Renal Tubular Acidosis

Marc Goldstein, M.D.

University of Toronto, Canada

RENAL TUBULAR ACIDOSIS

Metabolic acidosis due to failure of the renal regulation of ACID-BASE BALANCE

RENAL REGULATION OF ACID-BASE BALANCE

- REABSORPTION OF FILTERED HCO_3^-
- REGENERATION OF CONSUMED HCO_3^-

PROXIMAL HCO_3^- REABSORPTION

NH_3

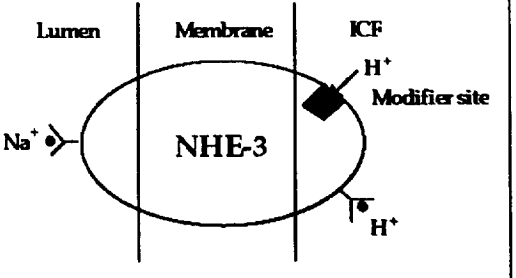
HIGH CAPACITY, LEAKY MEMBRANE

NO STEEP H^+ GRADIENT.

FAILURE OF PROXIMAL H^+ SECRETION :

PROXIMAL RTA

PROXIMAL TUBULE Na^+/H^+ EXCHANGER



REGULATION OF PROXIMAL H^+ SECRETION

- **INTRA CELLULAR [H^+]**
- **LUMINAL [H^+]**
- **STIMULI FOR Na^+ REABSORPTION**
- PARATHYROID HORMONE

BICARBONATE "REABSORPTION"

- 85-90% OF FILTERED HCO_3^- IS REABSORBED IN THE PCT
- 500 mmoles LEAVE PCT and 100 mmoles ENTER DCT
- 400 MMOLES REABSORBED BY PARS RECTA OF PCT OR TAL OF LOH

All mediated by NHE-3

PROXIMAL RTA

ACIDEMIA DESPITE HCO_3^- ADMINISTRATION

BICARBONATURIA DESPITE ACIDEMIA (>15% FILTERED LOAD)

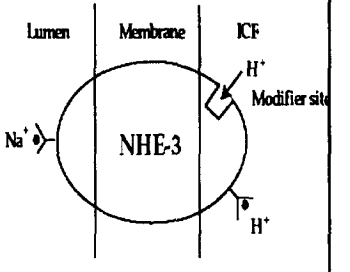
ASSOCIATED DEFECTS

GLUCOSURIA, PHOSPHATURIA

AMMINO ACIDURIA

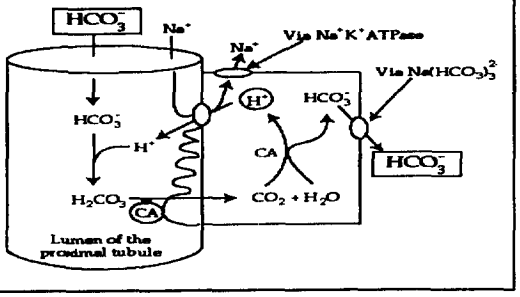
MECHANISM

- DEFECTIVE TRANSPORTER
- ALKALINIZATION OF THE PROXIMAL TUBULAR CELL



ALKALINIZATION OF PROXIMAL TUBULAR CELL

- BICARBONATE EXIT STEP



DIAGNOSIS

- ACIDEMIA IS ASSOCIATED WITH REDUCED CITRATE EXCRETION DUE TO INCREASED ICF [H^+].
- PROXIMAL RTA DUE TO ALKALINIZED CELL WILL HAVE NORMAL CITRATE EXCRETION

NEW HCO_3^- SYNTHESIS

Bicarbonate Regeneration

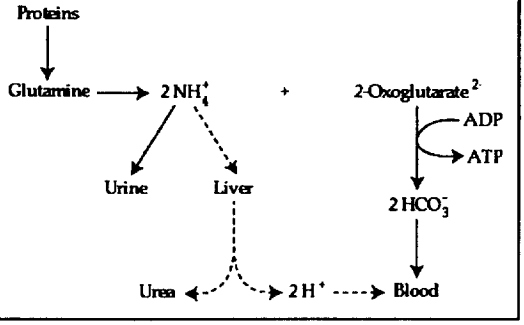
- **NH_4^+ EXCRETION**
  - **AMMONIAGENESIS**
  - **NH_4^+ TRAPPING**
    - ***INCREASED pNH_3***
    - ***DISTAL H^+ SECRETION***

AMMONIAGENESIS

- **PCT:** GLUTAMINE TO NH_4^+ & HCO_3^-
- GENERATES ATP
- NH_4^+ ENTERS PCT ON NHE-3
- STIMULI:
  - ***CHRONIC METABOLIC ACIDOSIS***
  - ***HYPOKALEMIA***

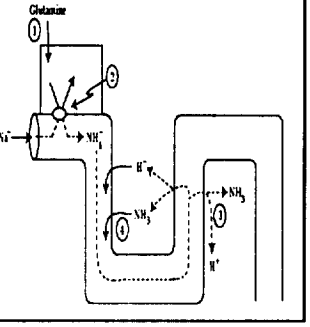
AMMONIAGENESIS ACID-BASE IMPACT

Importance of NH_4^+ Excretion



GENERATION OF MEDULLARY pNH_3

- **NH_4^+ REABSORPTION IN TAL .**
- **$[NH_3]$ RISES IN MED. INTERSTITIUM**
- **NH_3 ENTERS DESC. LIMB LOH**
- **MEDULLARY pNH_3 RISES**

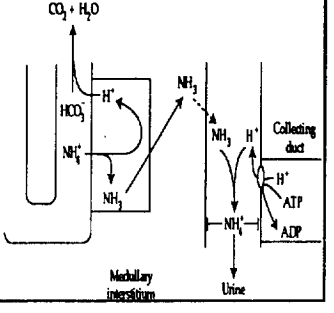


NH_4^+ TRAPPING IN COLLECTING DUCT

The role of H^+ secretion

① NH_3 ATTRACTED BY LOW CD $[NH_3]$
$NH_3 + H^+ \rightarrow NH_4^+$

② NH_3 TRAPPED IN CD AS NH_4^+ AS A RESULT OF H^+ SECRETION



DISTAL NEPHRON H^+ SECRETION

H^+ATPase

LOW CAPACITY STEEP GRADIENT

- REABSORB 100 MMOLES HCO_3^-
- PROMOTE NH_4^+ EXCRETION

NH_4^+ EXCRETION IS HCO_3^- GENERATION

Impaired NH_4^+ excretion is Distal RTA

CAN FAIL DUE TO:

IMPAIRED AMMONIAGENESIS

MEDULLARY DISEASE

IMPAIRED DISTAL H^+ SECRETION

IF ENHANCED NH_4^+ EXCRETION IS ABSENT IN ACIDEMIA

The diagnosis is Renal Tubular Acidosis

DIAGNOSTIC TESTS FOR DISTAL RTA

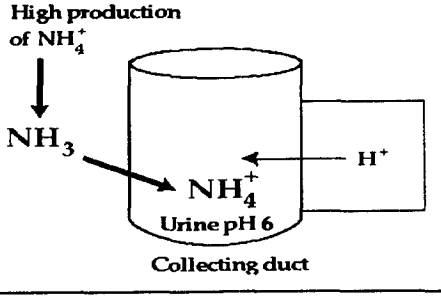
- **URINE pH (Not a good test)**
- **URINE NH_4^+ EXCRETION**
  URINE NET CHARGE
  URINE OSMOLAR GAP
- **URINE PCO_2**

WHAT DOES URINE pH REVEAL?

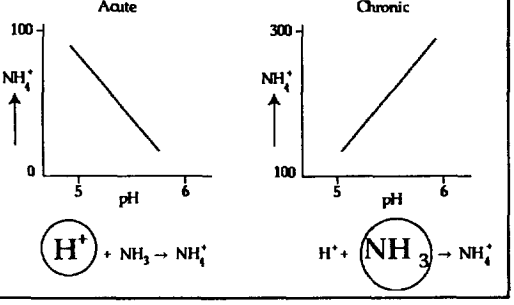
BICARBONATURIA

IMPAIRED AMMONIAGENESIS

FAILURE OF URINE pH TO PREDICT ACID EXCRETION



URINE pH and RENAL ACID EXCRETION



IS DISTAL RTA PRESENT?

Assess NH_4^+ Excretion

NH_4Cl: URINE NET CHARGE

URINE :$[Na^+ + K^+] - [Cl^-]$ = NEGATIVE

NH_4A: URINE OSMOLAL GAP

U_{OSM} MEASURED VS CALC

U [Na+K]X2 +[GLUCOSE] + [UREA]

NH_4^+ EXCRETION IS HCO_3^- GENERATION

Impaired NH_4^+ excretion is Distal RTA

CAN FAIL DUE TO:

IMPAIRED AMMONIAGENESIS

MEDULLARY DISEASE

IMPAIRED DISTAL H^+ SECRETION

IMPAIRED AMMONIAGENESIS

- **IN THE PRESENCE OF NORMAL DISTAL NEPHRON H^+ SECRETION**

The Urine pH will be low (<5.0)

WHY IS AMMONIAGENESIS IMPAIRED?

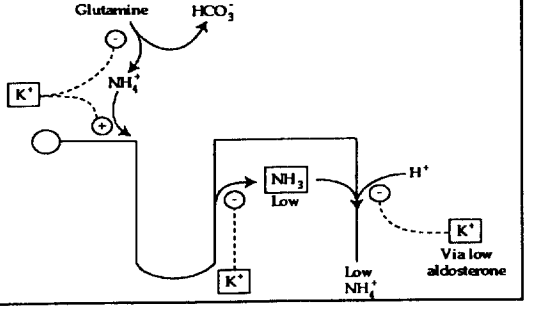
GLUTAMINE DEFICIENCY

ATP LIMIT

HYPERKALEMIA

ALKALINE PROXIMAL CELL

IMPACT OF HYPERKALEMIA ON NH_4^+ EXCRETION



MEDULLARY DEFECT

MAXIMUM URINE OSMOLALITY WITH WATER DEPRIVATION

DISTAL H^+ SECRETION DEFECT

- **PUMP DEFECT:**

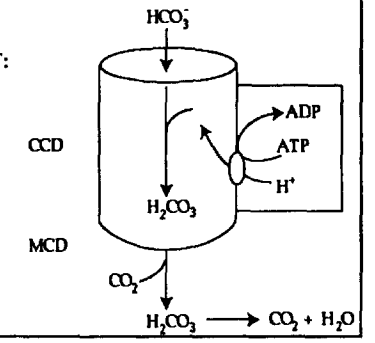
INTERSTITIAL DISEASE
IMMUNE COMPLEXES (SJOGRENS)
CHLORIDE SHUNT
LOW ALDOSTERONE BIOACTIVITY
IMPAIRED HCO_3^- EXIT

DISTAL H^+ SECRETION DEFECT

- **PUMP DEFECT:**

How to make the diagnosis?

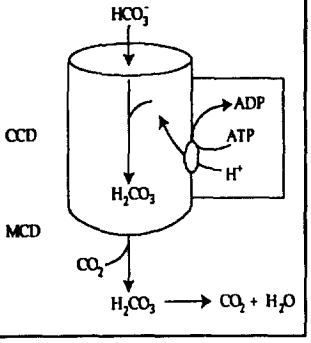
PCO_2 OF ALKALINE URINE



DISTAL H^+ SECRETION DEFECT

- **BACK LEAK OF H^+:**
  AMPHOTERICIN B

PCO_2 OF ALKALINE URINE



POTASSIUM AND RTA

- ***Patients with RTA may have hypokalemia***
  BICARBONATURIA PROMOTES K^+ EXCRETION.

- ***Patients with RTA may have hyperkalemia***
  HYPERKALEMIA CAUSES IMPAIRED AMMONIAGENESIS.
  IMPAIRED DISTAL Na^+ REABSORPTION IMPAIRS BOTH H^+ AND K^+ SECRETION.