IV.C. ACID-BASE BALANCE

C.a. IMPORTANCE OF pH

proper pH is required for 1) membrane excitability, 2) enzyme function, 3) chemical reactions, 4) electrolyte concentrations

C.b. MECHANISMS OF ACID-BASE BALANCE

C.b.A. CONCEPTS

acids dissociate into H^+ & some anion
- strong acids dissociate readily into H^+ & the anion –> /// H^+ in solution
- weak acids dissociate only slightly into H^+ & the anion –> / H^+ in solution

bases accept/remove H^+ from solution
- strong bases readily remove H^+ –> /// H^+ in solution
- weak bases minimally remove H^+ –> / H^+ in solution

pH = negative log of H^+ concentration
range is from 0 to 14
a pH of 0 = 1g H^+//ℓ solution = 6.023×10^{23} H^+// ℓ soln; if the soln were H_20, this is equivalent to 1 out of 55 H_20 molecules being dissociated
a pH of 7 = 6.023×10^{16} H^+// ℓ soln ($10^{23} \times 10^{-7}$); if the soln is H_20, this means 1 out of 550,000,000 H_20 molecules is dissociated.
Since pH of extracellular body fluids is normally 7.35-7.45, the H^+ concentration is *very, very* small. (Na^+ 40,000 X & K^+ is 1000 X more abundant)

C.b.B. METABOLIC ACID PRODUCTION

cellular respiration using complete oxidation~catabolism w glucose & other carbohydrates as high-energy electron source
–> $C0_2$ & the volatile acid, H_2C0_3, both of which are removed by the lungs

cellular respiration using oxidation~catabolism w proteins & fats or incomplete oxidation of carbohydrates as high-energy electron source
–> fixed~nonvolatile acids which are metabolized by the liver & removed by the kidneys

C.b.B.a. VOLATILE ACID PRODUCTION

$$C0_2 + H_20 \xleftrightarrow{\text{carbonic anhydrase}} H_2C0_3 \longleftrightarrow H^+ + HC0_3^- \qquad (E1)$$

if ↑ $C0_2$: ↑ $C0_2 + H_2O$ –> / H_2C0_3 –> / H^+ + / $HC0_3^-$ (E2)

if ↓ $C0_2$: ↓ $C0_2 + H_2O$ –> / H_2C0_3 –> / H^+ + / $HC0_3^-$ (E3)

C.b.B.b. FIXED ACID PRODUCTION

lipid oxidation –> ketoacids & phosphoric acid ⎫
protein oxidation –> sulfuric acid ⎬ starvation, diabetes (normal total = 50-100 mmol/day; immediately buffered to sodium salt of acid)
incomplete oxidation of carbohydrates –(1)–> lactic acid ⎭ anaerobic (Key: 1: CF III.A.-2: cellular respiration)

C.b.B.b.(A.) COMPENSATION

If ↑ H^+ is from ↑ fixed acid production, –>

$$\uparrow(H^+ + HC0_3^- \rightarrow H_2C0_3) \rightarrow \begin{cases} \rightarrow \downarrow HC0_3^- \\ \rightarrow (/\ H^+) \\ \rightarrow \uparrow H_2C0_3 \end{cases} \qquad (E4)$$

If ↓ H^+ is from ↓ in fixed acid production, –>

$$\uparrow(H_2C0_3 \rightarrow H^+ + HC0_3^-) \rightarrow \begin{cases} \rightarrow \uparrow HC0_3^- \\ \rightarrow (/\ H^+) \\ \rightarrow \downarrow H_2C0_3 \end{cases} \qquad (E5)$$

C.b.C. CALCULATION OF PLASMA pH

extracellular fluid pH = f(extent of H_2C0_3 dissociation & ratio $HC0_3^-$::$C0_2$ where both are expressed in mMol// ℓ)

pH = pK (H_2C0_3 buffer = 6.1 at normal body temps) + log $HC0_3^-$//CO_2 (modified Henderson-Hasselbach equation) (E6)
(example: normal ratio of $HC0_3^-$//$C0_2$ = 20::1 = 20; log 20 = 1.3 ∴ normal pH = 6.1 + 1.3 = 7.4)

ratio < 20:1 –> / plasma pH; reverse when ratio > 20:1

C.b.D. REGULATION OF pH

1) intracellular & extracellular acid-base buffering systems: rapid response (moment by moment), but very crude
2) respiratory elimination of $C0_2$: fairly rapid response (minutes) but loses its ability to regulate pH as pH nears normal
3) renal elimination of H^+ or $HC0_3^-$: slow (hours - days) but continues until pH is returned to normal/near normal

C.b.D.a. MAJOR ACID-BASE BUFFERING SYSTEMS

C.b.D.a.(A.) $HC0_3^-$ BUFFERING SYSTEM

strong acid + weak base –> weak acid + salt e.g.:
HCl + $NaHC0_3$ –> H_2C0_3 + NaCl

strong base + weak acid –> weak base + H_20 e.g.:
Na0H + H_2C0_3 –> $NaHC0_3$ + H_20

(plasma buffer & interstitial fluid buffer) (F 16.17, p 438) (TP IVC-1)

C.b.D.a.(B.) PHOSPHATE BUFFERING SYSTEM

strong acid + weak base –> weak acid + salt e.g.:
HCl + Na_2HP0_4 –> NaH_2P0_4 + NaCl

strong base + weak acid –> weak base + H_20 e.g.:
Na0H + NaH_2P0_4 –> Na_2HP0_4 + H_20

(especially important as a filtrate buffer in renal tubules, e.g. see T IVB-2, footnote b & F 16.19, p 439), but also as intracellular buffer TP IVC-2 TP IVC-1 (F 16.17, p 438)

C.b.D.a.(C.) PROTEIN BUFFERING SYSTEM

TP IVC-3
aa-H <–> aa^- + H^+ (F 12.7, p 312)

TP IVC-1
(especially important as an intracellular buffer) (Fig 16.17, p 436) but also works as plasma buffer (pp's)

C.b.D.b. RESPIRATORY CONTROL MECHANISMS

$C0_2$ readily crosses blood-**CSF** barrier to **CSF** where it reacts w H_20 –> H_2C0_3 –> H^+ + $HC0_3^-$
H^+ immediately stimulates respiratory center receptors in the 4th ventricle

C.b.D.c. RENAL CONTROL MECHANISMS

C.b.D.c.(A.) HYDROGEN ION & BICARBONATE ION COUNTERBALANCE (F 16.18, p 439, as modified) TP IVC-4

C.b.D.c.(B.) INTRATUBULAR BUFFERING SYSTEMS

phosphate buffering system (see C.b.D.a.(B.), above)
ammonia buffering system (F 16.19, p 439) TP IVC-2

C.b.E. ION EXCHANGE MECHANISMS & THEIR EFFECTS ON pH

C.b.E.a. K^+-H^+ ION EXCHANGE (F 16.20, p 440 & 16.21, p 440) TP IVC-5)

C.b.E.b. Cl^--$HC0_3^-$ ION EXCHANGE (chloride shift, F 12.7, p 312) TP IVC-6

in plasma at tissue: ↑ $C0_2$ –(E2)–> ↑ $HC0_3^-$ –> ↑ Cl^- into **RBC**; (at alveolus) ↓ $C0_2$ –(E3)–> ↓ $HC0_3^-$ –> ↑ Cl^- into plasma
NB: body Na^+ levels can influence this exchange by combining w $HC0_3^-$

C.c. ALTERATIONS IN ACID-BASE BALANCE

C.c.A. GENERAL

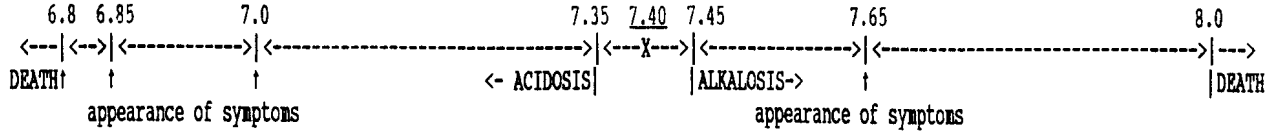

Figure IVC-1. Conditions Ascribed to Variations in Fluid pH TP IVC-7

acidosis~acidemia = ↓ alkali [biological bases involving an alkali metal such as Na^+ or K^+] or ↑ acids
alkalosis~alkalemia = ↑ alkali or ↓ acids

Since $NaHC0_3$ is the main extracellular alkali, & since its concentration is determined by $C0_2$ & $HC0_3^-$ levels, these two compounds are normally the ones that are tracked in acidosis/alkalosis.

C.c.A.a. METABOLIC VERSUS RESPIRATORY ACID-BASE DISORDERS

metabolic a-b disorders ↑ or ↓ in H^+ –(E4 & E5)–> ↓ or ↑ in $HC0_3^-$ –(E6)–> ↓ or ↑ in pH and metabolic acidosis or alkalosis, resp.

respiratory a-b disorders ↑ or ↓ in $C0_2$ –(E2 & E3) –>↑ or ↓ in H_2CO_3 –(E6)–> ↓ or ↑ in pH and respiratory acidosis or alkalosis, resp.

C.c.A.b. PRIMARY VERSUS COMPENSATORY MECHANISMS

primary mechanism (event that initiates alkalosis or acidosis)
compensatory mechanism (mechanism that attempts to maintain a homeostatic pH)
primary & compensatory *cannot* involve the same systems, ∴ lungs can correct for renal induced changes & *vice versa*

compensatory mechanisms become more effective w/ time, thus there are differences between the levels of pH changes that occur in acute acid-base disorders versus those that occur in chronic acid-base disorders

C.c.A.c. GENERAL MANIFESTATIONS OF ACID-BASE DISORDERS

1) those associated w/ the primary disorder

2) those related to the altered pH:

↑ H^+ => / H^+-K^+ exchange =(1)=> / extracellular K^+ –(2)–> < kalemia>
=(1)=> / intracellular K^+ =(3)=> lower resting potential: (remember, intracellular H^+ readily binds w/ the anionic proteins there) / distance => to threshold (polarization) –> / NERVE-MUSCLE EXCITABILITY~ IRRITABILITY potential

↓ H^+ =(4)=> < calcemia> =(5)=> / NERVE-MUSCLE EXCITABILITY~ IRRITABILITY

Key: 1: F 16.20: 1° acidosis –> 2° hyperkalemia
2: CF IVB-1: similarity in electrolyte concentration of interstitium & plasma
3: P IVB-4: discussion of resting potential & action potential
4: P IVB-9: w ↓ H^+, there is ↑ Ca^{++} binding to protein, instead of H^+
5: P IVB-10: ↓ Ca^{++} –> open Na^+ channels

Path IVC-1. Pathophysiological Consequences of Acidemia & Alkalemia on Nerve-Muscle Excitability HWA

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3) those related to the homeostatic, compensatory mechanism

C.c.B. METABOLIC ACIDOSIS [=(E4)=> primary deficit in plasma bicarbonate]

C.c.B.a. ETIOLOGIC FACTORS

1) increased metabolic acid gain by increased production of nonvolatile acids OR decreased renal secretion of acids (S IV.C.b.B.b.)

↑ production of non-volatile acids
↓ renal secretion of acids ==> / metabolic acid gain

2) elevated (excessive) $HC0_3^-$ loss

C.c.B.b. INCREASED METABOLIC ACID GAIN

1) ↑ lactic acid, 2) ↑ ketoacids, 3) inability of kidneys to excrete metabolic acids (or conserve bicarbonate)

1,2,3 => / H^+
$HC0_3^-$ =(1)=> / H_2C0_3
=(1)=> / $HC0_3^-$

Key: 1: E_4

Path IVC-2. General Relationship of Decreased pH to Decreased Bicarbonate Concentration

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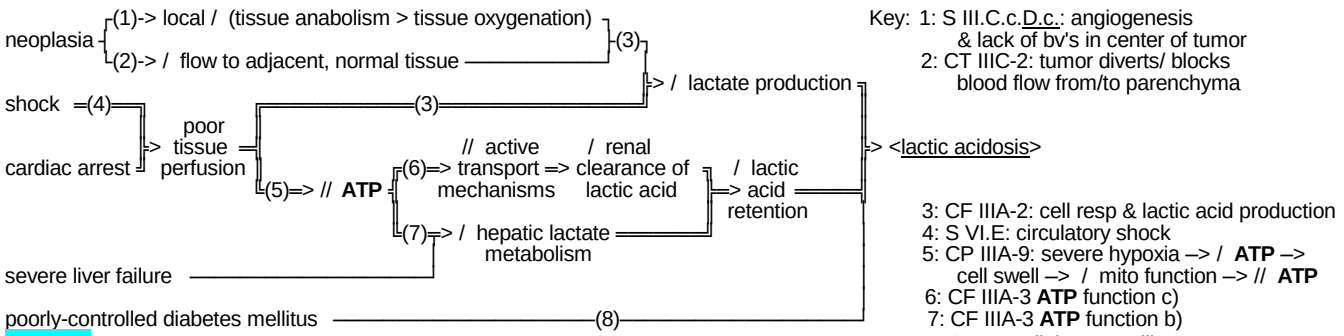
C.c.B.b.(A.) LACTIC ACIDOSIS

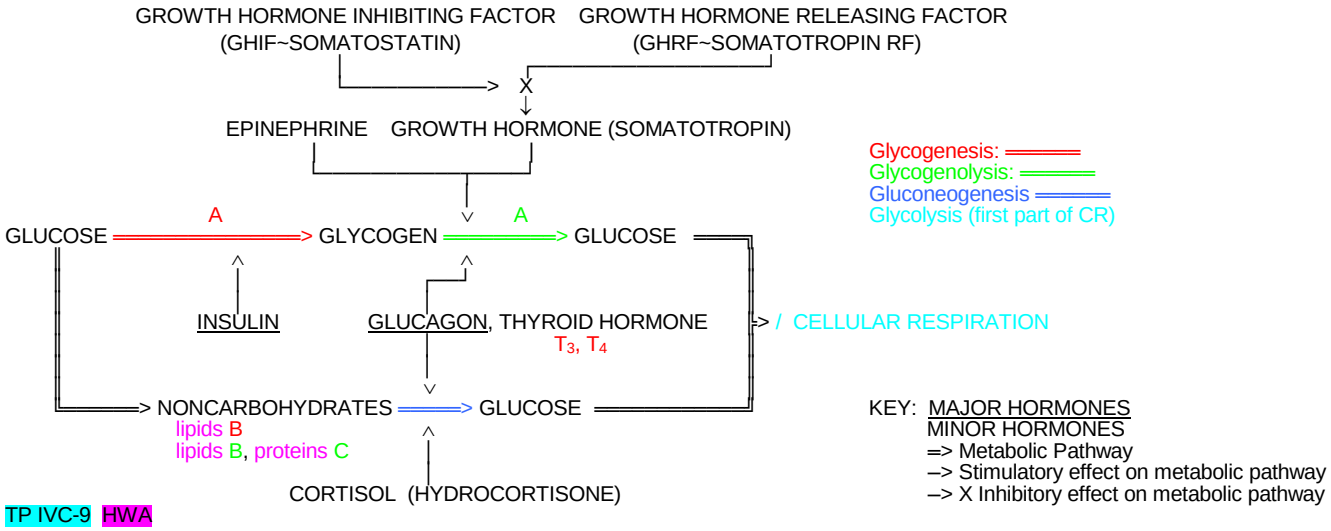


TP IVC-8

Path IVC-3. Etiology of Lactic Acidosis

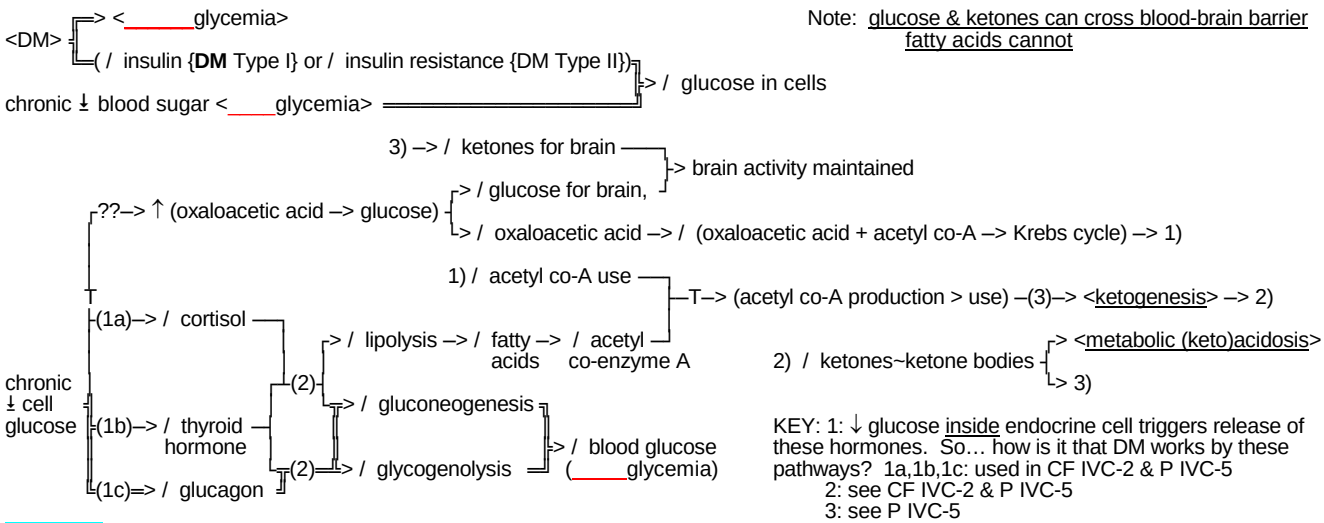
C.c.B.b.(B.) KETOACIDOSIS

C.c.B.b.(B.a.) KETOGENESIS



TP IVC-9 HWA

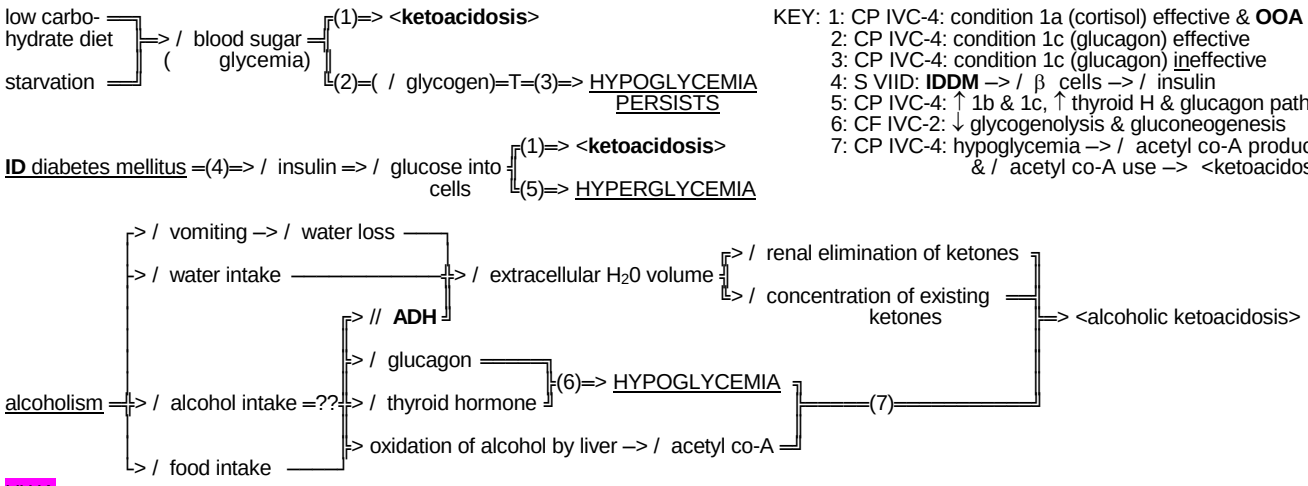
Critical Figure IVC-2. Hormones Responsible for the Four, "Big-G" Metabolic Processes



TP IVC-9a

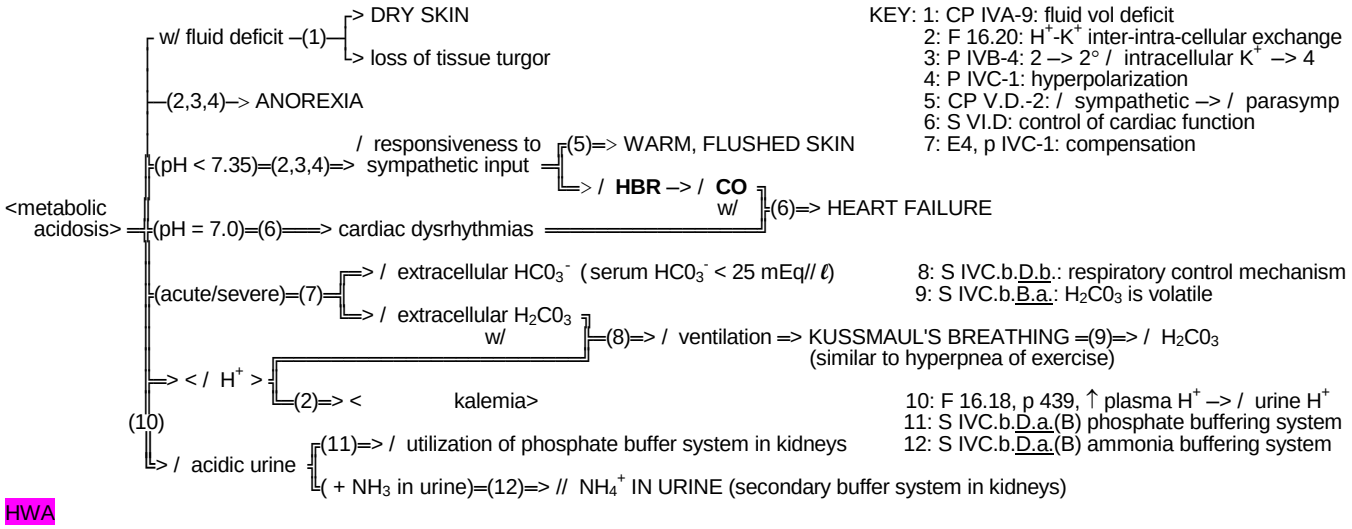
Critical Path IVC-4. Metabolic Pathways Triggered by Low Cellular Glucose Levels (14, pp 552 & 831) (SN 164, p376)

C.c.B.b.(B.b.) ETIOLOGY OF KETOACIDOSIS



Path IVC-5. Etiology of Ketoacidosis

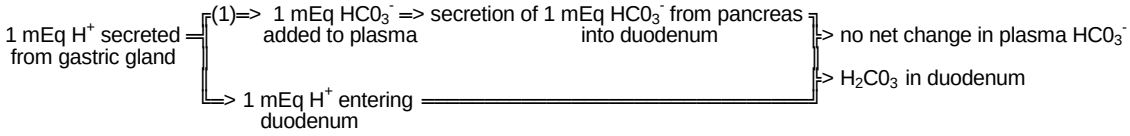
C.c.B.c. MANIFESTATIONS OF METABOLIC ACIDOSIS [plasma $HC0_3^-$ ≤ 20 mEq/ℓ]



Path IVC-6. Manifestations of Metabolic Acidosis

C.c.C. METABOLIC ALKALOSIS [primary ↑ in plasma $HC0_3^-$]

C.c.C.a. LOSS OF HYDROGEN IONS



Path IVC-7. Normal Course of Events Relative to H^+, Cl , & $HC0_3^-$ in the Stomach & Duodenum

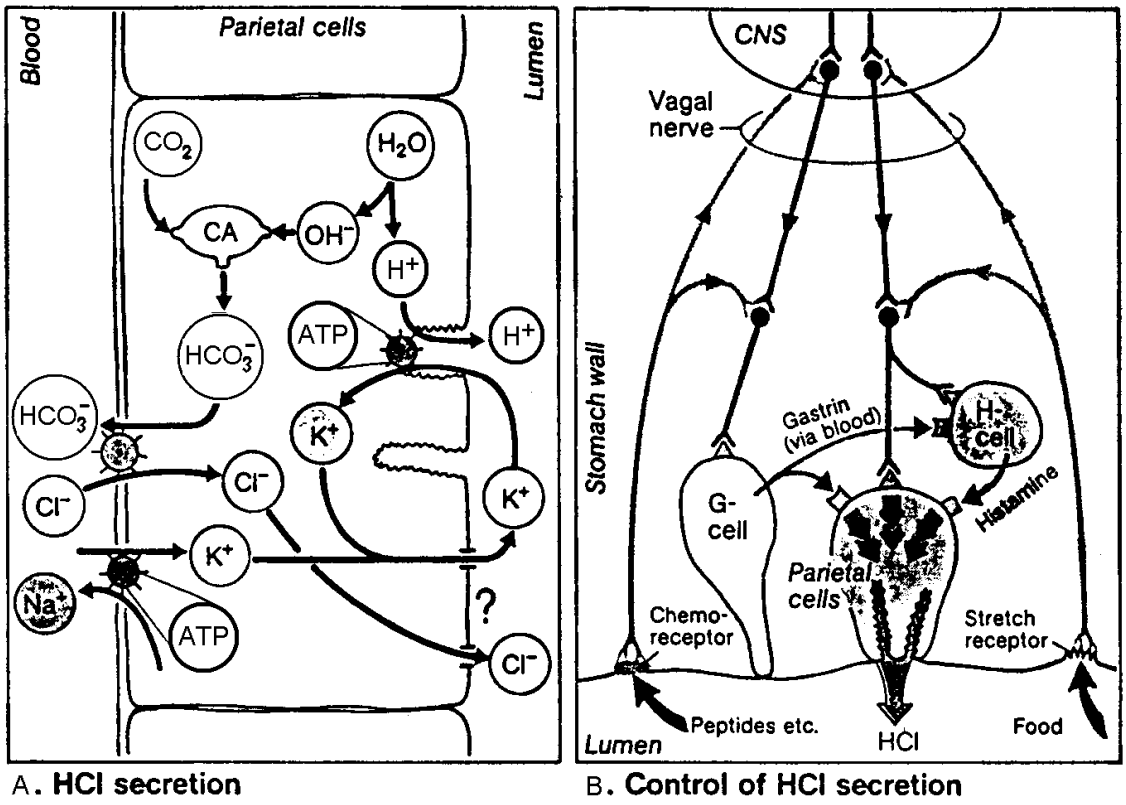


Figure IVC-3. Mechanism of HCl Secretion from Parietal Cell of Gastric Gland TP IVC-10

prolonged vomiting
nasogastric suction
=> loss of acidic stomach fluid ═══(1)═══

some diuretic therapies –> / Na^+ reabsorption upstream (in **PCT**) –> / Na^+ reabsorption downstream (**DCT**) –(2)–> hypokalemia –> / H^+-K^+ exchange –(3)=> / plasma H^+ =(E5)=> / HCO_3^-

hyperaldosteronism –(4)–> / H^+ secretion in kidneys

KEY: 1: P IVC-7. normal recycling of H^+ in the gut
2: F IVB-2: coupling of K^+ sec to Na^+ reabsorption
3: F 16.20: 1^o hypok –> 2^o ↓ H^+
4: F IVB-2: coupling of H^+ sec to Na^+ reabsorption

Path IVC-8. Etiology of Hydrogen Ion Loss (diuretic therapies from 36, p 497) HWA

C.c.C.b. ELEVATED $HC0_3^-$ RETENTION

two sources of $HC0_3^-$: $C0_2$ from cellular respiration [–(E1)–> $HC0_3^-$] or $HC0_3^-$ recycling by kidneys (F 16.18, p 439)

these two mechanisms normally work inversely to maintain a homeostatic $HC0_3^-$ level

excessive alkali ingestion (e.g. Alka-Selzer)

cardiopulmonary resuscitation –> $NaHCO_3$ administration

chronic respiratory acidosis ^ <—(1)— hyper-calcemia –(6)–> / respiration =(1,2)=> / H^+ =(3)=> / H^+ secretion =(4)=> reabsorption / HCO_3^-

NH_3 in filtrate =(5)=> in filtrate / NH_4^+

Cl^- in filtrate => in filtrate / NH_4Cl => / capacity for Cl^- in filtrate => / Cl^- secretion into filtrate => / Cl^- loss from plasma => anions in plasma => capacity of plasma to retain $HC0_3^-$

=> / Cl^- loss in urine

=> < / $HC0_3^-$ retention>

KEY: 1: E2: ↑ $C0_2$ –> / H^+
2: S IVC.c.E. (next page)
3: F 16.18a: ↑ H^+ –> / H^+ secretion
4: F 16.18a: ↑ H^+ secretion –> / HCO_3^- reabsorption
5: S IV.C.b.D.c.(B.) role of ammonia as filtrate buffer
6: P IVB-11: ↑ Ca^{++}–> / response of Na^+ channels

TP IVC-11

Path IVC-9. Etiology of Increased Bicarbonate Retention in Metabolic Alkalosis

C.c.D. RESPIRATORY ACIDOSIS [primary ↑ in plasma carbonic acid]

1) primary ↑ in $C0_2$ –(E2)–> / H_2C0_3 –> / H^+

C.c.D.a. ACUTE RESPIRATORY ACIDOSIS

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hypoventilation
defective respiratory movements
↑ $C0_2$ inhalation
=> / P_{C02} (_____capnea) => delayed signs ($C0_2$ diffuses across respiratory membrane 20X faster than 0_2)
=> / P_{02} (_____xemia) => SIGNS & SYMPTOMS (S VII.A) (below)

HWA

Path IVC-10. Etiology of Conditions Leading to Acute Respiratory Acidosis

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C.c.D.b. CHRONIC RESPIRATORY ACIDOSIS

COPD => / P_{CO_2} =(1)=> <chronic respiratory acidosis> => / H^+ =(3)=> / renal H^+ secretion
=(3)=> / renal $HC0_3^-$ reabsorption
=> near normal pH => drives medullary respiratory center => 1)
=> in brain => vasodilation => / **CSF** =(2)=> HEADACHE, ETC.
/ H^+ no longer
TP IVC-13

w/

<intercurrent respiratory infection> =(4)=> / hypoxemia => treat w/ / 0_2)
=> abolished ventilatory drive => // ventilation => 2)

1) => shift to dependence upon 0_2 receptors in carotid bodies

2) =(5)=> worsening of ventilation::perfusion ratio
=> / RATE OF RESPIRATION
=> / DEPTH OF RESPIRATION
=> // P_{0_2}
=> rapid // arterial P_{CO_2} =(1)=> // H_2CO_3 => <acute respiratory acidosis>
=> LIFE-TREATENING SITUATION

KEY: 1: (E2): / $CO_2 \rightarrow$ / H^+
2: CP VA-4: from stress to pain
3: F16.18a: ↑ H^+ secretion → / $HC0_3^-$ reabsorption
4: S VI.G: Respiratory Function; retained secretions & bronchopasm
5: S.VI.G: Respiratory Function

TP IVC-12
portions used 60, p 128-9

Path IVC-11. Manifestations of Chronic & Acute Respiratory Acidosis

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C.c.E. RESPIRATORY ALKALOSIS [primary ↓ in plasma carbonic acid]

1) primary ↓ in $C0_2$ –(E3)–> / H_2C0_3 –> / H^+

2) hyperventilation => / removal of $C0_2$ =(E3)=> / $HC0_3^-$ =(E6)=> <respiratory alkalosis>
=(1)=> // H_2C0_3

Key: 1: S IV.C.b.B: H_2C0_3 is volatile

C.d. SUMMARY

ACIDOSIS (/ pH)

Metabolic (changes in $HC0_3^-$)
↑ H^+ => / (H^+ + $HC0_3^-$ => H_2C0_3) => / H^+ + / $HC0_3^-$ E4
↓ H^+ => / (H_2C0_3 => H^+ + $HC0_3^-$) => / H^+ + / $HC0_3^-$ E5

ALKALOSIS (/ pH)

ACIDOSIS (/ pH)

Respiratory (changes in H_2C0_3)
↑ $C0_2$ => / H_2C0_3 => / H^+ E2
↓ $C0_2$ => / H_2C0_3 => / H^+ E3

ALKALOSIS (/ pH)