Equilibrio acido-base

$pH_{extracell}$ = 7.35 ÷ 7.45

Produzione di acidi = A. 20.000 mmoli di acido carbonico (CO_2)
B. 80 mmoli di acidi "non volatili"

Capacità tampone totale ≈ 15 mmoli x kg^{-1} (1.050 totali) / 80 = ~ 13 gg di "autonomia" se non vi fosse rigenerazione del bicarbonato

A. Volatili

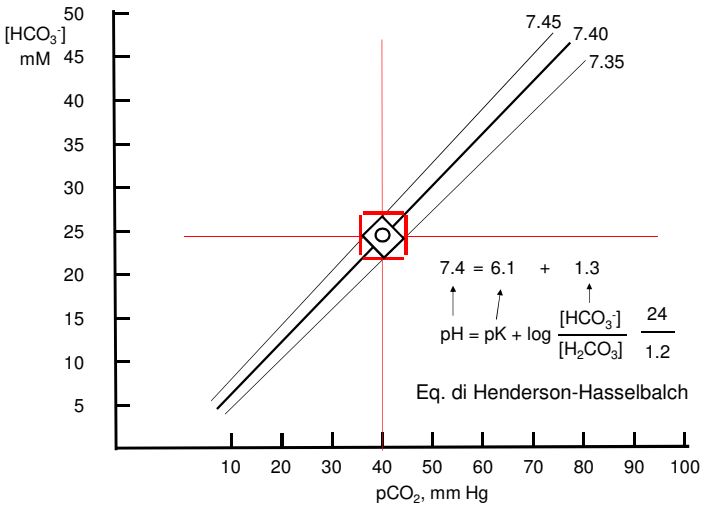
polmone

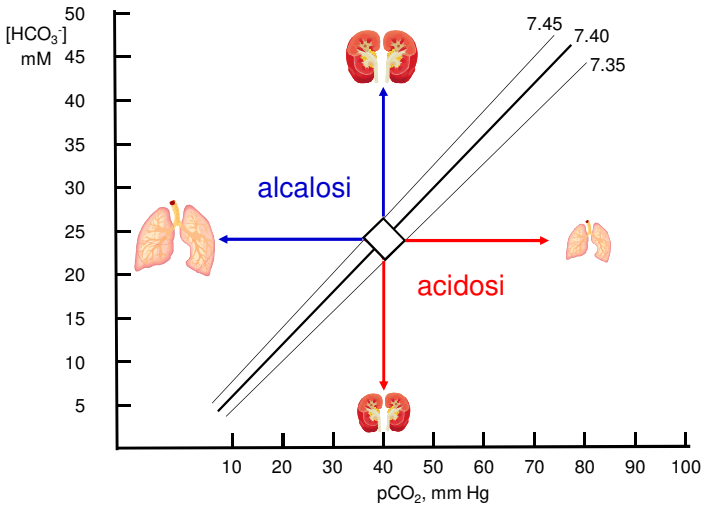
CO_2 (metabolismo) $\overset{CA}{\leftrightarrow}$ $H_2CO_3 \leftrightarrow H^+ + HCO_3^- \leftrightarrow H_2CO_3 \overset{CA}{\leftrightarrow} CO_2$

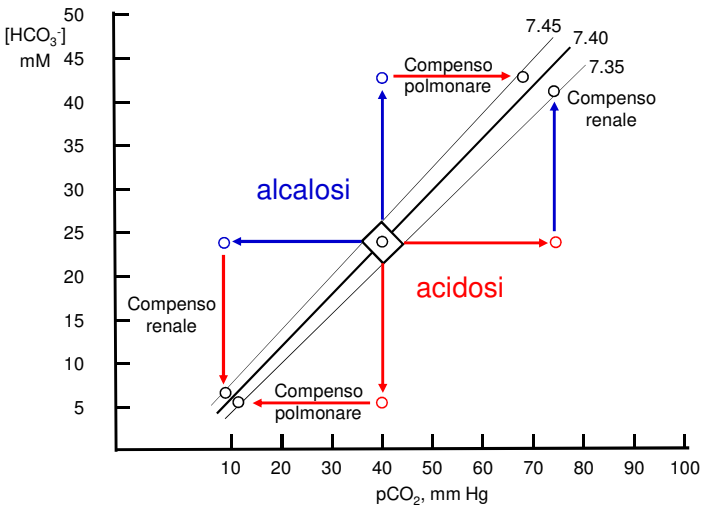
40 mm Hg — 1.2 mM — 24 mM — 40 mm Hg

B. Non volatili

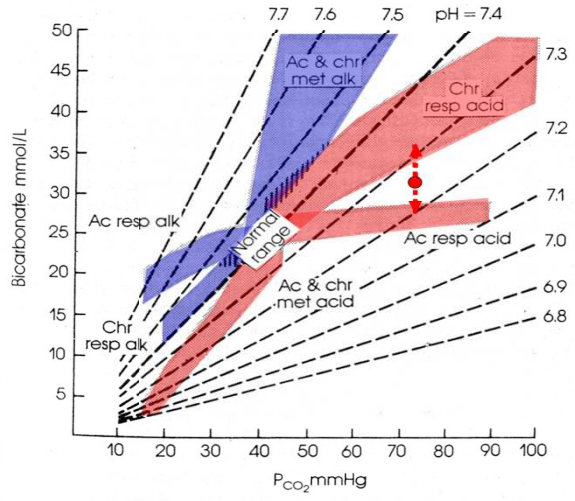
1. Aa solforati (Met, Cys): $H_2SO_4 \rightarrow H^+ + HSO_4^-$
2. Acidi grassi, carboidrati (combustione incompleta): Acidi organici $\rightarrow H^+ + A^-$
3. Nucleoproteine: Acido urico $\rightarrow H^+ +$ urato$^-$
4. Composti organici del P: $H_3PO_4 \leftrightarrow H^+ + H_2PO_4^- \leftrightarrow H^+ + HPO_4^{2-}$







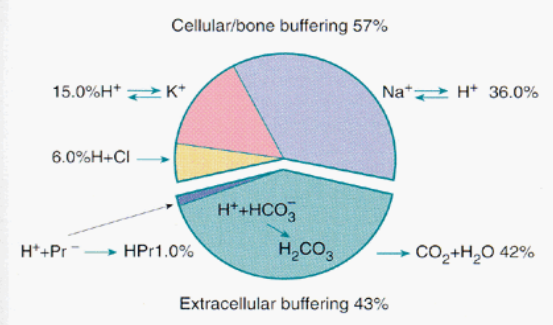
Da Harrison's principles of internal medicine, 13th edition



René Magritte,1953
Menil Collection, Houston

Buffers in the human body

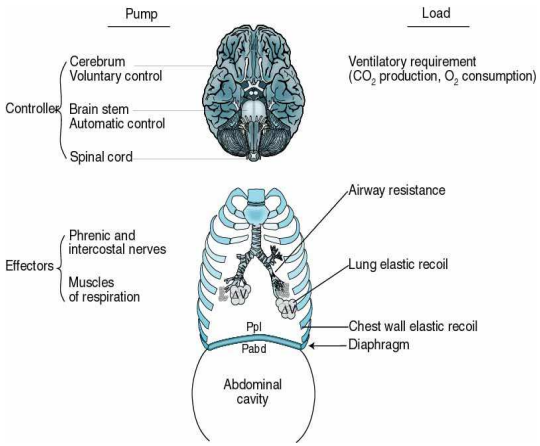
Buffer	Acid	Conjugate base	Main buffering action
hemoglobin	HHb	Hb^-	erythrocytes
proteins	HProt	$Prot^-$	intracellular
phosphate buffer	$H_2PO_4^-$	HPO_4^{2-}	intracellular
bicarbonate	$CO_2 \rightarrow H_2CO_3$	HCO_3^-	extracellular

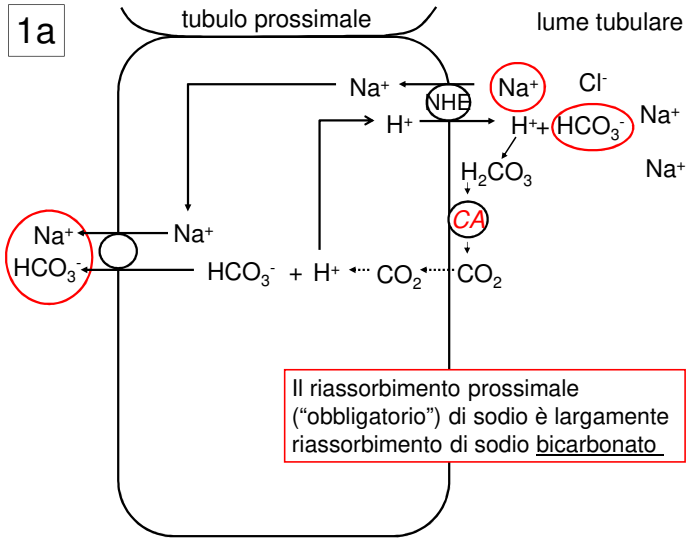


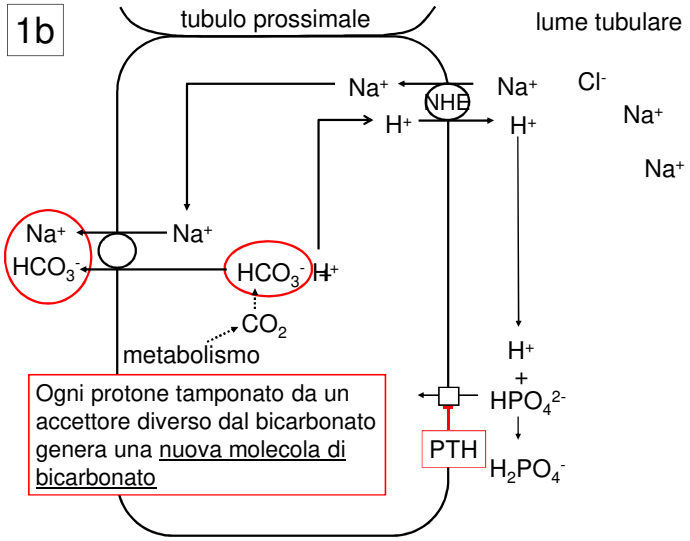
Equilibrio acido-base

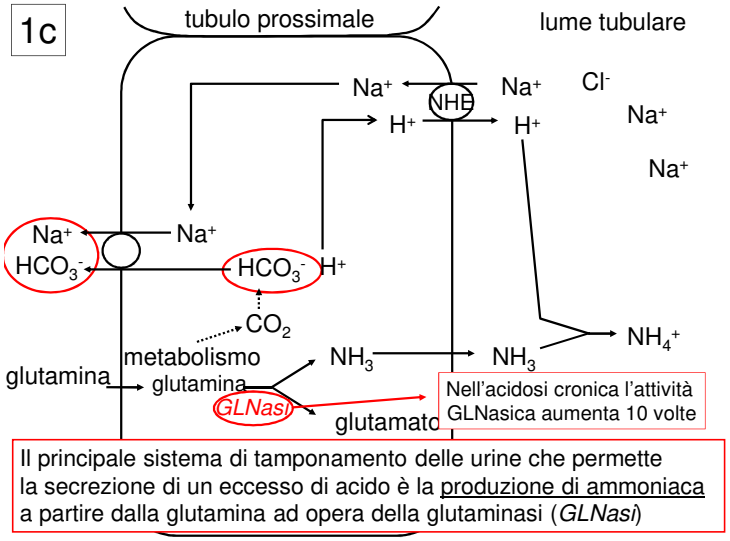
Acidemia	pH < 7.35
Alcalemia	pH > 7.45
Acidosi	Processo che tende ad aumentare [H^+] e a ridurre il pH
Alcalosi	Processo che tende a ridurre [H^+] e ad aumentare il pH
Acidosi metabolica	Condizione in cui l'evento primario è la riduzione di HCO_3^-
Alcalosi metabolica	Condizione in cui l'evento primario è l'aumento di HCO_3^-
Acidosi respiratoria	Condizione in cui l'evento primario è l'aumento della $PaCO_2$
Alcalosi respiratoria	Condizione in cui l'evento primario è la diminuzione della $PaCO_2$
Disordine misto	Condizione in cui è presente più di un disturbo primario dell'equilibrio acido-base
Compenso	Risposta fisiologica all'acidosi o all'alcalosi che determina un parziale ritorno del pH verso i livelli normali

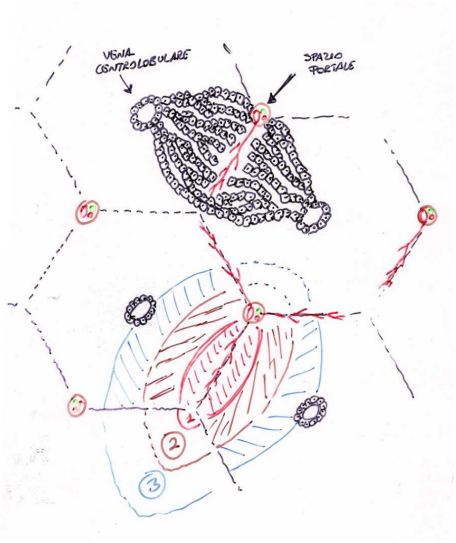
Controllo del sistema ventilatorio

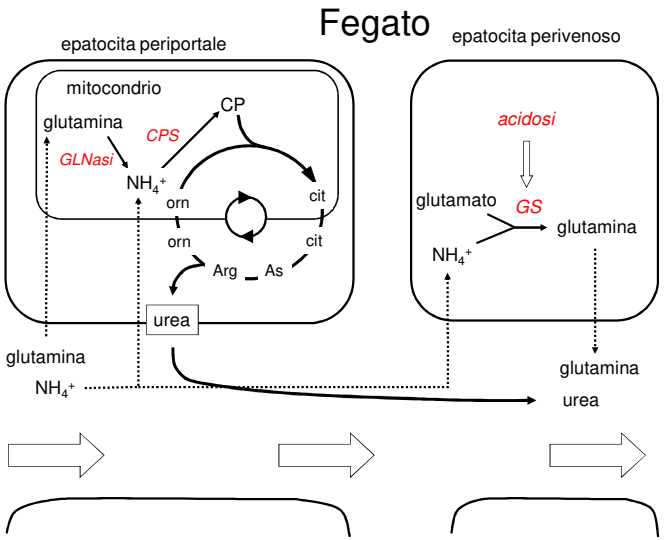


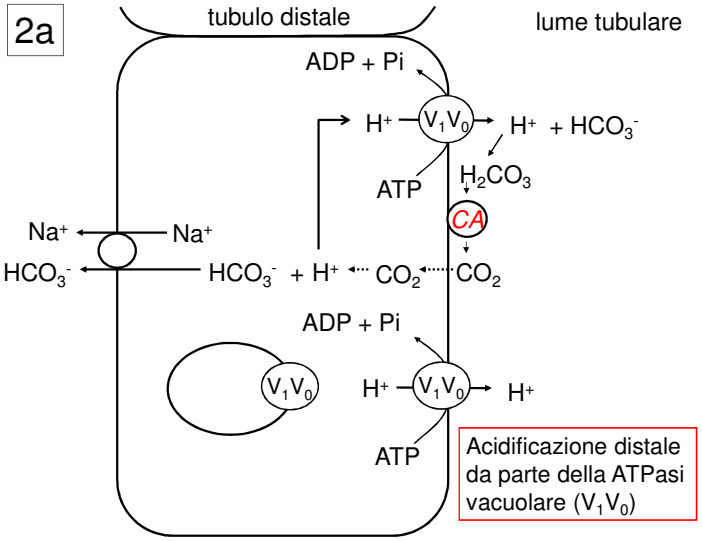


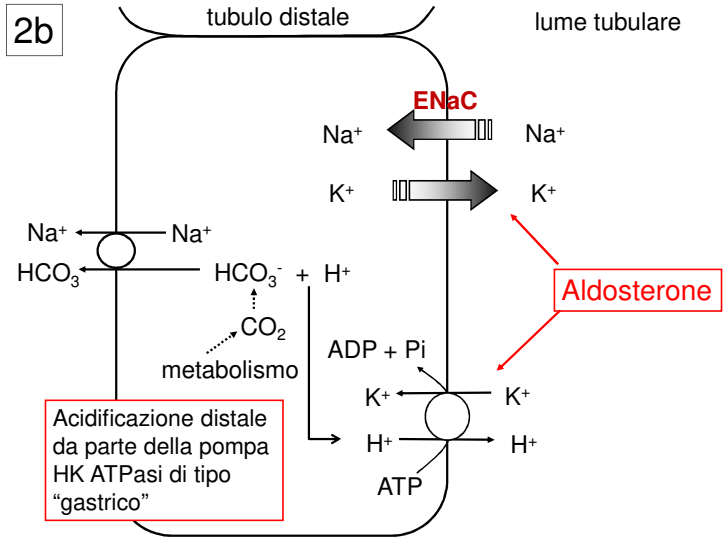

1b
tubulo prossimale
lume tubulare
Na+
NHE
H+
Cl-
HCO3-
CO2
metabolismo
HPO4 2-
PTH
H2PO4-
Ogni protone tamponato da un accettore diverso dal bicarbonato genera una nuova molecola di bicarbonato


1c
tubulo prossimale
lume tubulare
Na+
NHE
H+
Cl-
HCO3-
CO2
metabolismo
glutamina
NH3
NH4+
GLNasi
glutamato
Nell'acidosi cronica l'attività GLNasica aumenta 10 volte
Il principale sistema di tamponamento delle urine che permette la secrezione di un eccesso di acido è la produzione di ammoniaca a partire dalla glutamina ad opera della glutaminasi (GLNasi)


VENA CENTROLOBULARE
SPAZIO PORTALE
1
2
3


Fegato
epatocita periportale
epatocita perivenoso
mitocondrio
glutamina
GLNasi
CPS
CP
NH4+
orn
cit
Arg
As
urea
acidosi
glutamato
GS
glutamina
NH4+
glutamina
NH4+
glutamina
urea





Pompa HK ATPasi

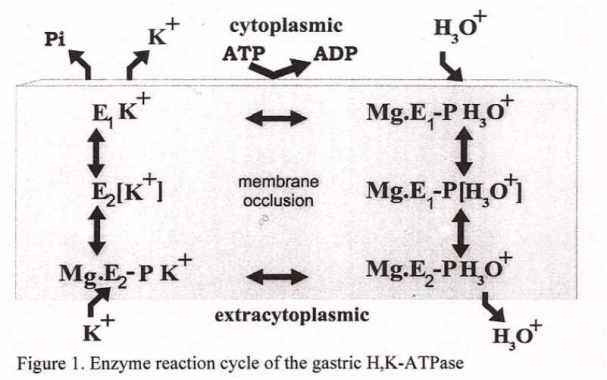
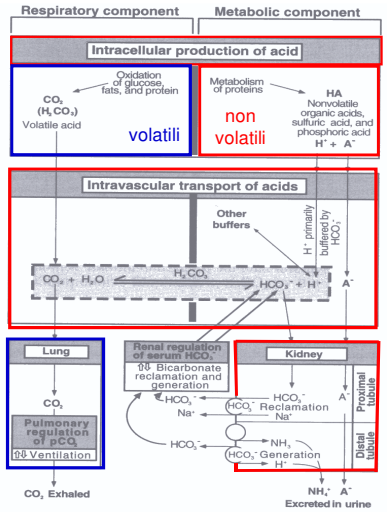
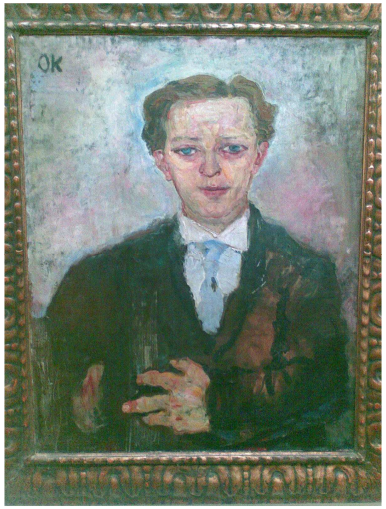


Figure 1. Enzyme reaction cycle of the gastric H_2K-ATPase





Principali conseguenze di

Acidosi grave

Cardiovascolari
- Diminuzione della gittata cardiaca
- Aritmie
- Ipotensione
- Resistenza ai farmaci ipertensivi
- Costrizione venosa con aumento del volume circolante

Metaboliche
- Resistenza all'insulina

Gastroenteriche
- Atonia gastrica
- Riduzione del flusso ematico al fegato

Cerebrali
- Compromissione del sensorio

Ossigenazione
- Modificata affinità Hb per O_2 (risultante del bilancio acidosi + 2,3 DPG e della durata della acidosi)

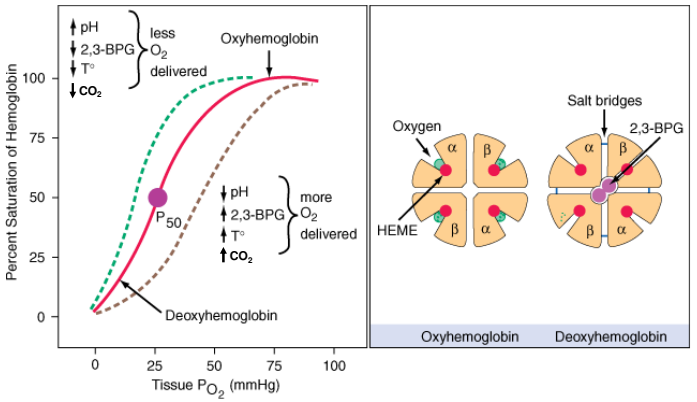
Alcalosi grave

Cardiovascolari
- Vasocostrizione arteriosa
- Riduzione del flusso coronarico
- Riduzione della soglia per l'angina
- Predisposizione ad aritmie refrattarie sopraventricolari e ventricolari

Respiratorie
- Ipoventilazione con ipercapnia ed ipossiemia
- Aumento della vasocostrizione polmonare ipossica → peggioramento VA/Q

Metaboliche
- Glicolisi anaerobia e produzione di acidi organici
- Ipokaliemia
- Diminuzione della concentrazione di calcio ionizzato nel plasma
- Ipomagnesiemia ed ipocalcemia con tetania

Cerebrali
- Riduzione del flusso vascolare
- Crisi epilettiche, letargia, delirio e stupor



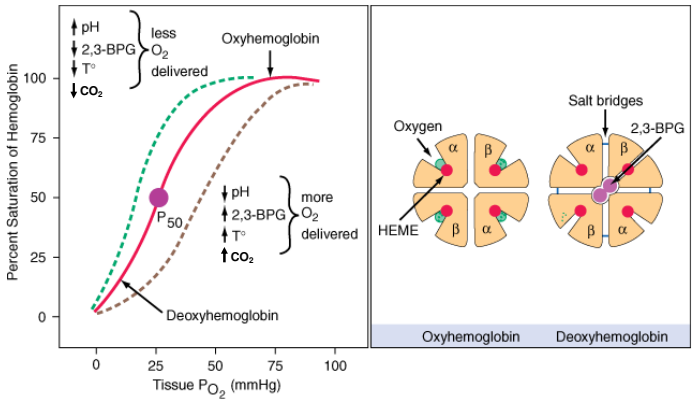
Pediatr Res. 1981 May;15(5):809-12.

The adaptation of neonatal blood to metabolic acidosis and its effect on cisternal oxygen tension.

Berthiaume Y, Bureau MA, Bégin R.

Abstract

In eight newborn lambs, the adaption of blood to acidosis was studied by sequential measurements of P50 in vitro (pH 7.4; 37 degrees C) and P50 in vivo (animal's pH and temperature, 39 degrees C) during the course of HCl-induced metabolic acidosis. The benefit of the change in both P50 on tissue oxygen tension was studied by the change in O2 partial pressure at the level of the cisterna magna. **Eight hr of acidosis** caused a significant (P less than 0.01) decrease in P50 in vitro which fell from 29.0 to 24.4 torr. Nonetheless, **because of pH effect on the hemoglobin affinity, the corresponding P50 in vivo was increased from 32.4 to 36.3 torr.** This latter decrease ~~rise~~ in the in vivo O2 affinity contributed to increase (P less than 0.01) the cisternal O2 tension. It is concluded that **the hemoglobin of the newborn is capable of adaption to metabolic acidosis by displacing the in vivo O2 dissociation curve to the right favouring a greater unloading of O2 at the tissue level and thus preventing tissue hypoxia during metabolic acidosis.**



Diabetologia. 1995 Aug;38(8):889-98.

Haemodynamic and metabolic effects in diabetic ketoacidosis in rats of treatment with sodium bicarbonate or a mixture of sodium bicarbonate and sodium carbonate.

Beech JS, Williams SC, Iles RA, Cohen RD, Nolan KM, Evans SJ, Going TC.

Source

Cellular Mechanisms Research Group, London Hospital Medical College, UK.

Abstract

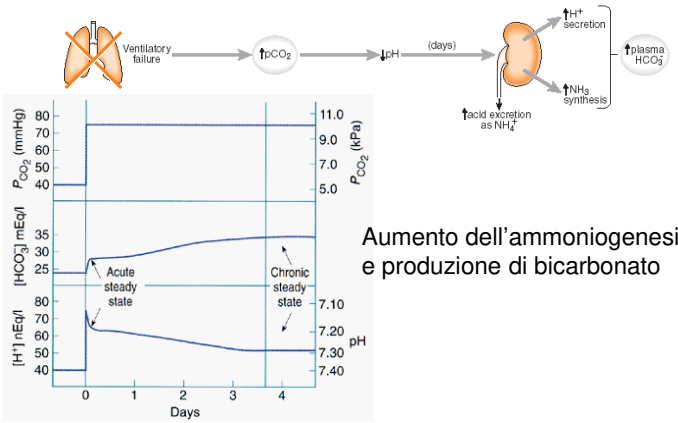
To examine factors determining the haemodynamic and metabolic responses to treatment of diabetic ketoacidosis with alkali, groups of anaesthetised and ventilated rats with either **diabetic ketoacidosis (mean arterial pH 6.86-6.96,** mean arterial blood pressure 63-67 mm Hg) or hypovolaemic shock due to blood withdrawal (mean pHa 7.25-7.27, mean arterial blood pressure 36-41 mm Hg) were treated with sodium chloride ('saline'), sodium bicarbonate or 'Carbicarb' (equimolar bicarbonate plus carbonate). **In the diabetic ketoacidosis series, treatment with either alkali resulted in deterioration of mean arterial blood pressure and substantial elevation of blood lactate, despite a significant rise in myocardial intracellular pH determined by 31P-magnetic resonance spectroscopy.** These effects were accompanied by falling trends in the ratios of myocardial phosphocreatine and ATP to inorganic phosphate. **Erythrocyte 2,3-bisphosphoglycerate was virtually absent in animals with diabetic ketoacidosis of this severity and duration.** In contrast, in shock due to blood withdrawal, infusion of saline or either alkali was accompanied by a transient elevation of mean arterial blood pressure and no significant change in the already elevated blood lactate; erythrocyte 2,3-bisphosphoglycerate was normal in these animals. **The effect of alkalinization in rats with severe diabetic ketoacidosis was consistent with myocardial hypoxia, due to the combination of very low initial erythrocyte 2,3-bisphosphoglycerate, alkali-exacerbated left shift of the haemoglobin-oxygen dissociation curve and artificial ventilation.** No evidence was found for any beneficial effect of 'Carbicarb' in either series of animals; **'Carbicarb' and sodium bicarbonate could be deleterious in metabolic acidosis of more than short duration.**

Acidosi respiratoria

Alterazione dell'equilibrio acido-base caratterizzata da aumento primitivo della $PaCO_2$; è causata da alterazioni della ventilazione.

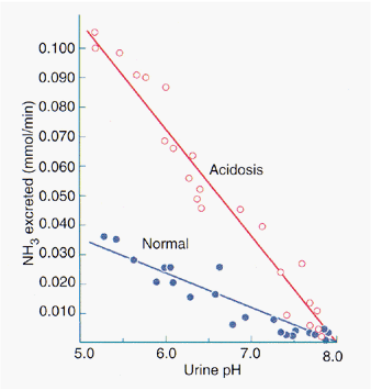
- Depressione dello stimolo respiratorio (ad esempio sedativi, narcotici, alcool, lesioni SNC su base vascolare, trauma cranico, encefalite)
- Insufficienza della pompa ventilatoria
  - primitiva (muscoli respiratori): farmaci e tossici (curarizzanti, esteri organofosforici), sclerosi multipla, miopatie;
  - secondaria (fatica da eccessivo aumento del lavoro respiratorio): malattie restrittive, ARDS, crisi asmatica, BPCO;
- Patologie polmonari con compromissione degli scambi gassosi: BPCO grave, edema polmonare acuto

Compenso dell'acidosi respiratoria



Aumento dell'ammoniogenesi e produzione di bicarbonato

Compenso renale dell'acidosi



Acidosi respiratoria

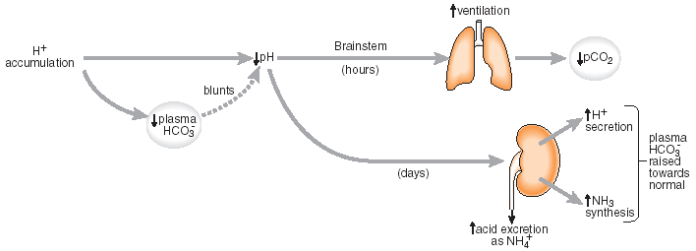
- Acuta
  - cefalea
  - alterazioni visus
  - tremori
  - agitazione – stato soporoso – coma
  - ipotensione
- Cronica
  - dispnea
  - agitazione – stato soporoso – coma
  - segni e sintomi della pneumopatia di base
  - segni e sintomi di cuore polmonare cronico

Acidosi metabolica

Alterazione dell'equilibrio acido-base caratterizzata da riduzione primitiva della concentrazione di bicarbonato

Compenso dell'acidosi metabolica

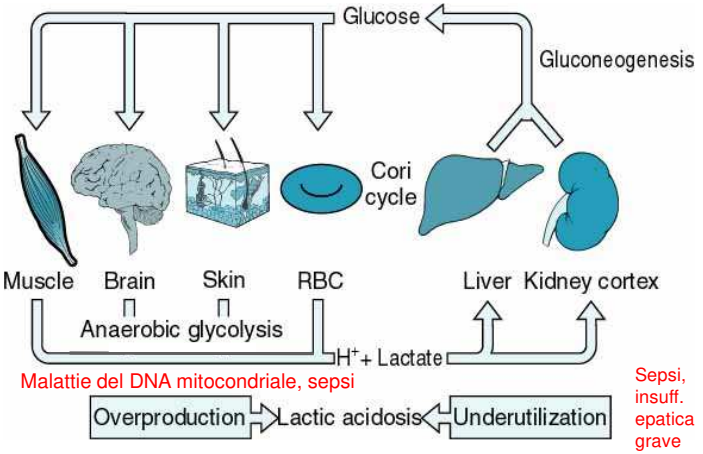
- Sistemi tampone extra- e intracellulari
- Polmone (se il sistema ventilatorio è adeguato)
- Rene (se non è la causa primitiva dell'acidosi metabolica)



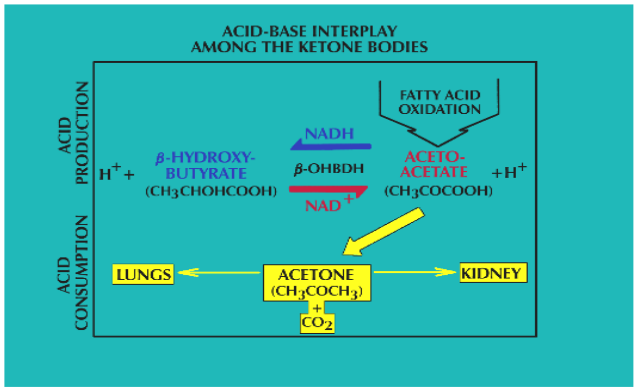
Cause di acidosi metabolica

1. Aumento di acidi non volatili (endogeni o esogeni)
   - Chetoacidosi (diabete, digiuno)
   - Lattica (malattie mitocondriali, shock)
   - Tossica (alcol etilico, alcol metilico, etilene glicole, salicilati, farmaci)

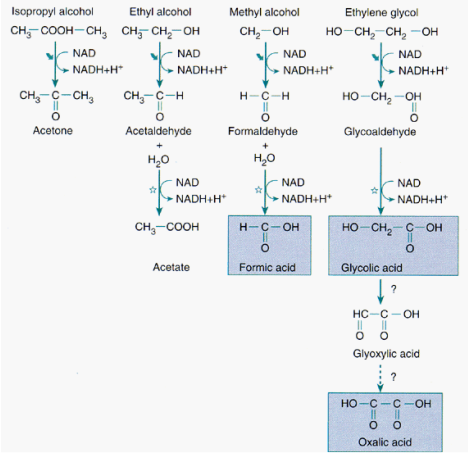
Acidosi lattica



Chetoacidosi



Acidosi da aumentata produzione di acidi secondaria ad introduzione esogena



Cause di acidosi metabolica

2. Insufficiente capacità escrezione di H^+ sotto forma di ioni ammonio
   - Insufficienza renale acuta e cronica
   - Ipoaldosteronismo

3. Perdita di bicarbonato
- per via gastroenterica (diarrea, fistole biliari, pancreatiche, intestinali etc.)
- per via renale (acidosi tubulari)

Alcalosi respiratoria

Alterazione dell'equilibrio acido-base caratterizzata da diminuzione primitiva della $PaCO_2$; è causata da alterazioni della ventilazione.

Cause di iperventilazione

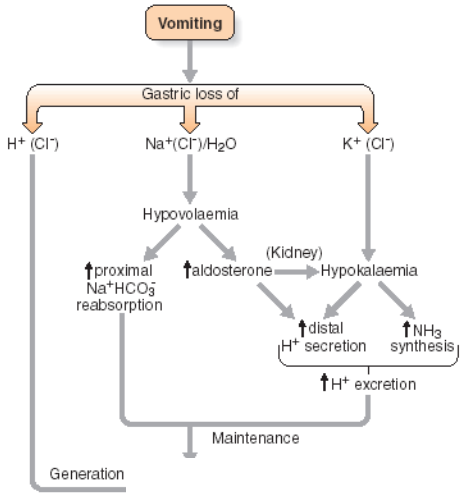
- Sepsi
- Anemia grave
- Ipossia
- Intossicazione da salicilati
- Pneumopatie
- Insufficienza epatica
- Compenso respiratorio acidosi metabolica

Alcalosi metabolica

Alterazione dell'equilibrio acido-base caratterizzata da aumento primitivo della concentrazione di bicarbonato; si genera attraverso perdita di H^+ o guadagno di basi

Compenso: ipoventilazione → aumento $PaCO_2$

- Perdita di fluido gastrico



Review article

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Mechanisms of the Effects of Acidosis and Hypokalemia on Renal Ammonia Metabolism

Ki-Hwan Han, M.D.

Department of Anatomy, Ewha Womans University School of Medicine, Seoul, Korea

Received:December 5, 2011
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Corresponding author: Ki-Hwan Han, M.D., Ph.D.
Department of Anatomy, Ewha Womans University School of Medicine, 911-1, Mok-6-dong, Yangcheon-gu, Seoul, 158-710, Korea
Tel: +82-2-2650-5710
E-mail: khhan@ewha.ac.kr

Renal ammonia metabolism is the predominant component of net acid excretion and new bicarbonate generation. Renal ammonia metabolism is regulated by acid-base balance. Both acute and chronic acid loads enhance ammonia production in the proximal tubule and secretion into the urine. In contrast, alkalosis reduces ammoniagenesis. Hypokalemia is a common electrolyte disorder that significantly increases renal ammonia production and excretion, despite causing metabolic alkalosis. Although the net effects of hypokalemia are similar to metabolic acidosis, molecular mechanisms of renal ammonia production and transport have not been well understood. This mini review summarizes recent findings regarding renal ammonia metabolism in response to chronic hypokalemia.

Key Words: kidney; ammonia; acids; hypokalemia

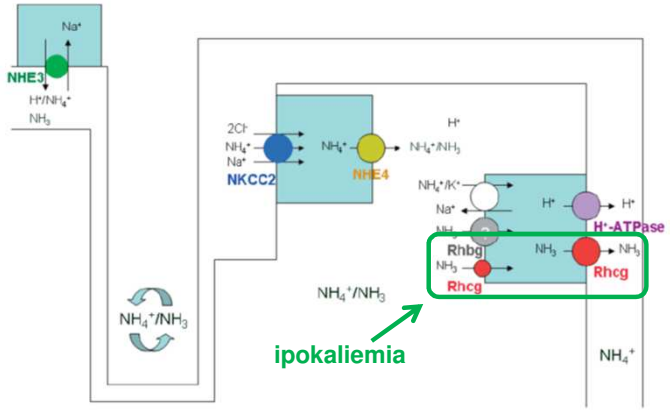


Fig. 2. Schematic Representation of the Ammonia Transport Mechanisms along the Nephron Segments. NHE3, Na^+/H^+ exchanger; NKCC2, Na^+-K^+(NH_4^+)-$2Cl^-$cotransporter 2; NHE4, Na^+-H^+(NH_4^+) exchanger 4.

Ammonia production and transport in response to acidosis

Metabolic acidosis stimulates ammonia production and transport by renal epithelial cells. Acidosis stimulates glutamine uptake into the proximal tubule and upregulates the expression of ammonia-producing enzymes, glutaminase, GDH, and PEPCK[6, 7, 9, 10]. Metabolic acidosis also increases the apical NHE3 activity and protein abundance in the proximal tubule[18].

Ammonia production and transport in response to hypokalemia

Ammonia production and excretion into urine are also regulated by potassium balance. Hypokalemia increases renal ammonia production in experimental animals and humans, whereas hyperkalemia decreases renal ammonia production[8, 23, 24]. Renal ammonia metabolism in response to hypokalemia has not been well understood, because there is increased ammonia excretion despite the development of metabolic alkalosis.

Alcalosi metabolica

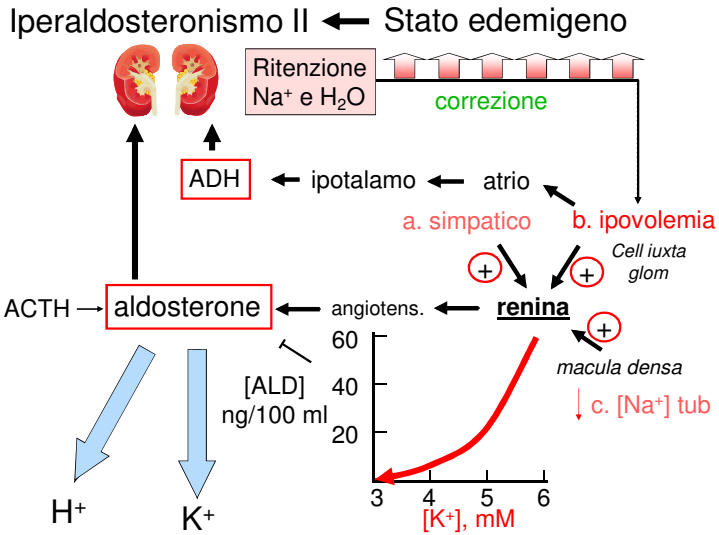
Meccanismi che mantengono elevata la bicarbonatemia

1. Deplezione di volume

- stimolo adrenergico
- riduzione GFR
- resetting del TGF
- effetti diretti del cloro

2. Iperaldosteronismo

- stimolo H^+-ATPasi del tubulo collettore
- stimolo pompa H^+/K^+ nefrone distale



Alcalosi metabolica

Alterazione dell'equilibrio acido-base caratterizzata da aumento primitivo della concentrazione di bicarbonato; si genera attraverso perdita di H^+ o guadagno di basi

Compenso: ipoventilazione → aumento $PaCO_2$

- Perdita di fluido gastrico
- Diuretici
- Alcalosi post-ipercapnica

Cloro-responsive o volume-sensibili (95%)

- Eccesso di attività mineralocorticoide

Cloro-resistenti o volume-insensibili (5%)

Mortalità
- pH 7.55 - 7.65: 41%
- pH > 7.65: 80%