THE HYPERKALEMIC SYNDROMES
**K⁺ BALANCE**

- **Cells (3400 mEq)**
- **ECF (60 mEq)**
- **External**
- **Intake**
- **Renal output**
- **Distal Na⁺ delivery**
- **Aldosterone**
- **Lumen voltage**

**Pump**
- **Insulin catechols**

**Leak**
- **pH; osmolality**
- **Membrane integrity**

- **K⁺ delivery**
- **K⁺ intake**
## TWO KINDS OF HYPERKALEMIC SYNDROMES

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RENAL HANDLING OF K$^+$

I. Complete proximal reabsorption

II. Aldo-mediated principal cell secretion
THE CCD PRINCIPAL CELL

Na

3Na

2K

K

Cl

- 20 mV

- 80 mV

0 mV

ATPase

• Predominant in late DCT and CCT

• Aldosterone-responsive

• Sensitive to: amiloride triamterene spironolactone

amiloride

K

Cl
ENaC
Epithelial Na Channel

- Each $\alpha$ subunit: amiloride-sensitive Na channel
- $\beta$ and $\gamma$ subunits: ↑surface delivery of ENaC
- Liddle's syndrome: $\beta$ subunit mutation
- pseudohypoaldo I: $\alpha$ or $\beta$ subunit mutation
- ARDS: $\alpha$ subunit mutation

News in Physiol. Sci.
12:55, 1997
MAJOR CAUSES OF HYPERKALEMIA

I. Diminished Renal Excretion
   - Reduced GFR
     - ATN
     - ESRD
   - Reduced Tubular Secretion
     - Addison’s disease
     - DCT disease
     - Principal cell disease
     - Potassium - sparing diuretics

II. Transcellular Shifts
   - Acidosis
   - Cell destruction
   - HPP
   - Diabetic hyperglycemia
   - Insulin - dependence
     - plus aldosterone lack
   - Depolarizing muscle paralysis
WNK 1, 4 mutations activate thiazide-sensitive NaCl transporter

- ↑ shunt Cl permeability; paracellin-mediated
- Na avid
- ↓ \( V_M \)
- ↓ K, H secretion: CCT
- low renin hypertension
- responsive to diuretics, Na restriction

DISTAL CONVOLUTED TUBULE DISEASE
GORDON’S SYNDROME (PSEUDOHYPOALDOSTERONISM II)
GORDON'S SYNDROME

A DCT DISEASE

WNK: with no lysine
WNK I: ↑ NCC activity
WNK IV: function unknown

Yang et al.
JCI 111:1039, 2003
# Hyperkalemic RTA Syndromes

## Principal Cell Disorders

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<th>Disorder</th>
<th>Principal Defect</th>
<th>Principal Features</th>
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<td>Pseudohypoaldosteronism I</td>
<td>Closed Na⁺ channel</td>
<td>↑K⁺; Na⁺ wasting; RTA</td>
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<tr>
<td>Interstitial disease</td>
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**Na\(^+\) CHANNEL BLOCKADE (PSEUDOHYPOALDOSTERONISM I)**

**Na Channel Blockade:**
- Prototype: amiloride Rx
- Na wasting
- ↓ \( V_M \)
- ↓ K, H secretion
- Aldosterone unresponsive
- \( \alpha \) or \( \beta \) subunit mutations in ENaC

**Principal Cell Diseases**

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Na Channel Blockade:
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PRINCIPAL CELL DISEASES
HYPORENINEMIC HYPOALDOSTERONISM
(GENERALIZED DISTAL NEPHRON DISEASE)

- Interstitial renal disease
- ↓ renin, aldosterone
- Na wasting
- ↓ V_M
- ↓ K, H secretion
- low renin hypertension
- furosemide benefits
TREATMENT REGIMENS FOR HYPERKALEMIA

K⁺ REMOVAL

KAYEXALATE: APPROXIMATELY 1 mEq K / Gm RESIN
(30 - 50 mEq / 30 - 60 MINUTES)

HEMODIALYSIS: K⁺ CLEARANCE: 200 ml / MINUTE
(85 mEq / HR)

PERITONEAL DIALYSIS: K⁺ CLEARANCE: 20 - 25 ml / MINUTE
(8.5 - 10 mEq / HR)

K⁺ ENTRY INTO CELLS

ALKALINIZATION: 0.6 mEq K⁺ / 0.1 pH UNIT

GLUCOSE AND INSULIN: 0.5 mEq K⁺ / 25 Gm GLUCOSE
CARDIAC PROTECTION IN HYPERKALEMIA

$Ca^{++} \text{ SCREENING OF SURFACE POTENTIAL}$

(A) High $[Ca^{2+}]_o$
- $\psi_0 = 0$
- $E_M = \text{resting potential}$

(B) Zero $[Ca^{2+}]_o$
- $\psi_0 = \text{negative}$
- $E_M = \text{resting potential}$
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HYPERKALEMIC PERIODIC PARALYSIS
A SKELETAL MEMBRANE DISORDER

• TTX-sensitive Na⁺ channel mutations

• Chromosome 17 mutation
  \[ \text{HPP}\]
  \[ \text{paramyotonia}\] \} \text{allelic variants}

• Human form: often with familial inbreeding
  Equine form: inbred quarter-horses

• HPP: episodic; may occur with normal K⁺ levels
  \[ \text{paramyotonia: cold-sensitive}\]

• K-sensitive; acetazolamide-responsive
# Properties of Some Na⁺ Channels

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<th>TTX - SENSITIVE</th>
<th>TTX - INSENSITIVE</th>
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<td><strong>Primary location</strong></td>
<td>Brain, Muscle</td>
<td>Heart</td>
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<tr>
<td><strong>Activation voltages</strong></td>
<td>- 60 (mV)</td>
<td>- 75 (mV)</td>
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THE GREAT HODGKIN-HUXLEY CONTRIBUTION

CLASSICAL CYCLE OF ELECTRICAL EXCITATION

Δ Membrane potential
Ionic fluxes
Gating of channels
Other stimuli
Other transport mechanisms
The Voltage Clamp Technique

Squid axon
outside
inside voltage sensitive

Command voltage
differential amplifier
THE HODGKIN-HUXLEY
EXPERIMENTAL STRATEGY

$E_M$

$-9 \text{ mV}$

$-65 \text{ mV}$

$I_M$

$\text{(mA/cm}^2\text{)}$

0

1

$10\% \text{ Na}$

$100\% \text{ Na}$

$I_{Na}$

$0$

$-1$

$\text{(C) Difference current}$

Time after start of test pulse (ms)

Hodgkin and Huxley, 1952
ELECTROPHYSIOLOGIC APPROACHES

VESICLE FUSION INTO BILAYERS

EXCISED PATCH TECHNIQUE

LOW-RESISTANCE SEAL

SUCTION

CELL-ATTACHED MODE (GIGAOHM SEAL)

DETACHMENT BY PULLING

EXCISED-PATCH MODE (INSIDE-OUT)

(STRYER, 1988)
MACROSCOPIC AND SINGLE Na⁺ CHANNEL BEHAVIOR

A. Traditional voltage clamp - Large membrane area
   
   voltage: -20 mV, -90 mV
   current: macroscopic sodium current

B. Patch Clamp - Very small membrane area
   
   voltage: -20 mV, -90 mV
   current: single records, single channel currents
   sum of 1000 records, macroscopic current
CATION CHANNEL KINETICS

Ptáček
Na$^+$ CHANNEL INACTIVATION: KEY FEATURES

1. INACTIVATION IS NOT, STRICTLY, VOLTAGE-DEPENDENT

2. ACTIVATION GATES MUST OPEN BEFORE INACTIVATION GATES CLOSE

3. THE SEEMING VOLTAGE-DEPENDENCE OF INACTIVATION RELATES TO THE VOLTAGE-DEPENDENCE OF ACTIVATION GATE OPENING
VOLTAGE-GATED CATION CHANNELS

Ptáček
SODIUM CHANNEL ACTIVITY: NORMAL

RESTING

OUT

IN

\[ V_M = -90 \]

LOW \( P_{Na} \)

ACTIVATION

\[ V_M \approx +20 \]

HIGH \( P_{Na} \)

INACTIVATION

\[ V_M \approx -50 \]

LOW \( P_{Na} \)

REPOLARIZATION

\[ V_M \approx -70 \]

LOW \( P_{Na} \)
HYPERKALEMIC PERIODIC PARALYSIS
A SKELETAL MEMBRANE DISORDER

- TTX-sensitive Na\(^+\) channel mutations
- Chromosome 17 mutation
  - HPP
  - paramyotonia
  - \{ allelic variants \}
- Human form: often with familial inbreeding
  - Equine form: inbred quarter-horses
- HPP: episodic; may occur with normal K\(^+\) levels
  - paramyotonia: cold-sensitive
- K-sensitive; acetazolamide-responsive
THE MAGNIFICENT FLAWED THOROUGHBRED
Pillars of the STUD BOOK
James Weatherby, 1791

Godolphin Arabian
1725

Darley Arabian
1688

Byerley Turk
1690
PILLARS OF THE
STUD BOOK

All Thoroughbred Genes

<table>
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<tr>
<th>ANCESTOR</th>
<th>PERCENT OF GENES IN PRESENT POPULATION</th>
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<tbody>
<tr>
<td>GODOLPHIN ARABIAN</td>
<td>14.6</td>
</tr>
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<td>DARLEY ARABIAN</td>
<td>7.5</td>
</tr>
<tr>
<td>CURWEN BAY BARB</td>
<td>5.6</td>
</tr>
<tr>
<td>BYERLEY TURK</td>
<td>4.8</td>
</tr>
<tr>
<td>BETHEL'S ARABIAN</td>
<td>3.3</td>
</tr>
<tr>
<td>WHITE DARCY TURK</td>
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<tr>
<td>OLD BALD PEG (MARE)</td>
<td>3.1</td>
</tr>
<tr>
<td>ST. VICTOR BARB</td>
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</tr>
<tr>
<td>LISTER TURK</td>
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<tr>
<td>LEEDES ARABIAN</td>
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32.5

50.3

SCIENTIFIC AMERICAN MAY, 1991
QUARTER HORSES

1. Sprint races ~ 0.25 miles
2. Primarily aerobic
3. Selective in-breeding: very muscular
4. Continued in-breeding:
   - HPP
   - Laryngeal neuropathy
   - Yearling osteoarthritis
THE HYPP INDEX HORSE

Impressive
1985 Fee: $15,000

We are pleased to announce that we have purchased all of Richard Brown's and Brown Quarries interest in Impressive. We thank the Brown family for selling this great stallion to us.

Faulkner Quarter Horses
Route 4 - Box 770 - Interstate 35 and Waterloo
Edmond, Oklahoma 73034  Exit 146
Allen E. Faulkner • (405) 341-8626
SODIUM CHANNEL ACTIVITY: HPP

RESTING

OUT

IN

V_M = -90

LOW P_{Na}

ACTIVATION

V_M ≅ +20

HIGH P_{Na}

HPP: TTX - SENSITIVE MUSCLE FIBERS

1. FAILURE OF INACTIVATION GATES TO CLOSE

2. PERSISTENT TTX - SENSITIVE i_{Na}
Na⁺ CHANNEL DEFECT IN HPP

Ptáček, 1998
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PARTIAL DEPOLARIZATION INACTIVATES CARDIAC ACTION POTENTIAL
THE CARDIAC ACTION POTENTIALS

GATING Ca^{++} Na^{+} Na^{+} Ca^{++} Na^{+} Na^{+}

TSIEN & HESS, 1986
SODIUM CHANNEL ACTIVITY: HYPERKALEMIA

RESTING

\[
 V_M = -70 \\
 \text{LOW} \ P_{Na}
\]

ACTIVATION

\[
 V_M \approx -20 \\
 \text{LOW} \ P_{Na}
\]

CARDIOTOXICITY

1. \( \uparrow K^+ \) DEPOLARIZES \( V_M \)
2. ACTIVATION GATES PARTIALLY OPEN
3. INACTIVATION GATES CLOSED
4. \( i_{Na} \) BLOCKED
SODIUM CHANNEL ACTIVITY: HPP

RESTING

VM = -90
LOW P_{Na}

ACTIVATION

VM ≈ +20
HIGH P_{Na}

HPP: TTX - SENSITIVE MUSCLE FIBERS

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SODIUM CHANNEL ACTIVITY: HYPERKALEMIA

RESTING

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$V_M = -70$

LOW $P_{Na}$

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CARDIOTOXICITY

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3. INACTIVATION GATES CLOSED

4. $i_{Na}$ BLOCKED