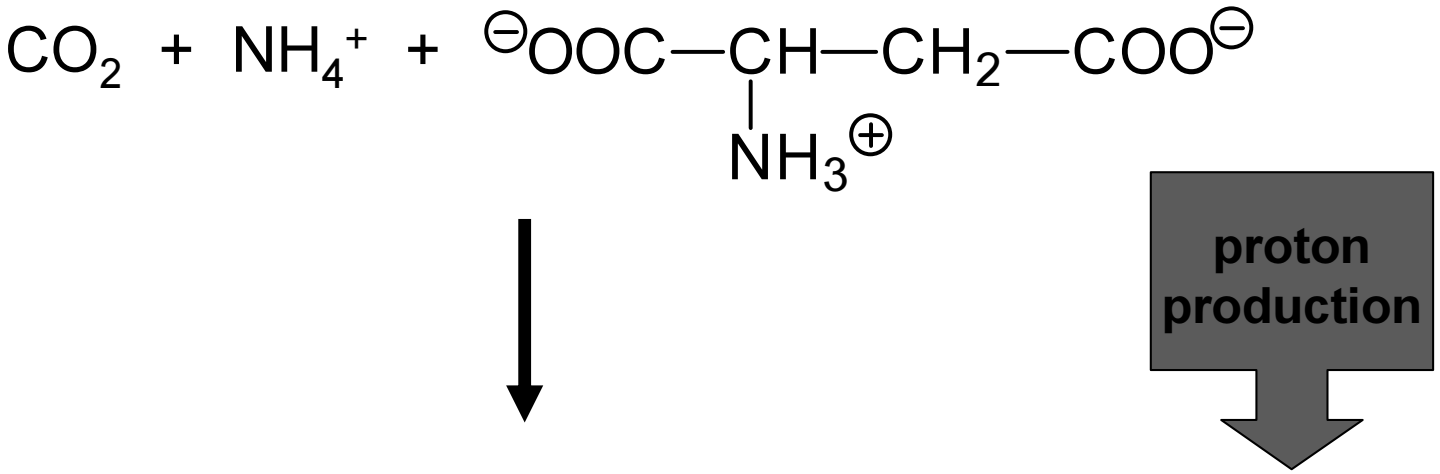
pH > 8 **pH 6-8** **pH 4-6**

Liver functions maintaining acid base balance

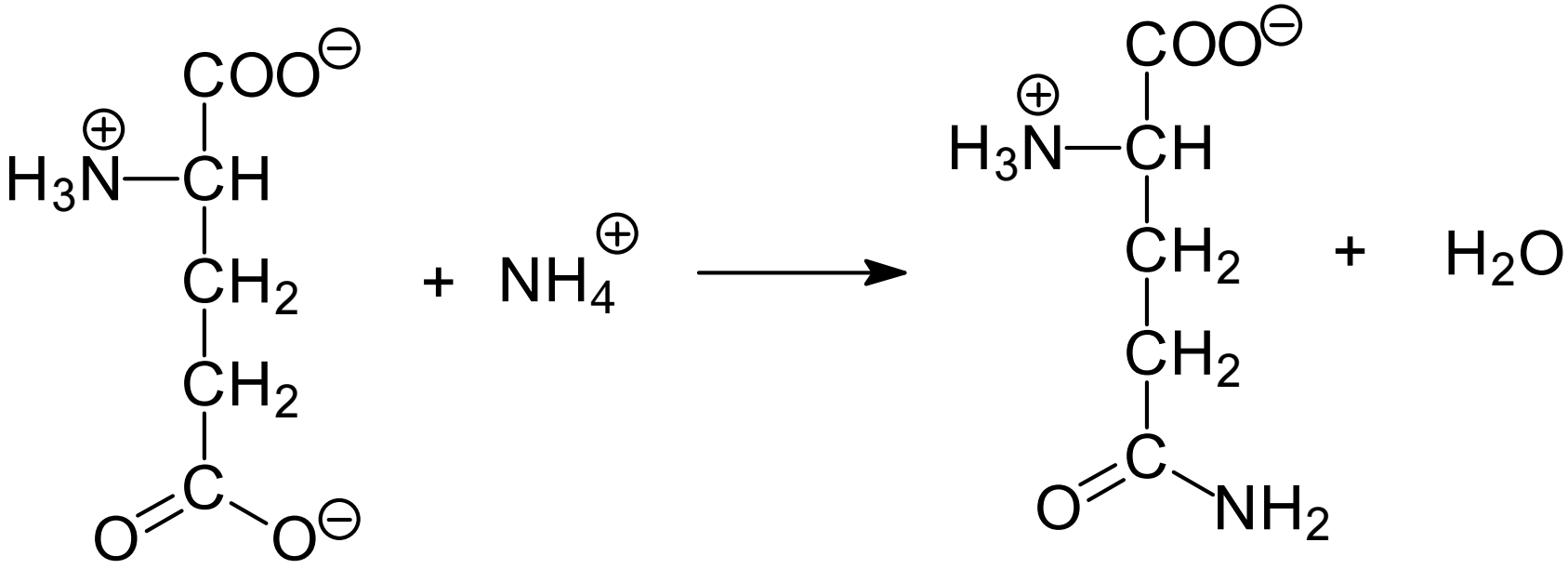
two ways of ammonia detoxication occur in liver:

- synthesis of urea $\Rightarrow$ **proton-productive process**
- synthesis of glutamine $\Rightarrow$ **proton-neutral process**

Synthesis of urea



Synthesis of glutamine



proton-neutral process

Liver functions maintaining acid base balance

- in acidosis, liver preferably makes glutamine instead of urea
- glutamine is transported by blood to kidneys, where it is hydrolyzed (glutaminase) - NH_4^+ cation is released into urine
- glutamate can be further deaminated and NH_4^+ cation is again released into urine

Parameters of acid base balance

Measured in arterial blood

- pH = 7.40 ± 0.04 = 7.36 – 7.44
- pCO_2 = 4.8 – 5.8 kPa
- supporting data: pO_2, tHb, sO_2, HbO_2, COHb, MetHb

Calculated

- $[HCO_3^-]$ = 24 ± 3 mmol/l (from H.-H. eq.)
- BE = 0 ± 3 mmol/l (from S.-A. nomogram, see physilogy)
- NBB_p = 42 ± 3 mmol/l
- NBB_b = 48 ± 3 mmol/l

Q.

Which buffer bases are in the plasma?

Buffer bases in (arterial) plasma

Buffer base	**mmol/l**
HCO_3^-	24
Proteins	16
HPO_4^{2-}	2
---	---
Total	**42**

Q.

Compare NBB_p with NBB_b and explain the difference.

A.

$NBB_p = 42 \pm 3$ mmol/l

$NBB_b = 48 \pm 3$ mmol/l

hemoglobin in erythrocytes

increases NBB_b by 6-8 mmol/l

Four types of acid-base disorders

$$pH = 6.1 + \log \frac{[HCO_3^-]}{0.23 \times pCO_2}$$

Changes in $[HCO_3^-]$

↓ metabolic acidosis

↑ metabolic alkalosis

Changes in pCO_2

↓ respiratory alkalosis

↑ respiratory acidosis

Maintanance of constant pH in body

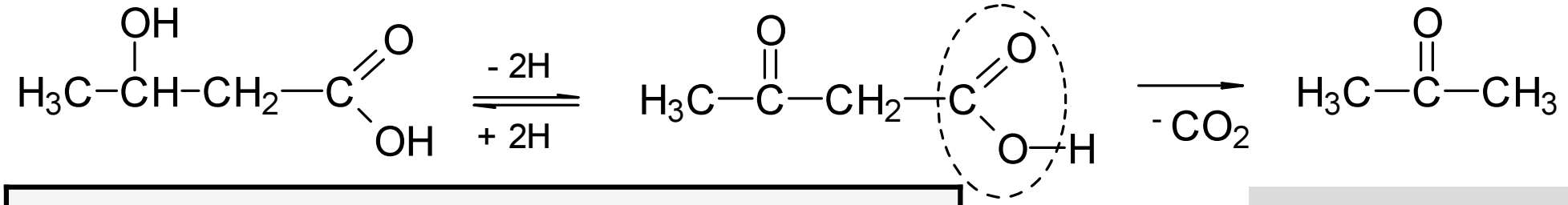
System / Organ	What is altered?	How quickly?
Buffers in ECF/ICF	pH	sec / min
Lungs	pCO_2	hours
Liver	way of NH_3 detoxication	days
Kidney	NH_4^+ / $H_2PO_4^-$ excretion HCO_3^- resorption	days

Causes of metabolic acidosis

- **Hypoxia of tissues** – insufficient supply of O_2 $\Rightarrow$ anaerobic glycolysis: glucose $\rightarrow$ 2 lactate
- elevated AG – lactoacidosis

- **Starvation, diabetes**
- TAG $\rightarrow$ FA (β-oxidation in liver)$\rightarrow$ acetyl-CoA (excess, over the capacity of CAC) $\Rightarrow$ KB production
- elevated AG - ketoacidosis

Ketone bodies



Acid	pK_A
Acetoacetic	3.52
β-Hydroxybutyric	4.70

acetone

non-electrolyte

Compare:

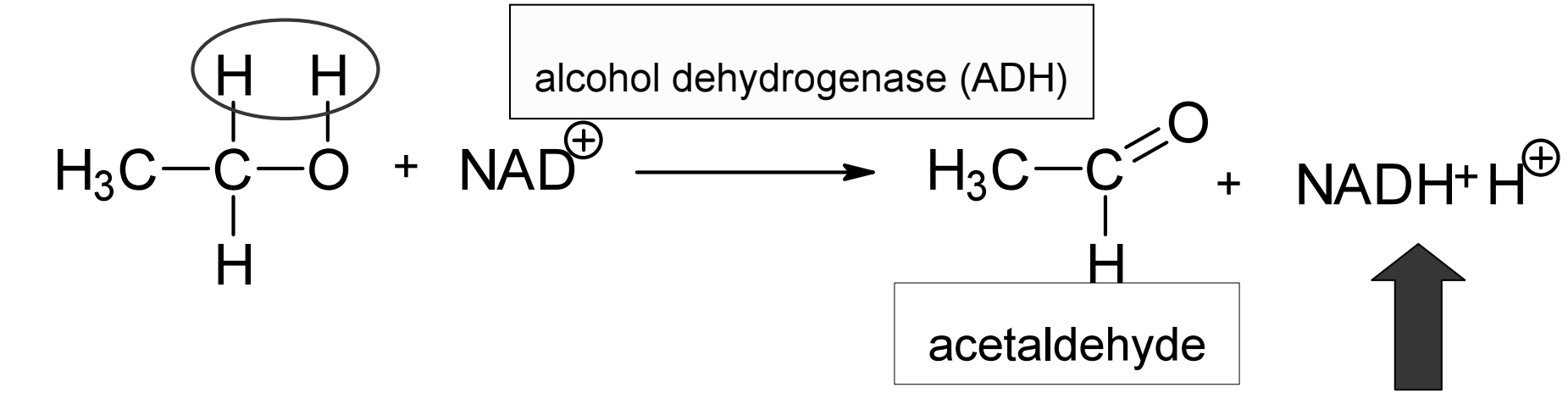
acetic acid pK_A = 4.75

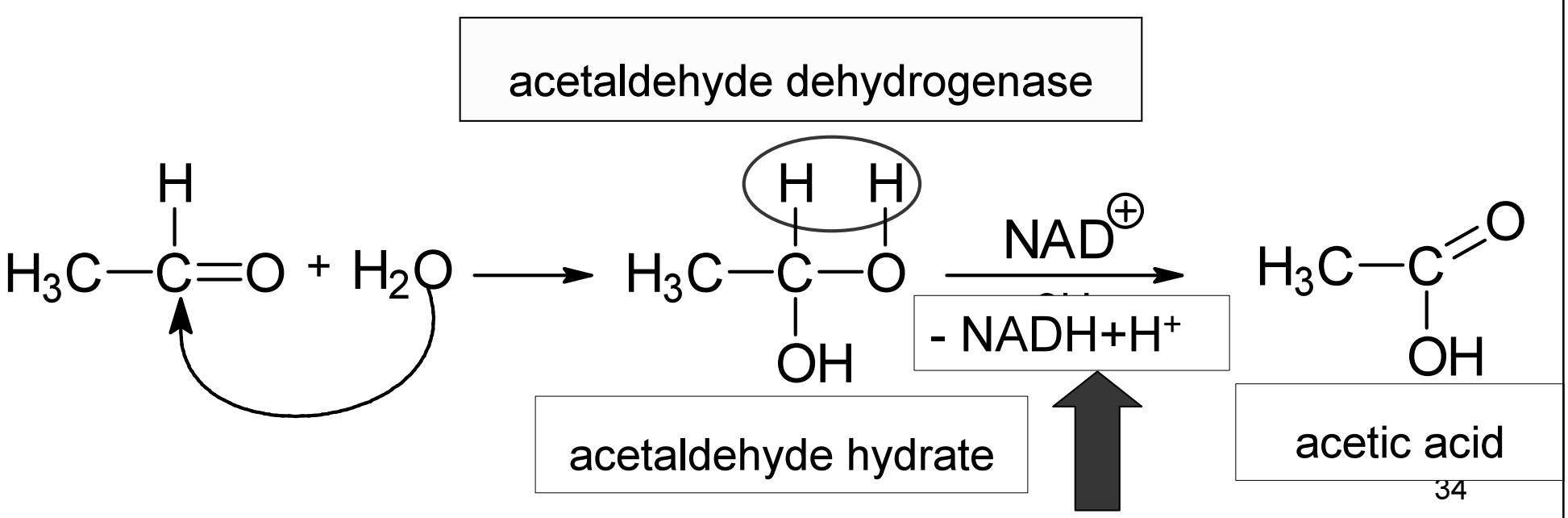
formic acid pK_A = 3.75

Q.

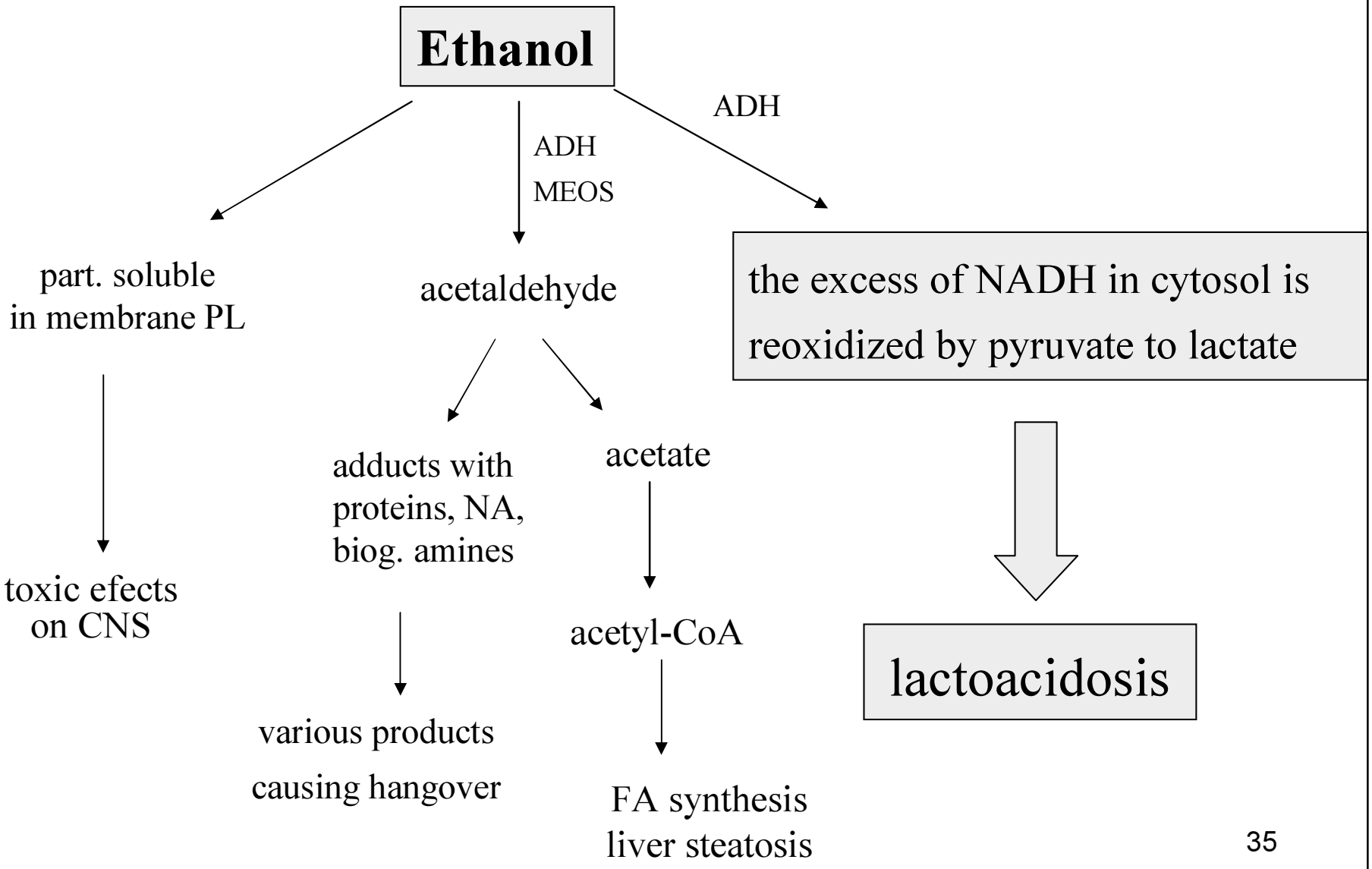
Explain why chronic alcoholism leads to lactoacidosis.

Metabolic oxidation of ethanol leads to excess of NADH





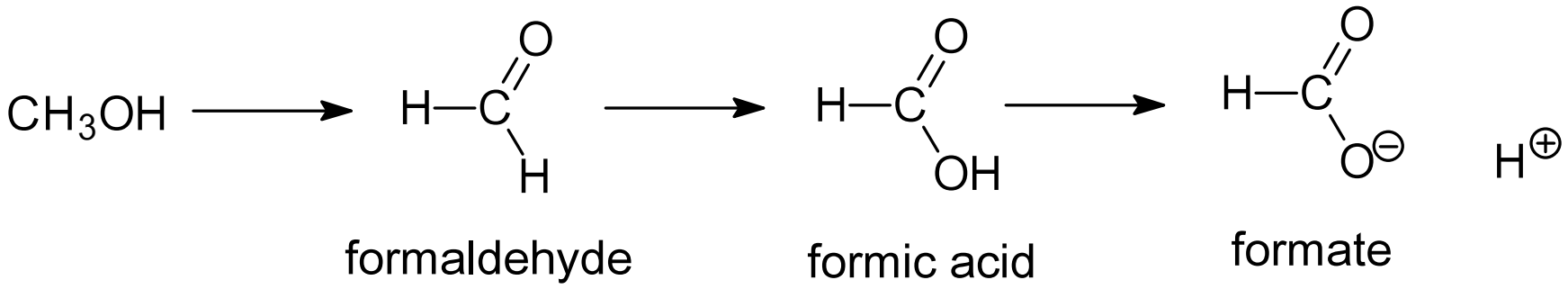
Metabolic consequences of EtOH biotransformation



Q.

Explain why methanol intoxication leads to metabolic acidosis.

Metabolic oxidation of methanol provides a rather strong formic acid



Consequences:

- formate in plasma ⇒ elevated AG ⇒ acidosis
- excess of NADH ⇒ lactoacidosis

Compare two acids

ethanol

acetic acid

$pK_A = 4.75$

$K_A = 1.8 \times 10^{-5}$

methanol

formic acid

$pK_A = 3.75$

$K_A = 1.8 \times 10^{-4}$

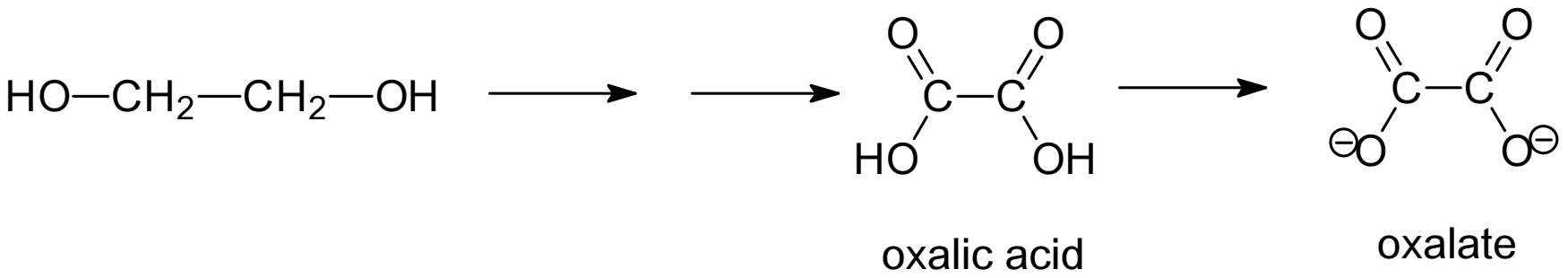
K_A (formic ac.) : K_A (acetic ac.) = 10 : 1

formic acid is 10 × stronger than acetic ac.

Q.

Explain why ethylene glycol poisoning leads to metabolic acidosis.

Intoxication by ethylene glycol



Consequences:

- oxalic acid is rather strong acid ($pK_{A1} = 1.25$, $pK_{A2} = 4.29$)
- oxalate in plasma ⇒ elevated AG ⇒ acidosis
- excess of NADH ⇒ lactoacidosis
- in urine ⇒ calcium oxalate concrements

Q.

Excessive infusions of isotonic solution lead to metabolic acidosis. Explain.

Excessive infusions of NaCl isotonic solution lead to metabolic acidosis

Blood plasma (mmol/l)	
Na^+	Cl^-
133-150	97-108

Isotonic solution (mmol/l)	
Na^+	Cl^-
154	154

Isotonic solution of NaCl has elevated concentration of Cl^- compared to plasma

Blood plasma is diluted by infusion solution $\Rightarrow$ **$[HCO_3^-]$ decreases**

pCO_2 in alveolar air is **the same**

the ratio $[A^-] / [HA]$ in H.-H. equation decreases $\Rightarrow$ pH $<$ 7.40 (acidosis)

Q.

Explain lactoacidosis in thiamine deficit.

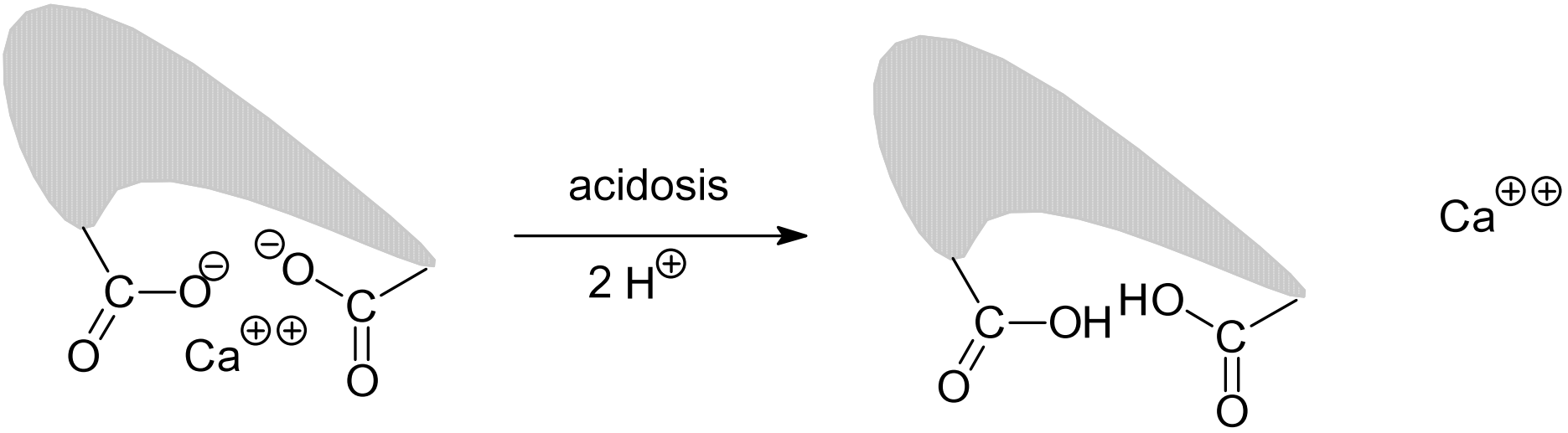
A.

- thiamine is the cofactor of aerobic decarboxylation of pyruvate
- thiamine deficit $\Rightarrow$ pyruvate cannot be converted to acetyl-CoA
- therefore pyruvate is hydrogenated to lactate
- **even in aerobic conditions: glucose $\rightarrow$ lactate**
- increased plasma lactate $\Rightarrow$ elevated AG $\Rightarrow$ lactoacidosis

Q.

In chronic acidosis Ca^{2+} ions are released from bones and plasma proteins and pass into urine. Explain.

A.



- calcium cations make electrostatic interactions with carboxylate anions in side chains of glutamate and aspartate (in various proteins)
- increased [H^+] (= decreased pH) of plasma leads to a partial cation exchange
- one calcium ion is liberated and replaced by two protons

Metabolic acidosis

Parameter	Physiol. st.	Ac. change	Compensation	Correction
$[HCO_3^-]$	24 mmol/l	↓		→ **N**
pCO_2	5.3 kPa	**N**	↓	
$[A^-] / [HA]$	20 : 1	< 20 : 1		
pH	7.40 ± 0.04	< 7.36		
		System	lungs	kidney
		Process	hyperventilation	HCO_3^- resorption NH_4^+ / $H_2PO_4^-$ excr.

Causes of metabolic alkalosis

- **Repeated vomiting** – the loss of chloride (Cl^-) anion $\Rightarrow$ hypochloremic alkalosis

- **Direct administration of buffer base HCO_3^-**

  per os: baking soda, some mineral waters

  intravenous infusions of sodium bicarbonate

- **Hypoalbuminemia**

  severe malnutrition

  liver damage, kidney damage

Q.

What is baking soda?

A.

$NaHCO_3$

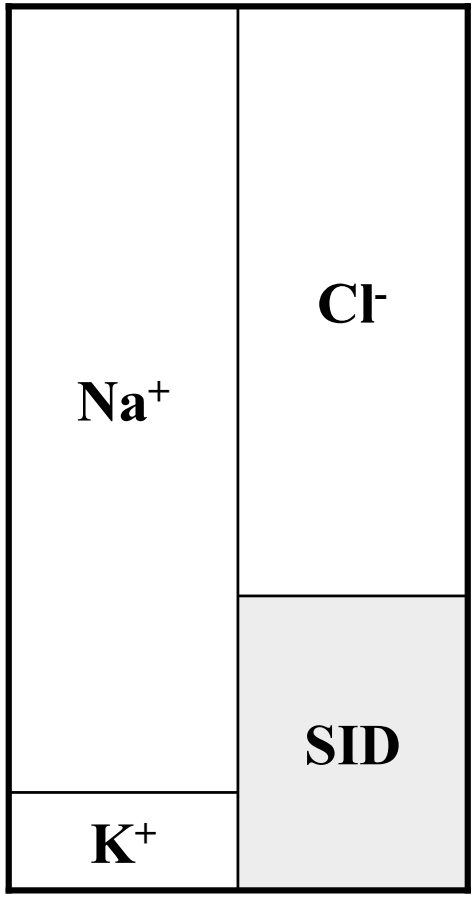
sodium hydrogencarbonate (sodium bicarbonate)

sold in pharmacy

Q.

How is SID changed in alkalosis?

SID corresponds to buffer bases of plasma



In alkalosis, SID increases

$$SID = HCO_3^- + HPO_4^{2-} + Prot^-$$

Q.

What is the acid-base status of a patient if:

pCO_2 = 5.5 kPa

$[HCO_3^-]$ = 39 mmol/l

pH = 7.6

Which parameter will be changed after compensation?

A.

pCO_2 = 5.5 kPa ..... **OK**

$[HCO_3^-]$ = 39 mmol/l ..... ↑ **elevated**

pH = 7.6 ..... ↑ **elevated**

status: metabolic alkalosis

pCO_2 will increase during compensation (hypoventilation)

Q.

What is the effect of the following infusions (alkalizing / acidifying) ?

- NaCl
- $KHCO_3$
- NH_4Cl
- $NaHCO_3$
- sodium lactate

Solution	Effect	Explanation
NaCl	acid.	plasma dilution ⇒ $[HCO_3^-]$ ↓ while pCO_2 is constant
$KHCO_3$	alkal.	direct addition of the main buffer base
NH_4Cl	acid.	NH_4^+ excreted by urine, Cl^- remains in plasma ⇒ $[HCO_3^-]$ ↓
$NaHCO_3$	alkal.	direct addition of the main buffer base
Na lactate	alkal.	lactate anion goes from plasma to liver (gluconeogenesis), Na^+ remains in plasma ⇒ its pos. charge is balanced by extra HCO_3^- (similar effect like in vegetarian diet)*

* see Seminar No. 9

Metabolic alkalosis

Parameter	Physiol. st.	Ac. change	Compensation	Correction
$[HCO_3^-]$	24 mmol/l	↑		→ **N**
pCO_2	5.3 kPa	**N**	↑	
$[A^-] / [HA]$	20 : 1	> 20 : 1		
pH	7.40 ± 0.04	> 7.44		
		System	lungs	kidney
		Process	hypoventilation	HCO_3^- excretion