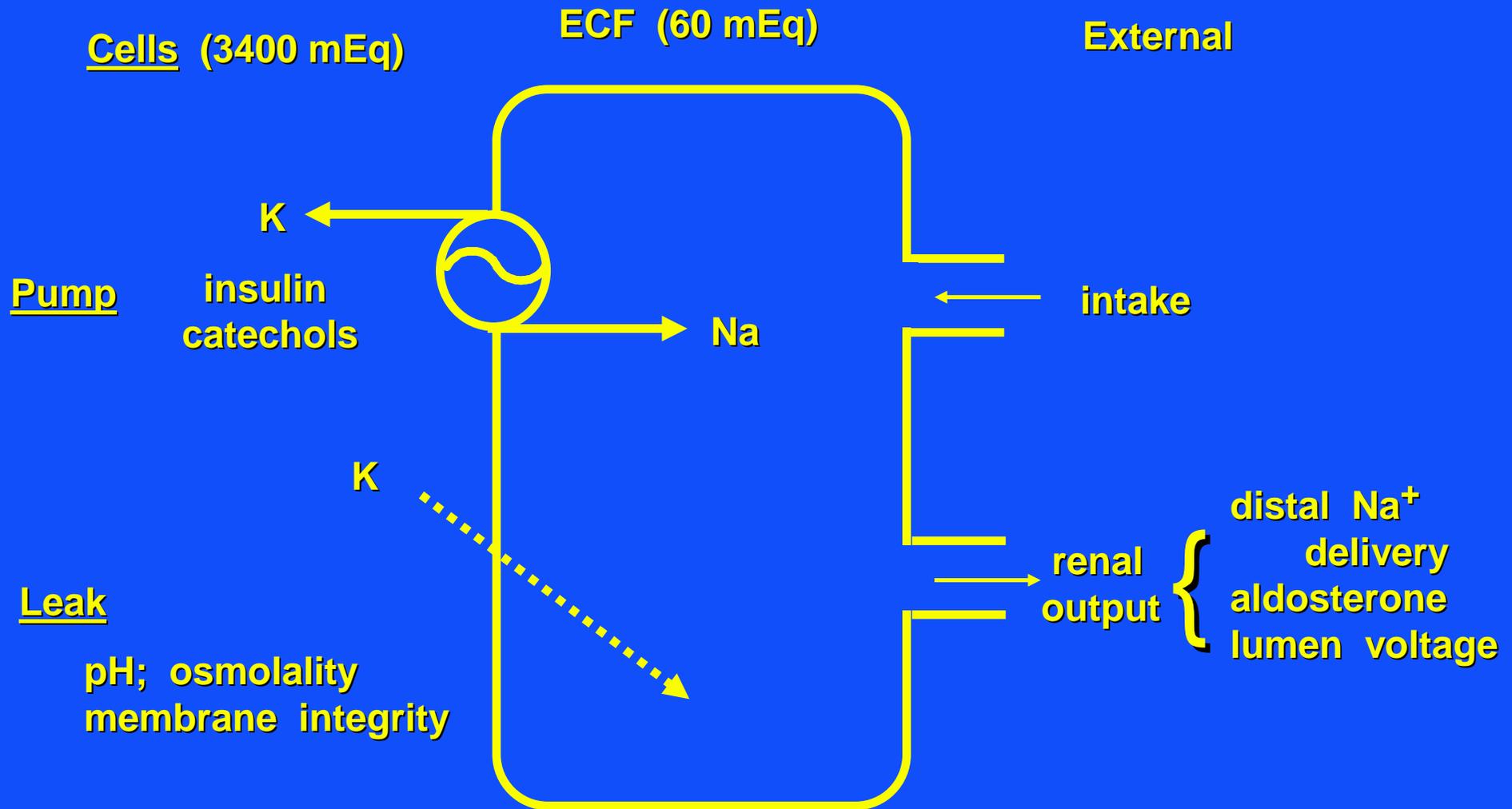


# **THE HYPERKALEMIC SYNDROMES**

# K<sup>+</sup> BALANCE



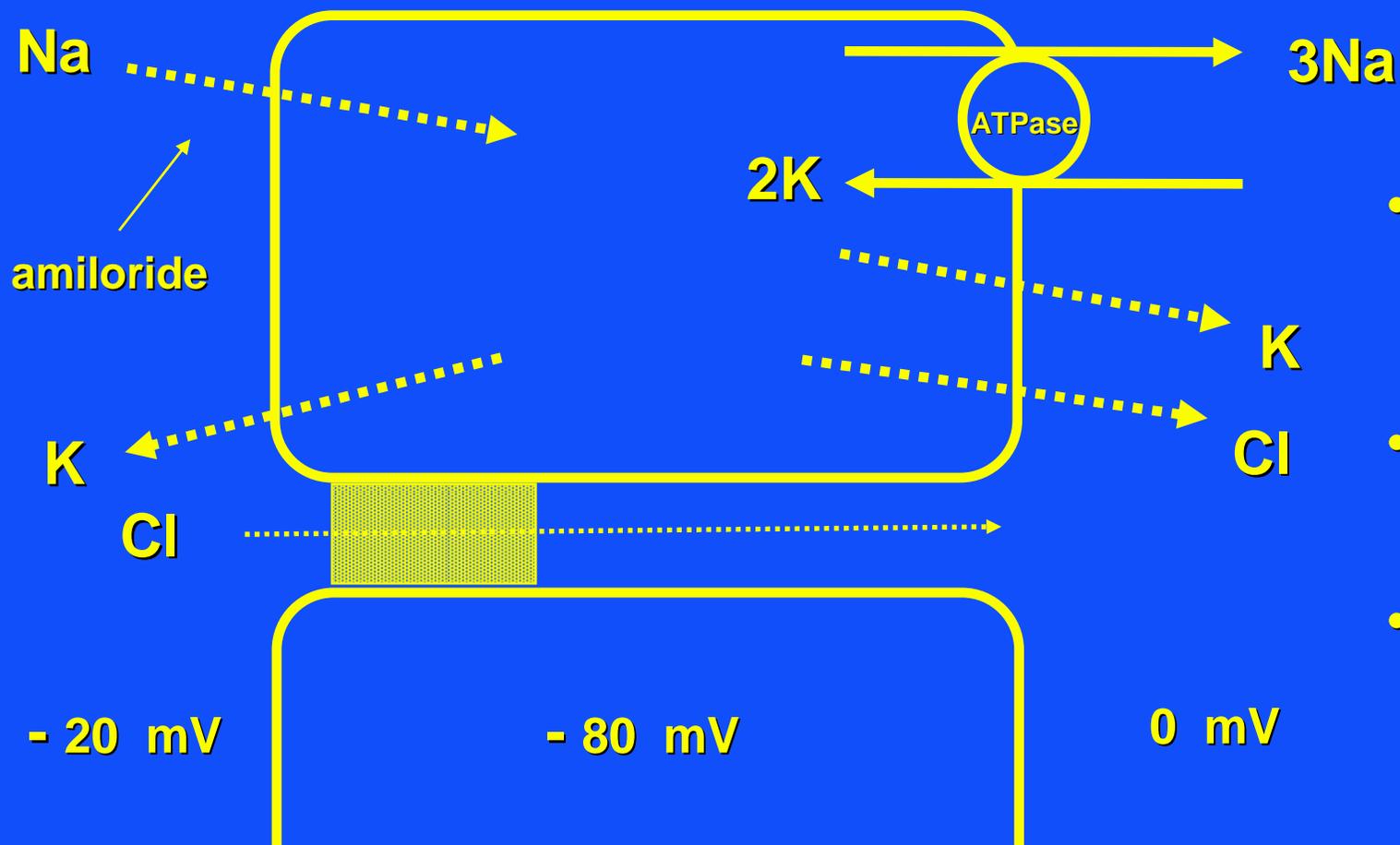
# TWO KINDS OF HYPERKALEMIC SYNDROMES

<u>Fiber</u>	<u>Activation Threshold</u>	<u>Disorder</u>
Skeletal muscle <i>TTX - sensitive</i>	- 60	{ periodic paralysis heart generally unaffected
Myocardium <i>TTX - insensitive</i>	- 75	{ cardiac standstill rare skeletal muscle paralysis

# RENAL HANDLING OF $K^+$

- I. Complete proximal reabsorption
- II. Aldo-mediated principal cell secretion

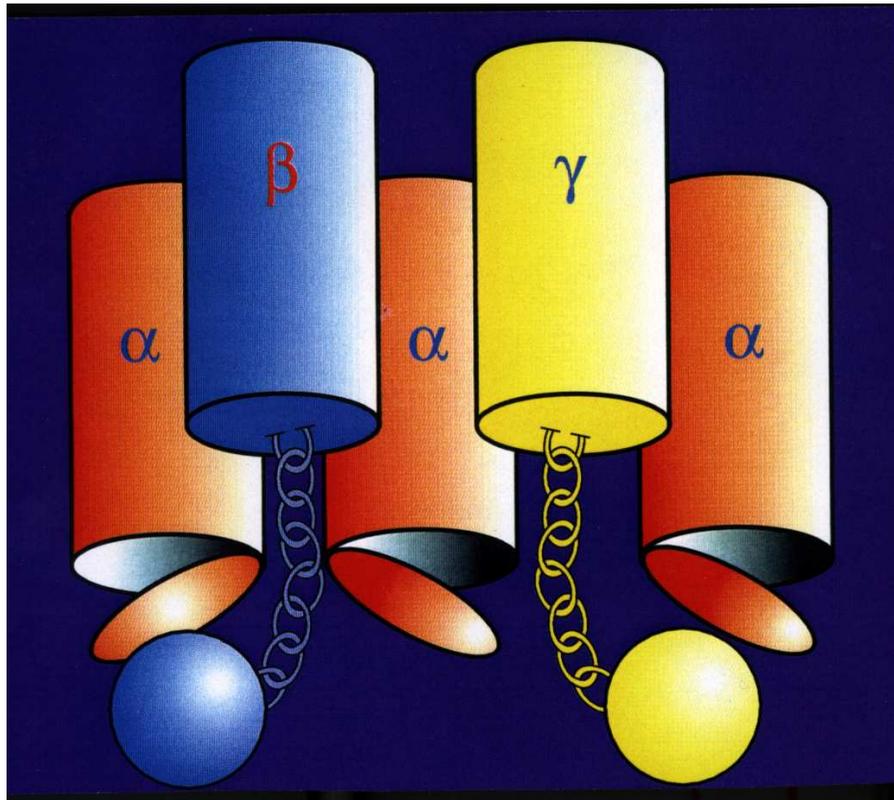
# THE CCD PRINCIPAL CELL



- Predominant in late DCT and CCT
- Aldosterone-responsive
- Sensitive to:
  - amiloride
  - triamterene
  - spironolactone

# ENaC

## *Epithelial Na Channel*



- Each  $\alpha$  subunit :  
*amiloride-sensitive Na channel*
- $\beta$  and  $\gamma$  subunits:  
 $\uparrow$  *surface delivery of ENaC*
- Liddle's syndrome:  
 *$\beta$  subunit mutation*
- pseudohypoaldosteronism 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*

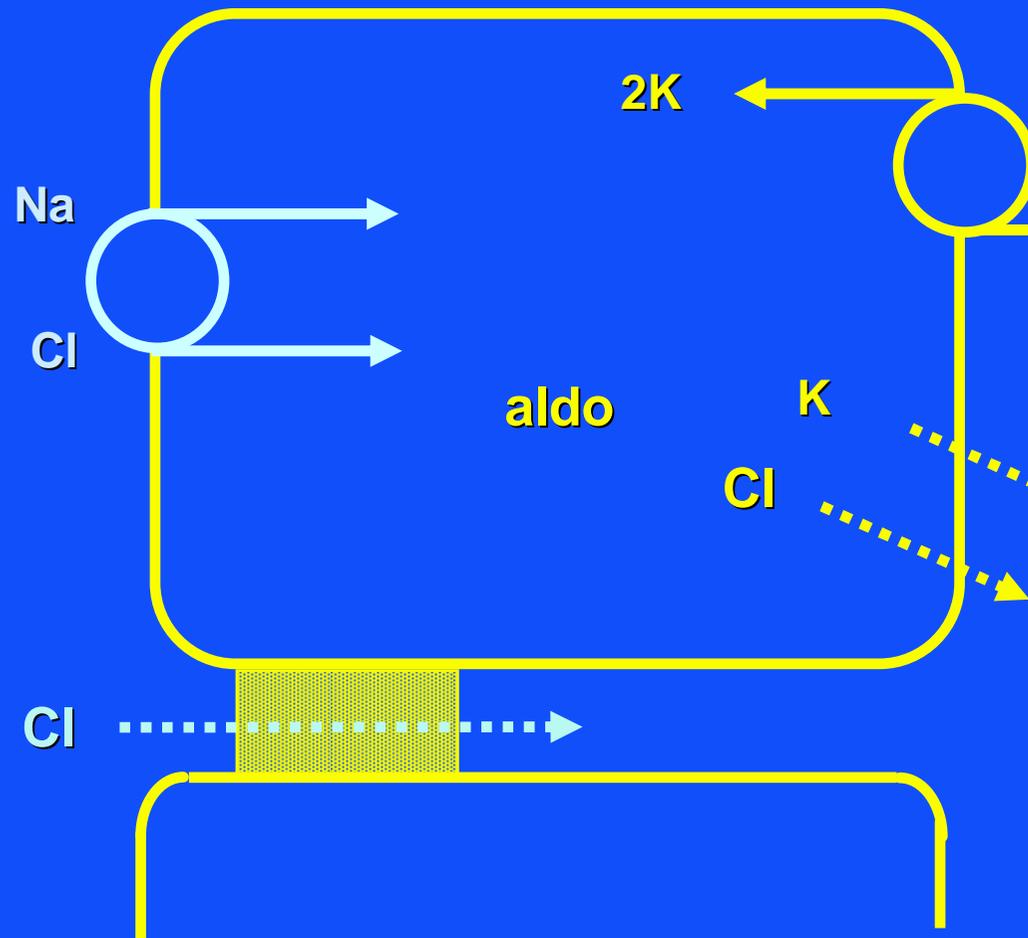
*Insulin - dependence*

*plus aldosterone lack*

*Depolarizing muscle*

*paralysis*

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

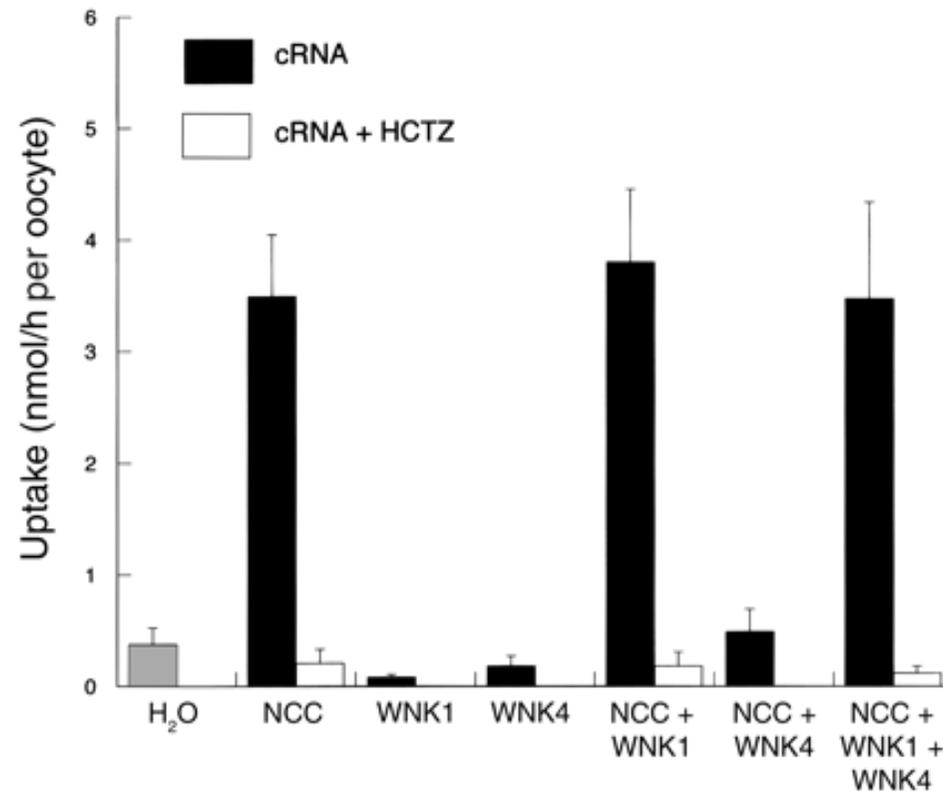


WNK 1, 4 mutations activate thiazide-sensitive NaCl transporter

- $\uparrow$  shunt Cl permeability; paracellin-mediated
- Na avid
- $\downarrow V_M$
- $\downarrow$  K, H secretion: CCT
- low renin hypertension
- responsive to diuretics, Na restriction

# 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

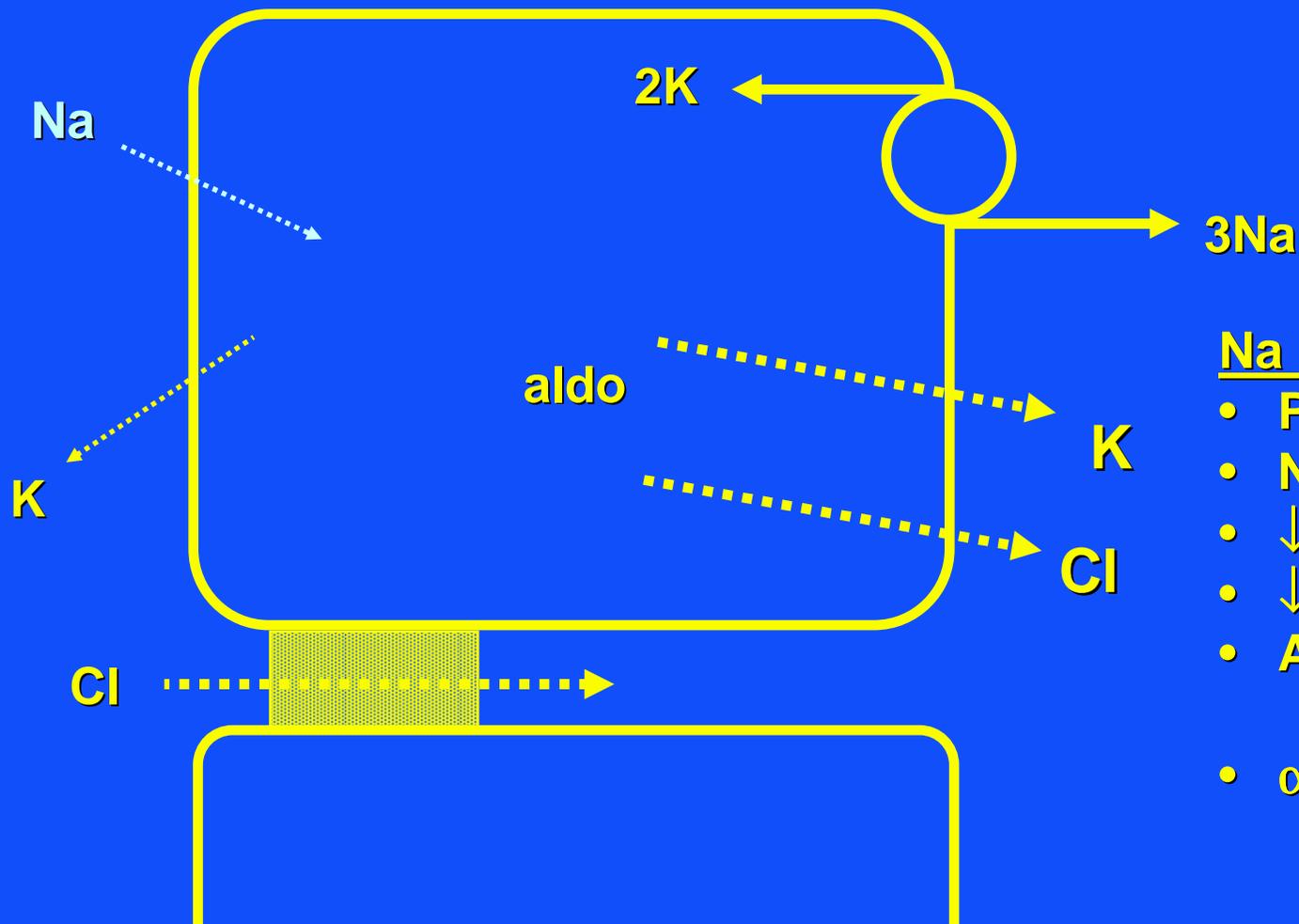
# HYPERKALEMIC RTA SYNDROMES

## *PRINCIPAL CELL DISORDERS*

DISORDER	PRINCIPAL DEFECT	PRINCIPAL FEATURES
Pseudohypoaldosteronism I	Closed Na <sup>+</sup> channel	↑ K <sup>+</sup> ; Na <sup>+</sup> wasting; RTA
Interstitial disease	Hyporeninemic hypoaldosteronism	↑ K <sup>+</sup> ; Na <sup>+</sup> wasting; RTA

# PRINCIPAL CELL DISEASES

## $\text{Na}^+$ CHANNEL BLOCKADE (PSEUDOHYPOALDOSTERONISM I)



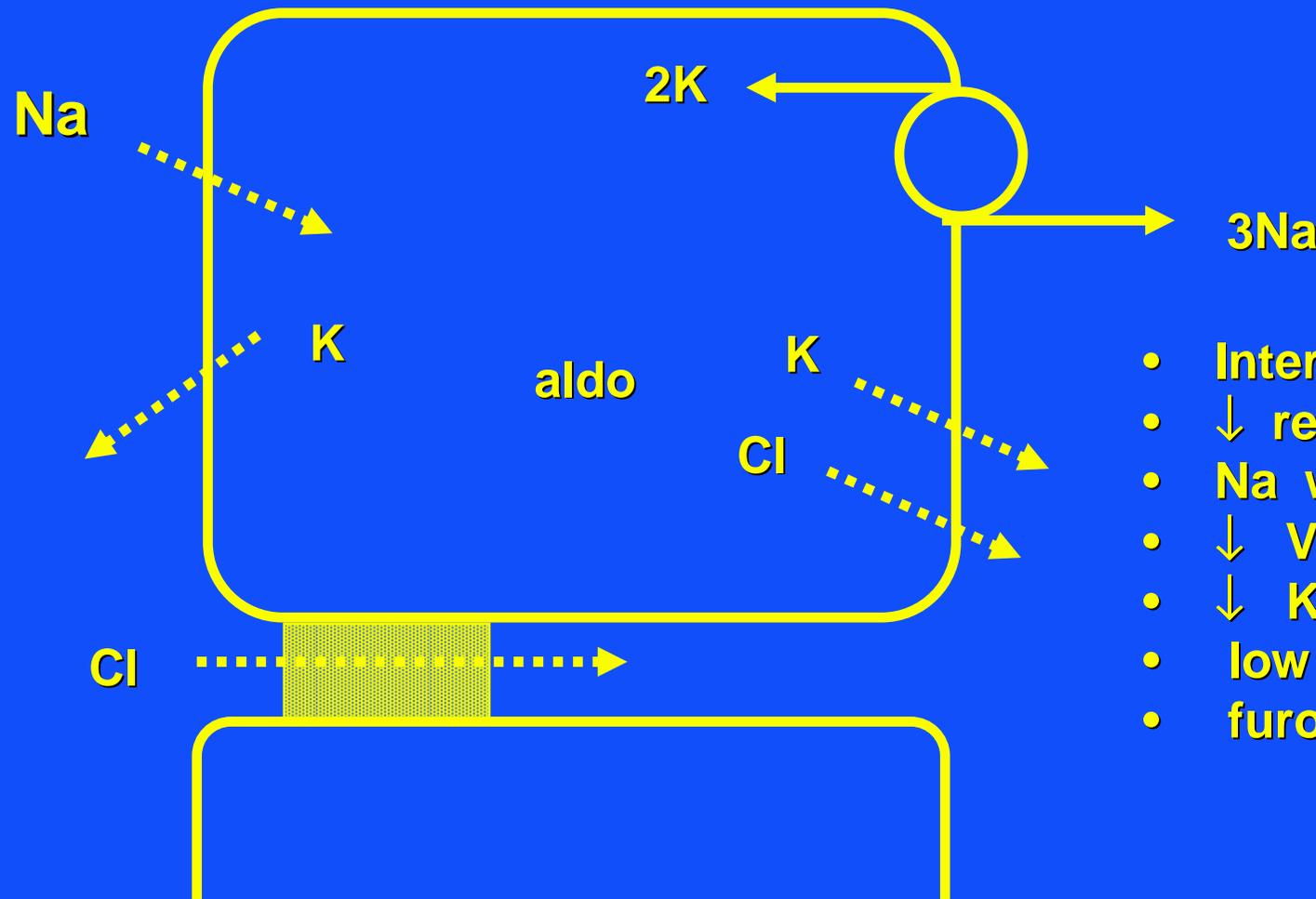
### Na Channel Blockade:

- Prototype: amiloride Rx
- Na wasting
- $\downarrow V_M$
- $\downarrow$  K, H secretion
- Aldosterone unresponsive
- $\alpha$  or  $\beta$  subunit mutations in ENaC

# 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<sup>+</sup> REMOVAL

KAYEXALATE:

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

HEMODIALYSIS:

K<sup>+</sup> CLEARANCE: 200 ml / MINUTE  
(85 mEq / HR)

PERITONEAL DIALYSIS:

K<sup>+</sup> CLEARANCE: 20 - 25 ml / MINUTE  
(8.5 - 10 mEq / HR)

## K<sup>+</sup> ENTRY INTO CELLS

ALKALINIZATION:

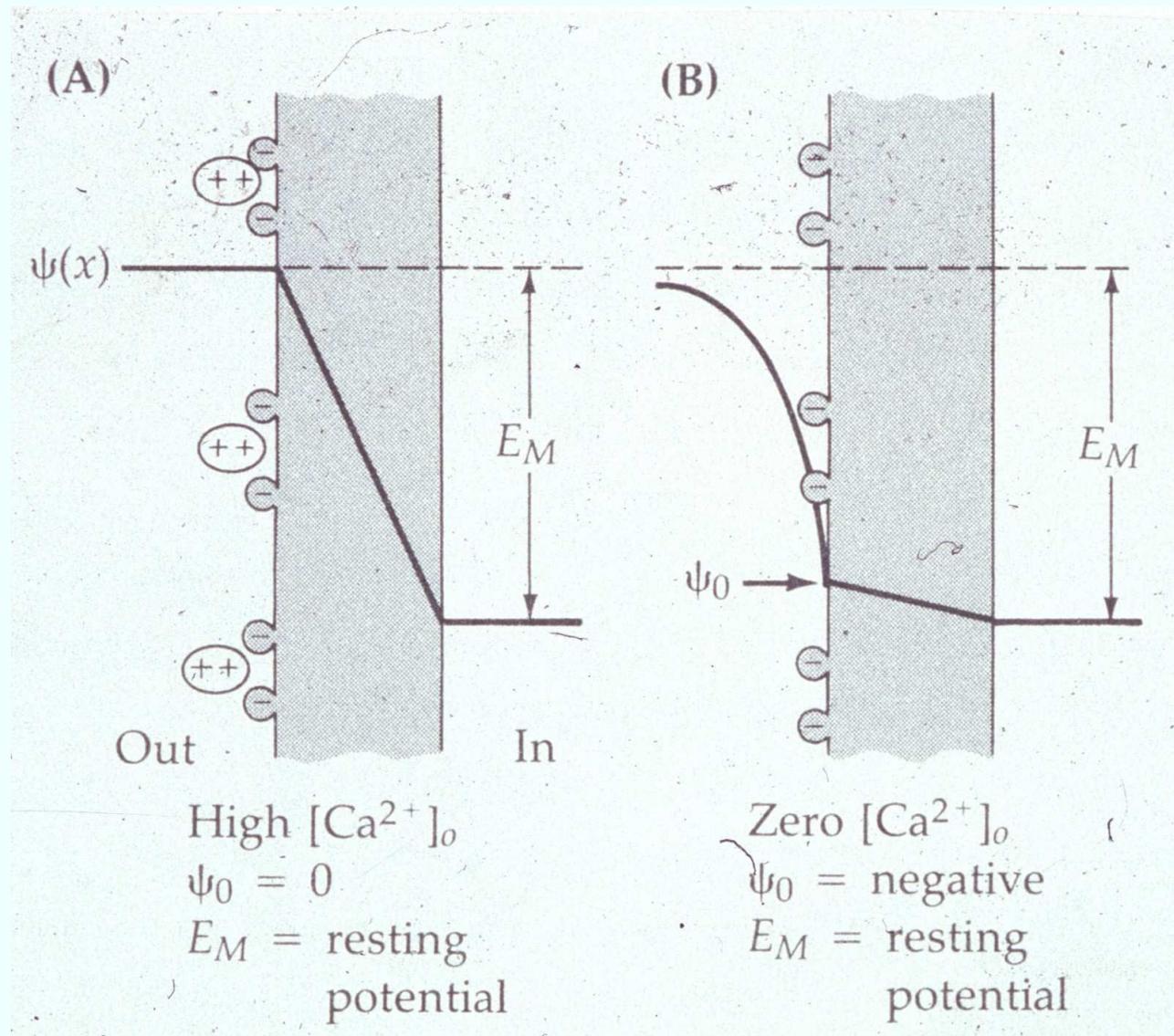
0.6 mEq K<sup>+</sup> / 0.1 pH UNIT

GLUCOSE AND INSULIN:

0.5 mEq K<sup>+</sup> / 25 Gm GLUCOSE

# CARDIAC PROTECTION IN HYPERKALEMIA

## $Ca^{++}$ SCREENING OF SURFACE POTENTIAL



# TWO KINDS OF HYPERKALEMIC SYNDROMES

<u>Fiber</u>	<u>Activation Threshold</u>	<u>Disorder</u>
Skeletal muscle <i>TTX - sensitive</i>	- 60	{ periodic paralysis heart generally unaffected
Myocardium <i>TTX - insensitive</i>	- 75	{ cardiac standstill rare skeletal muscle paralysis

# HYPERKALEMIC PERIODIC PARALYSIS

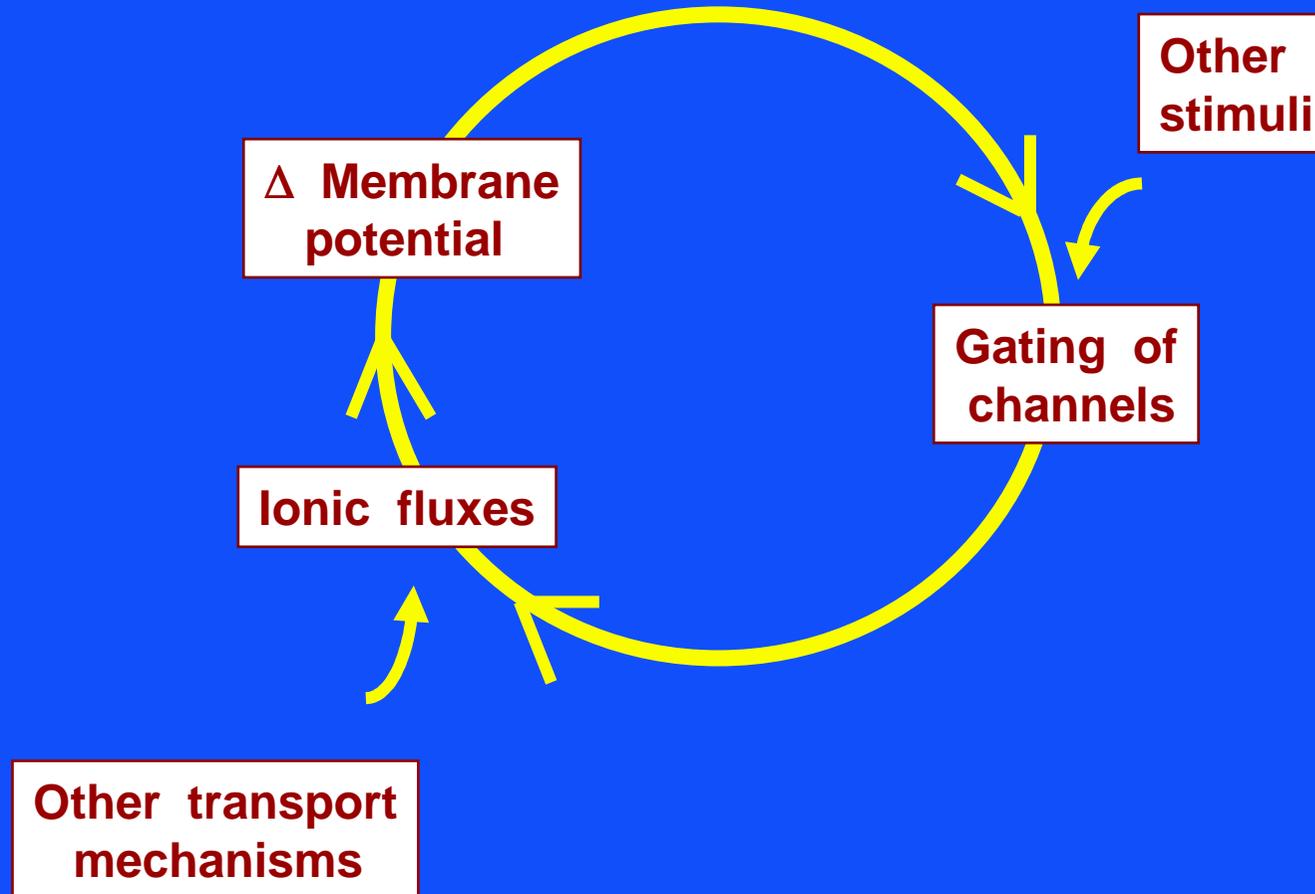
## A SKELETAL MEMBRANE DISORDER

- TTX - sensitive Na<sup>+</sup> 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<sup>+</sup> levels  
paramyotonia: cold-sensitive
- K-sensitive; acetazolamide-responsive

# PROPERTIES OF SOME Na<sup>+</sup> CHANNELS

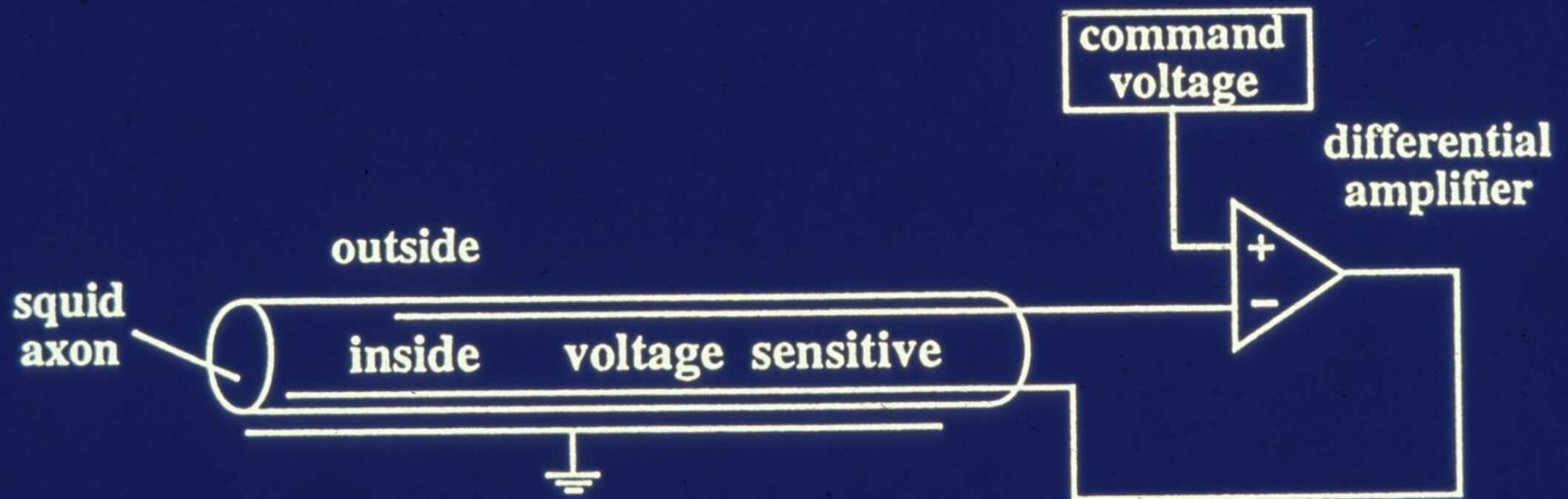
	<u>TTX - SENSITIVE</u>	<u>TTX - INSENSITIVE</u>
Primary location	Brain , Muscle	Heart
Activation voltages (mV)	- 60	- 75

# THE GREAT HODGKIN-HUXLEY CONTRIBUTION

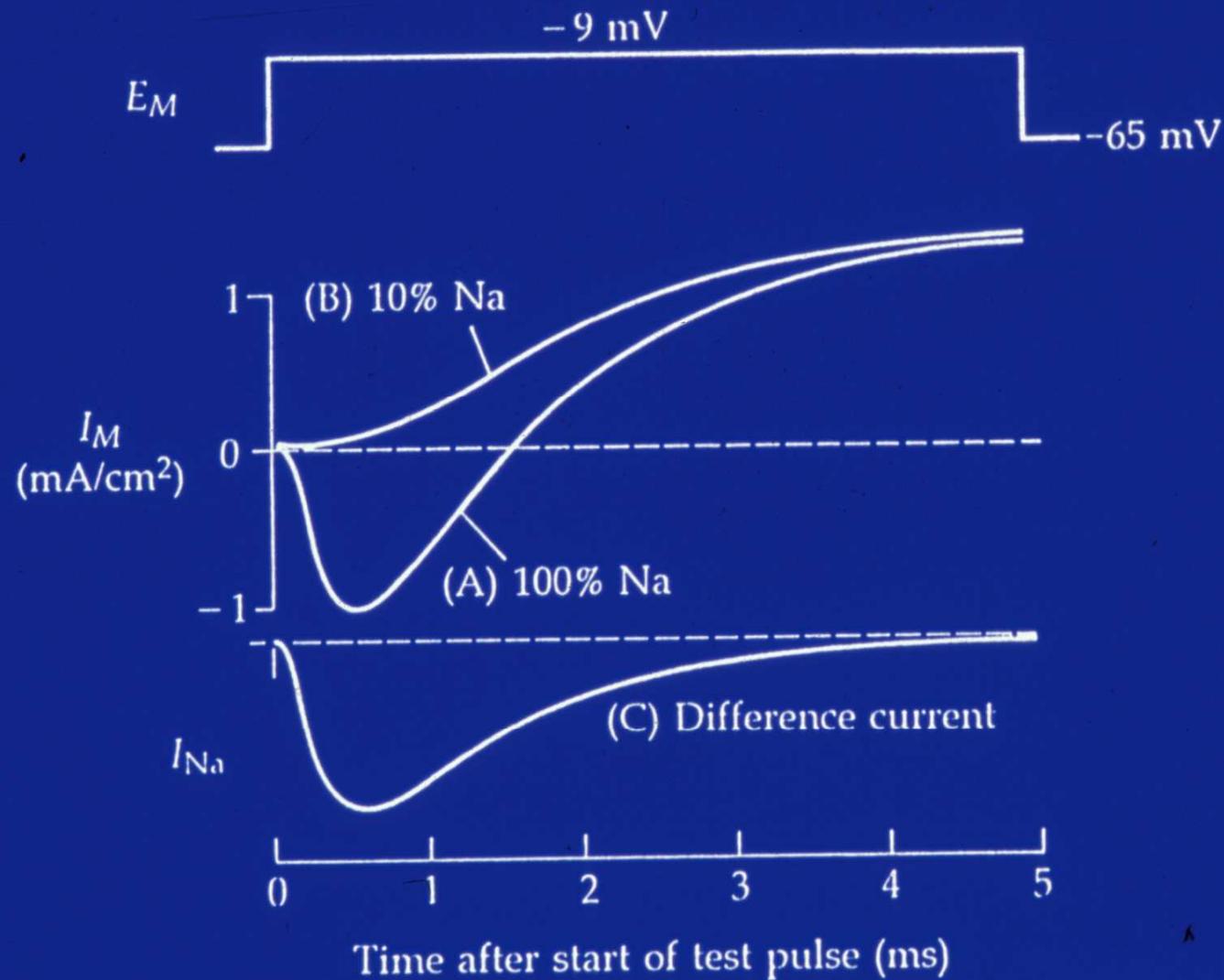


CLASSICAL CYCLE OF ELECTRICAL EXCITATION

# The Voltage Clamp Technique

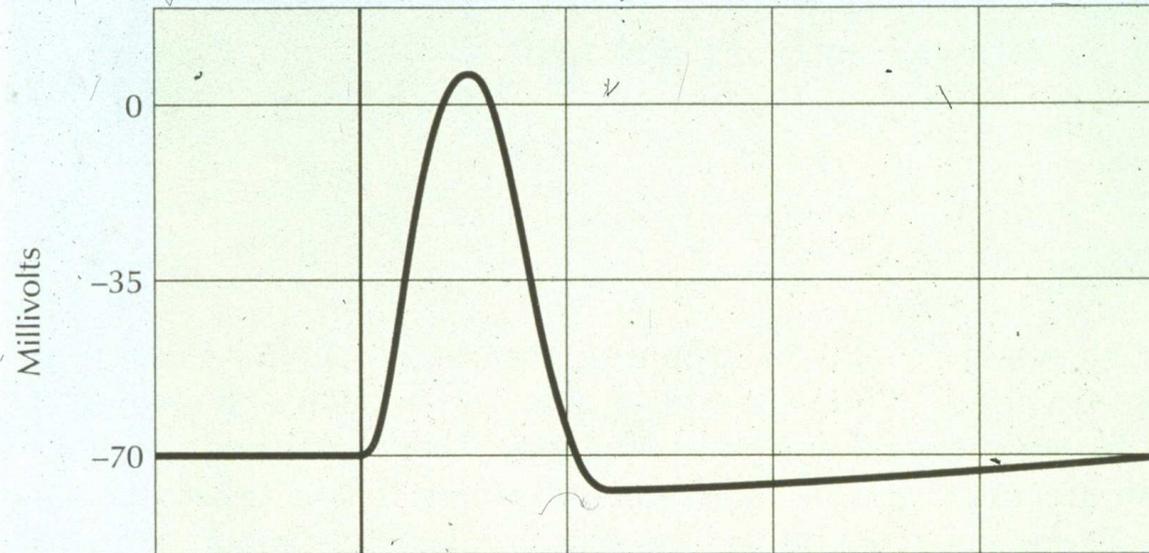


# THE HODGKIN-HUXLEY EXPERIMENTAL STRATEGY

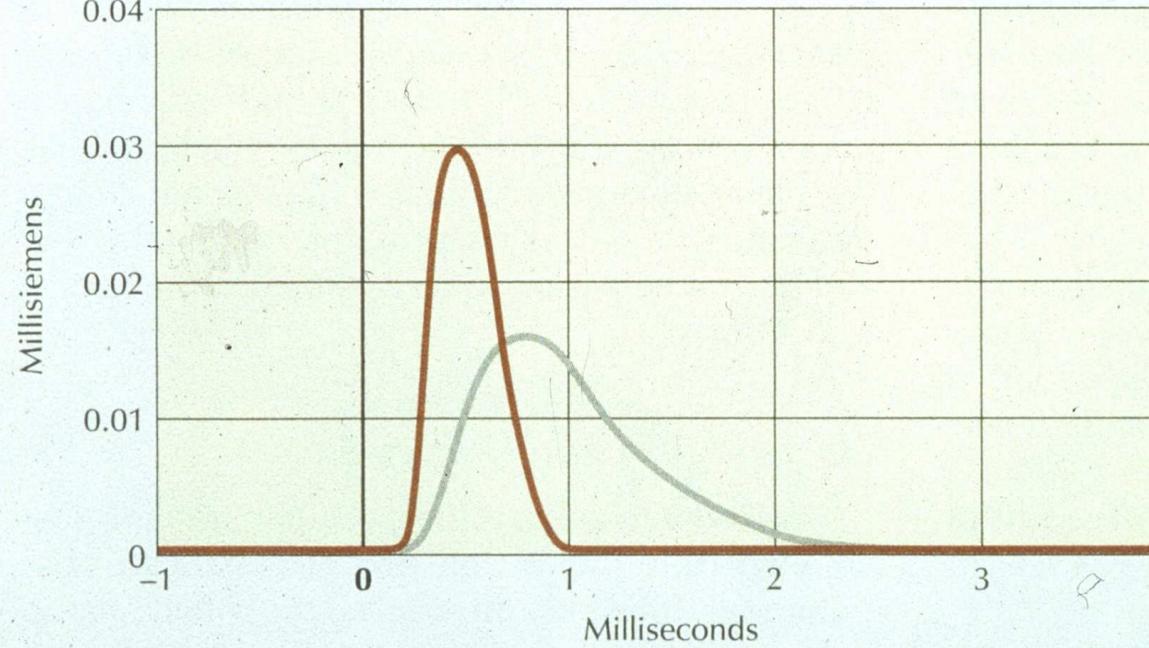


Hodgkin and Huxley, 1952

### Action Potential



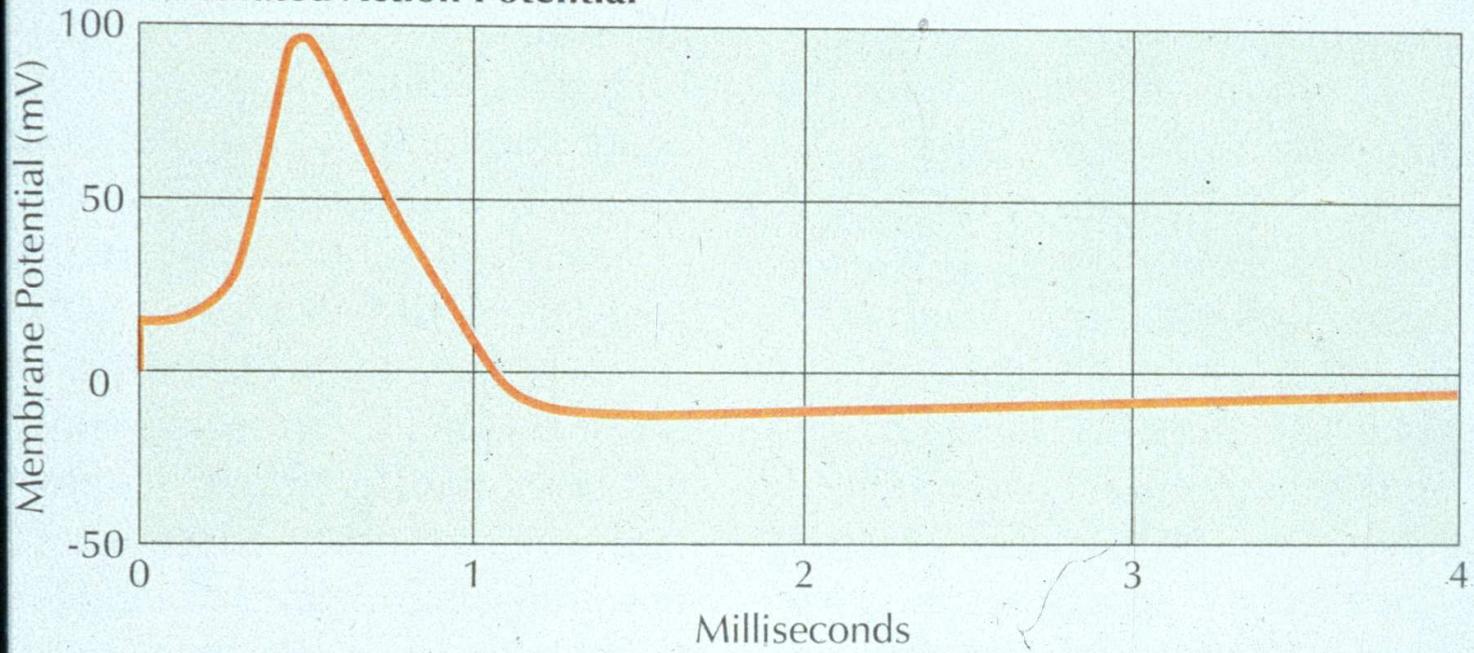
### Transmembrane Conductance



— Sodium

— Potassium

**Calculated Action Potential**

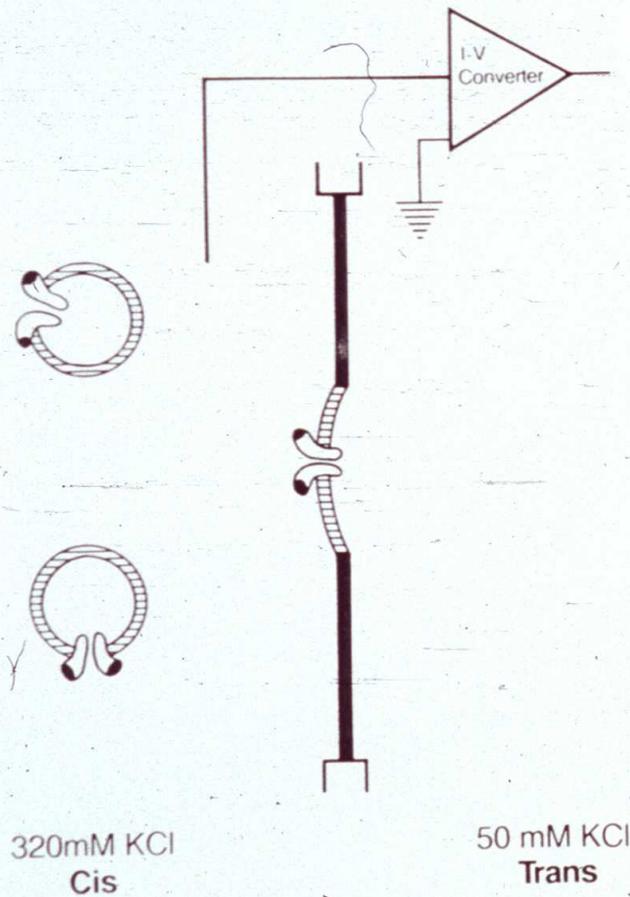


**Recorded Action Potential (Squid Axon)**

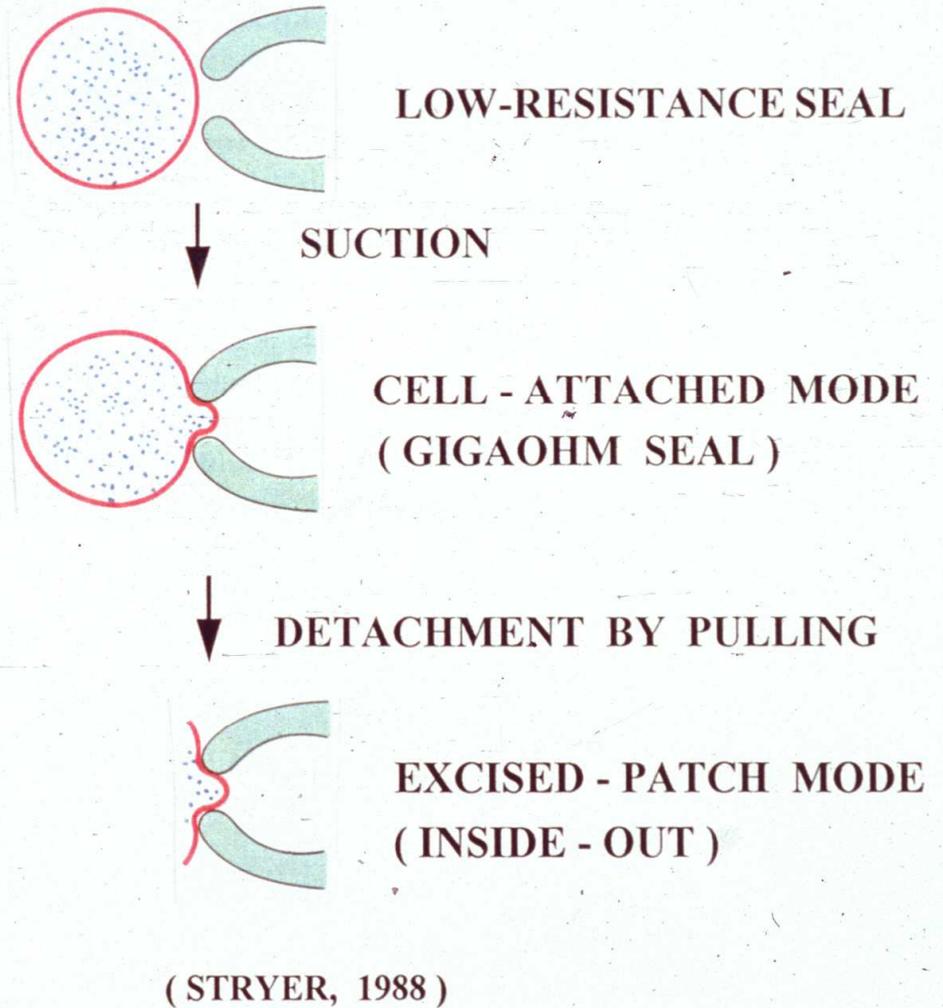


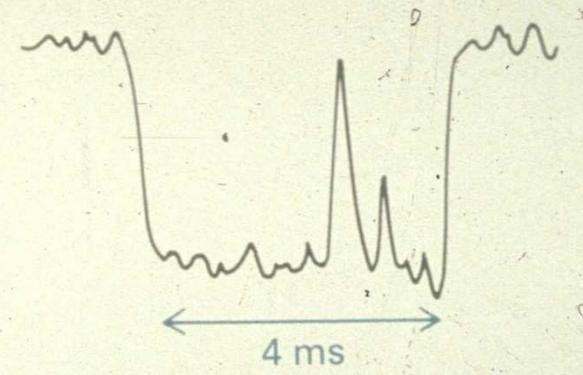
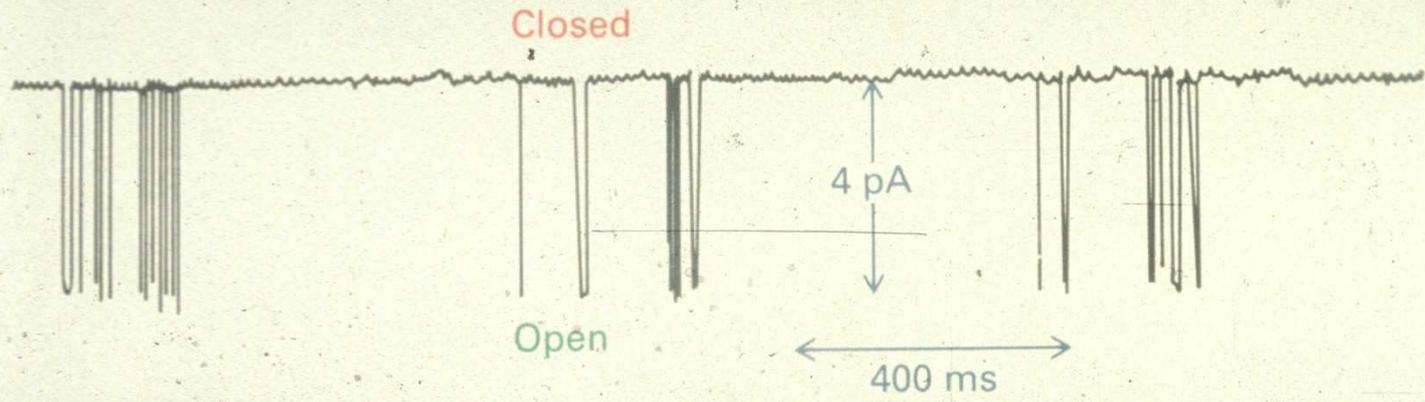
# ELECTROPHYSIOLOGIC APPROACHES

## VESICLE FUSION INTO BILAYERS



## EXCISED PATCH TECHNIQUE



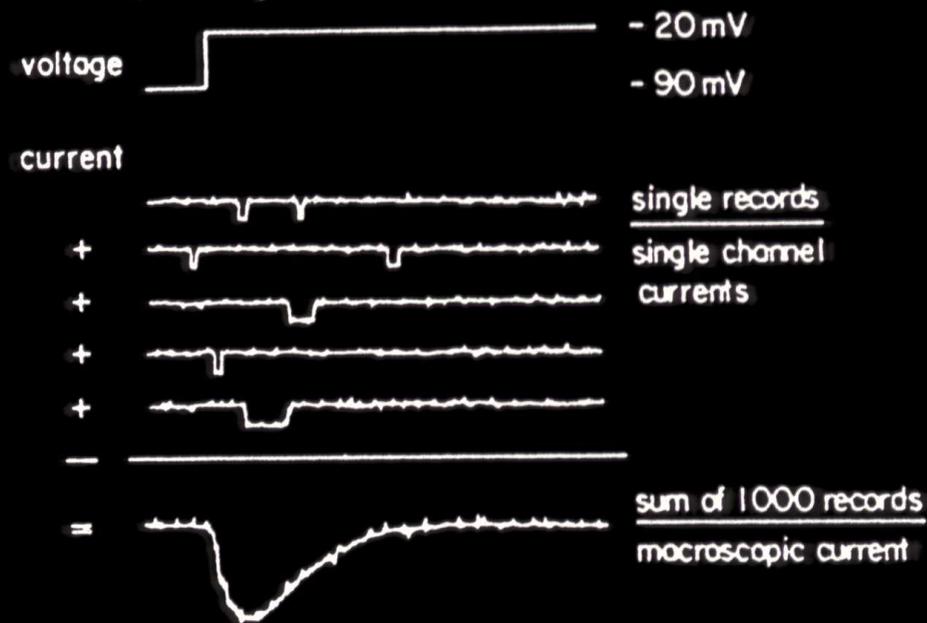


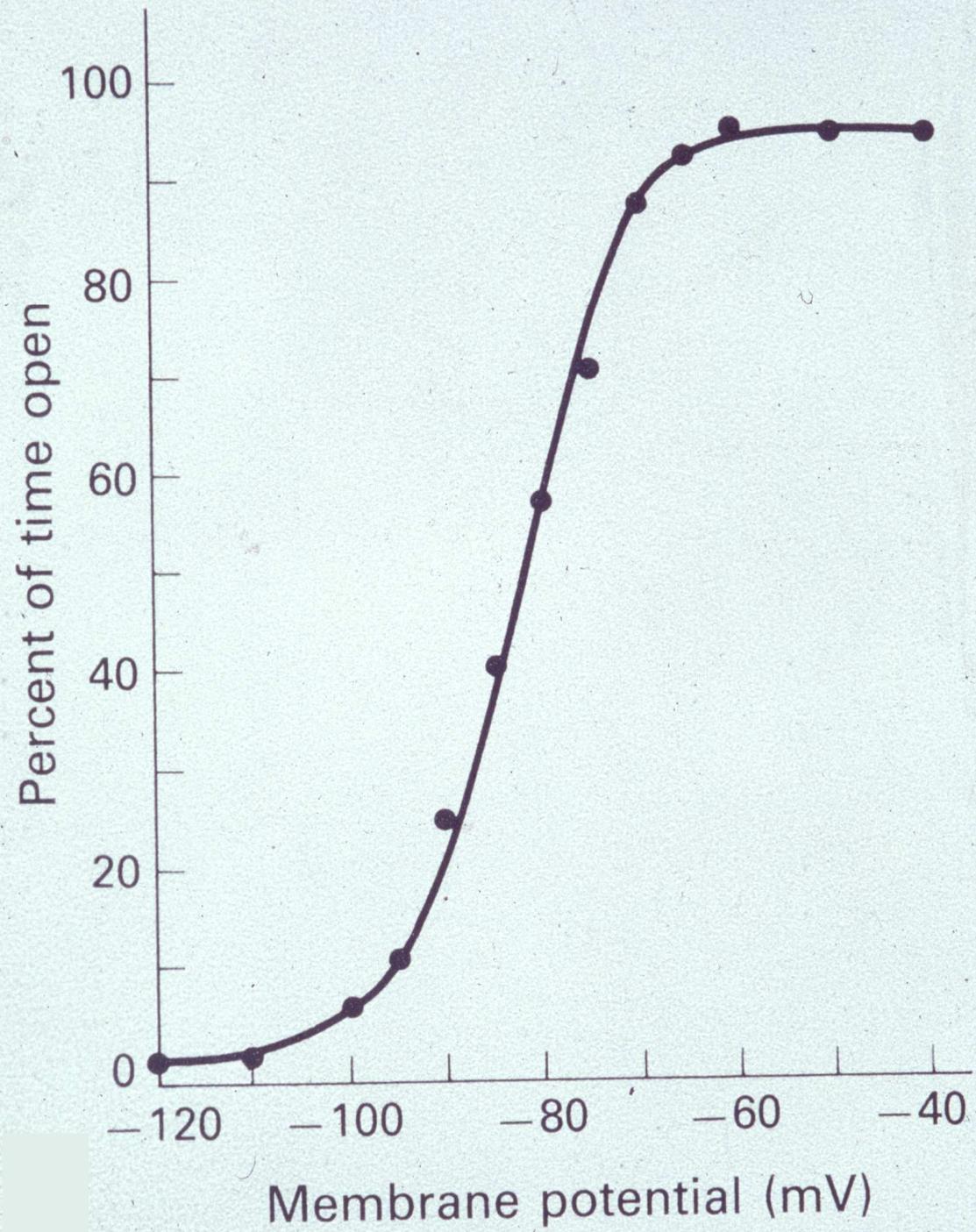
# MACROSCOPIC AND SINGLE Na<sup>+</sup> CHANNEL BEHAVIOR

## A. Traditional voltage clamp - Large membrane area

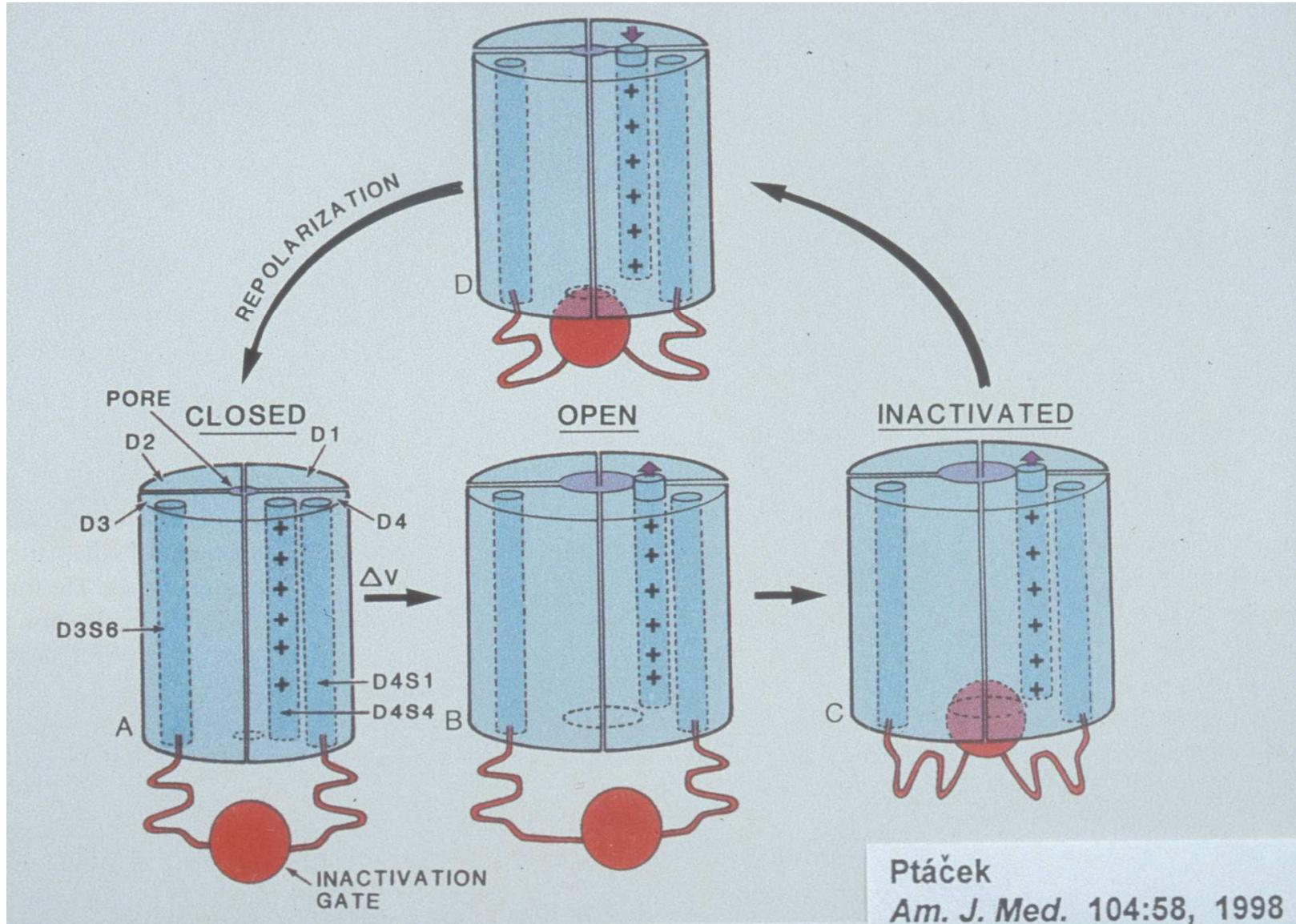


## B. Patch Clamp Very small membrane area





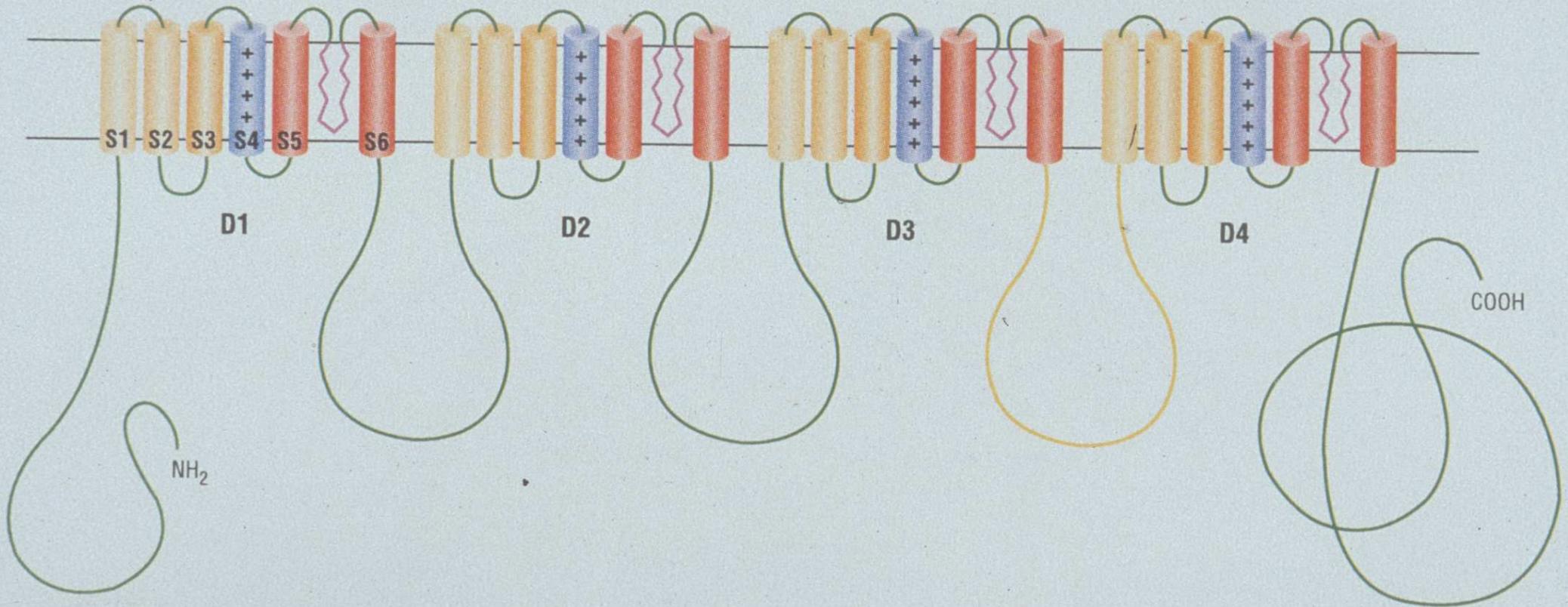
# CATION CHANNEL KINETICS



# **Na<sup>+</sup> 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**

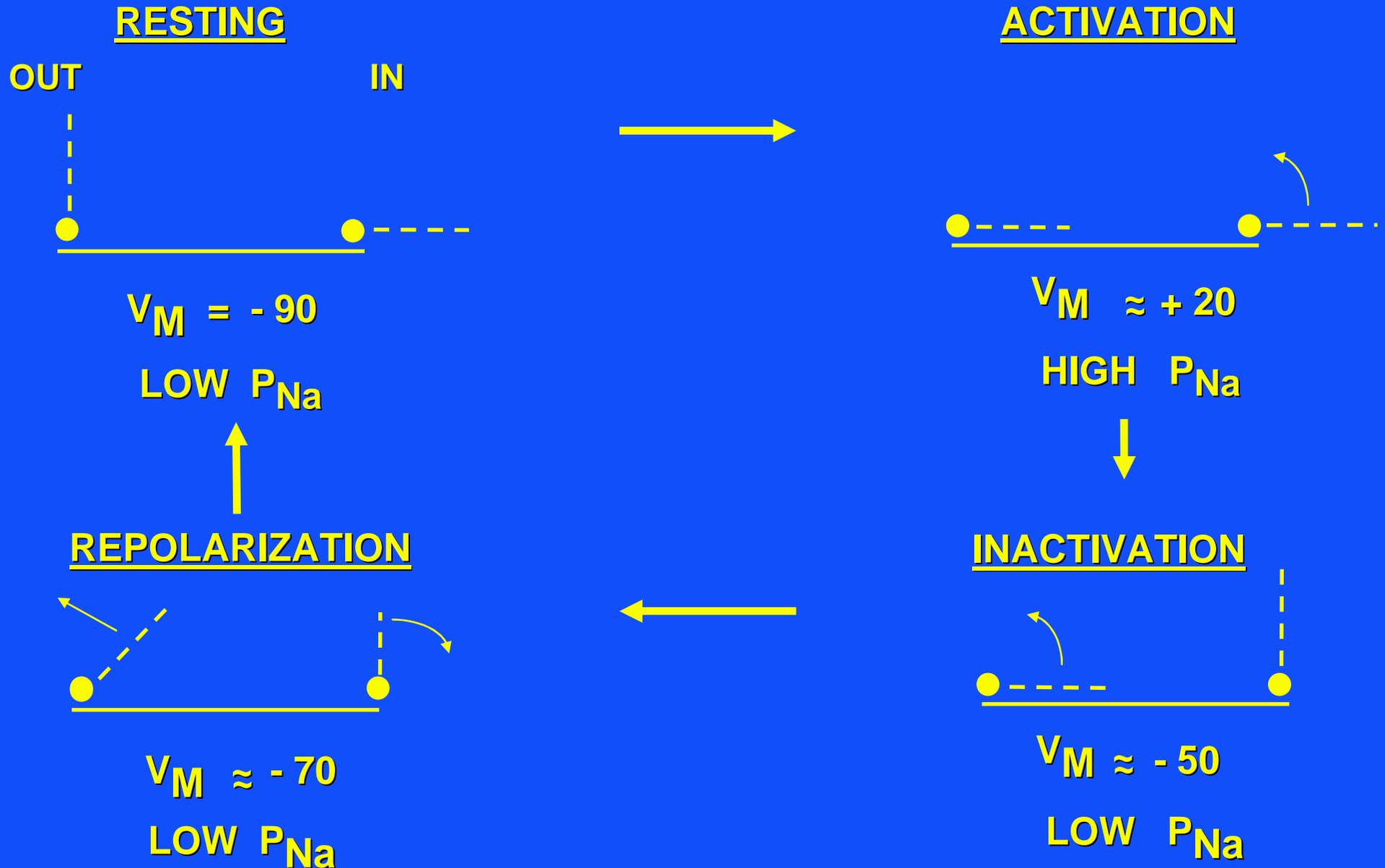
# VOLTAGE-GATED CATION CHANNELS



Ptáček

*Am. J. Med.* 104:58, 1998

# SODIUM CHANNEL ACTIVITY: NORMAL



# HYPERKALEMIC PERIODIC PARALYSIS

## A SKELETAL MEMBRANE DISORDER

- TTX - sensitive Na<sup>+</sup> channel mutations
- Chromosome 17 mutation
  - HPP
  - paramyotonia} allelic variants
- *Human form:* often with familial inbreeding  
*Equine form:* inbred quarter-horses
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paramyotonia: cold-sensitive
- K-sensitive; acetazolamide-responsive

# THE MAGNIFICENT FLAWED THOROUGHBRED



*Scientific American* May, 1991

# Pillars of the STUD BOOK

## James Weatherby, 1791

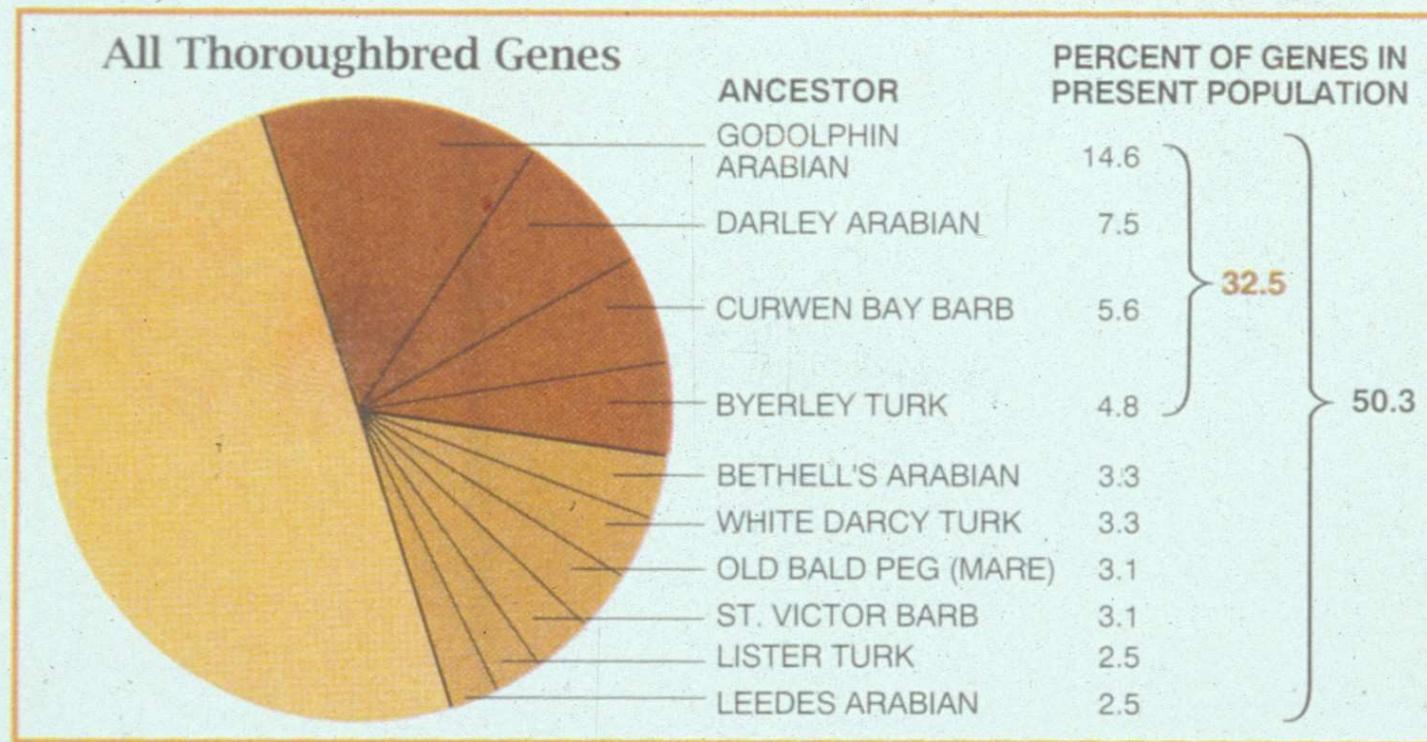


**Godolphin Arabian**  
1725

**Darley Arabian**  
1688

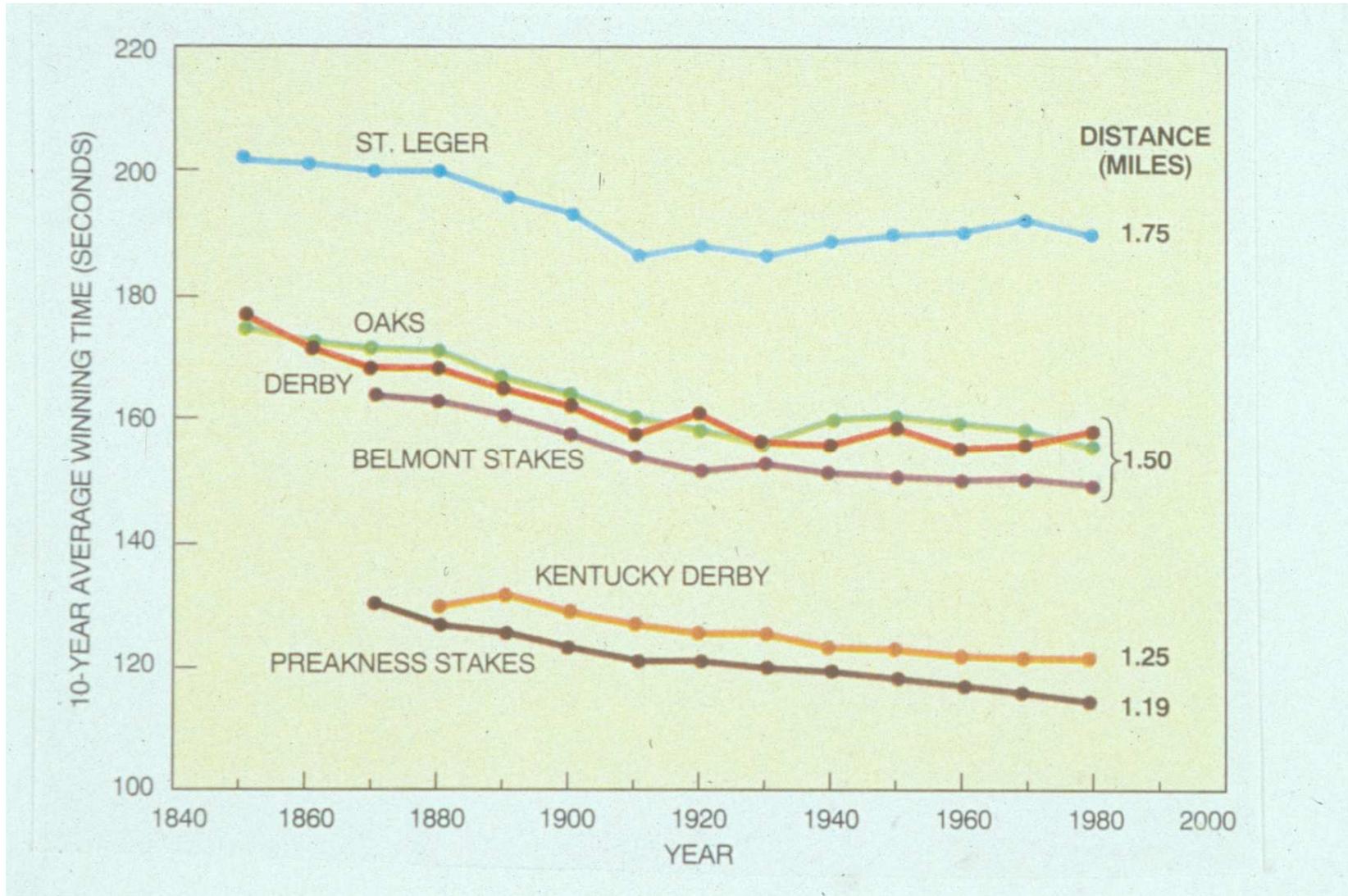
**Byerley Turk**  
1690

# PILLARS OF THE *STUD BOOK*



*SCIENTIFIC AMERICAN* MAY, 1991

# THE GREAT RACES



*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.



ALLEN FAULKNER

MOLLING GARY RANCH

Stallion Manager  
Mark Faulkner

*Faulkner Quarter Horses*

Route 4 - Box 770 - Interstate 35 and Waterloo

Edmond, Oklahoma 73034 Exit 146

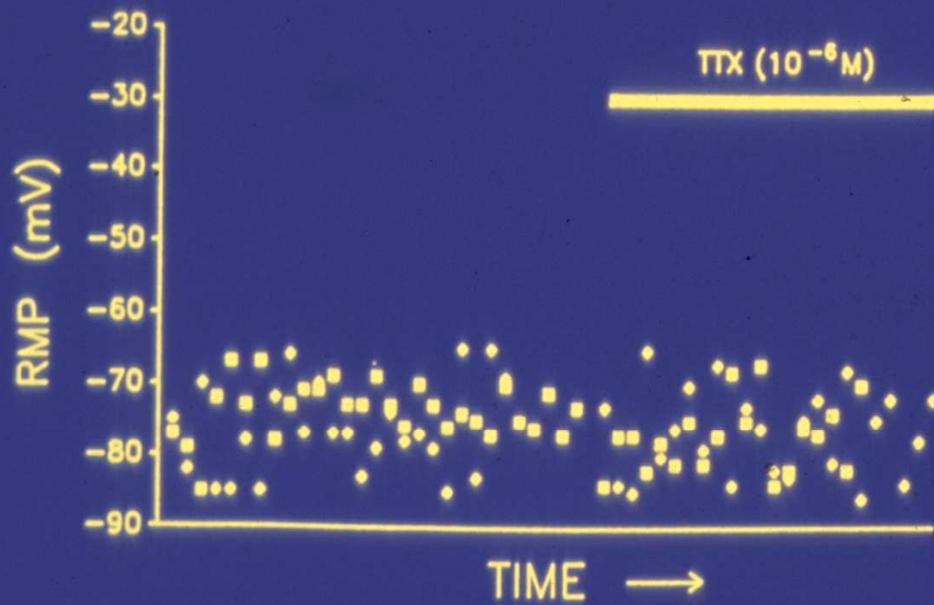
Allen E. Faulkner • (405) 341-8626



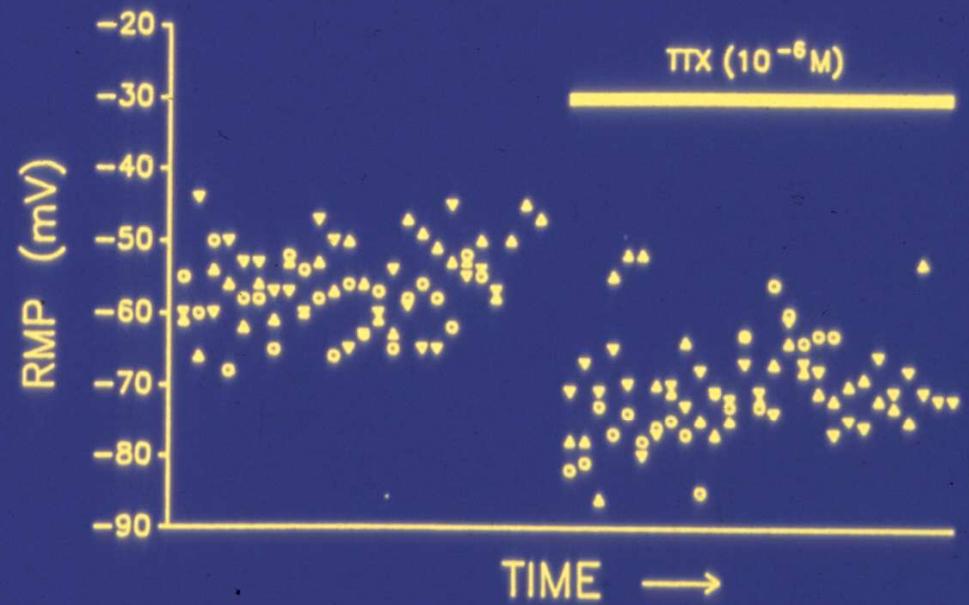
Attending Veterinarian  
DR. MIKE JOHNSTON  
Trainer  
Jeff LaGrow

# HPP IN HORSES

Normal

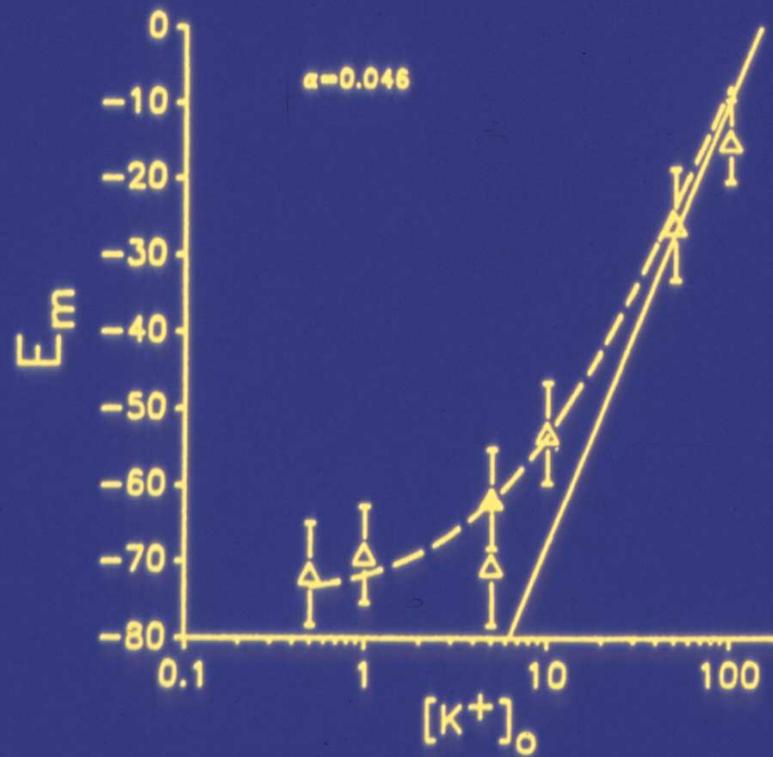


HPP

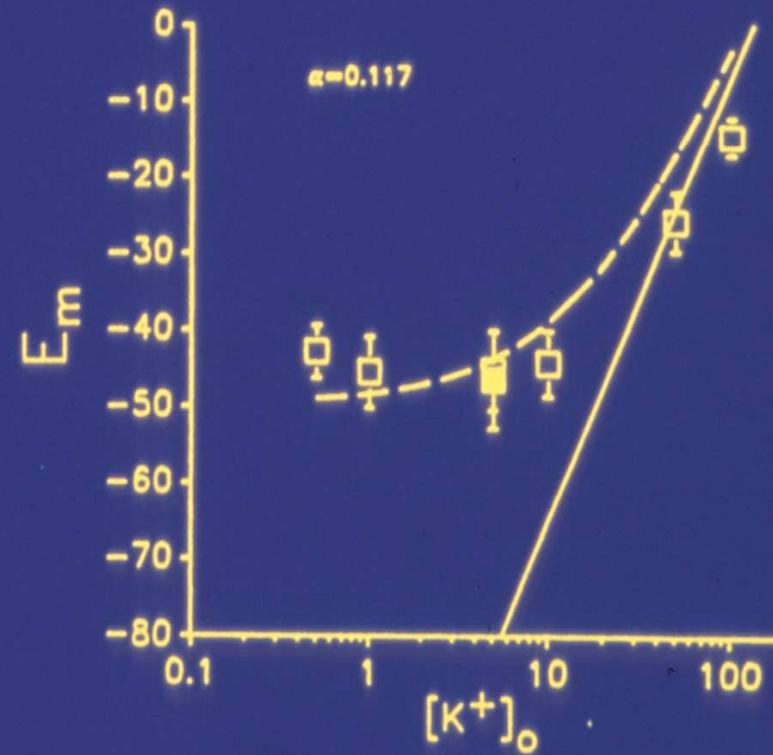


# HPP IN HORSES

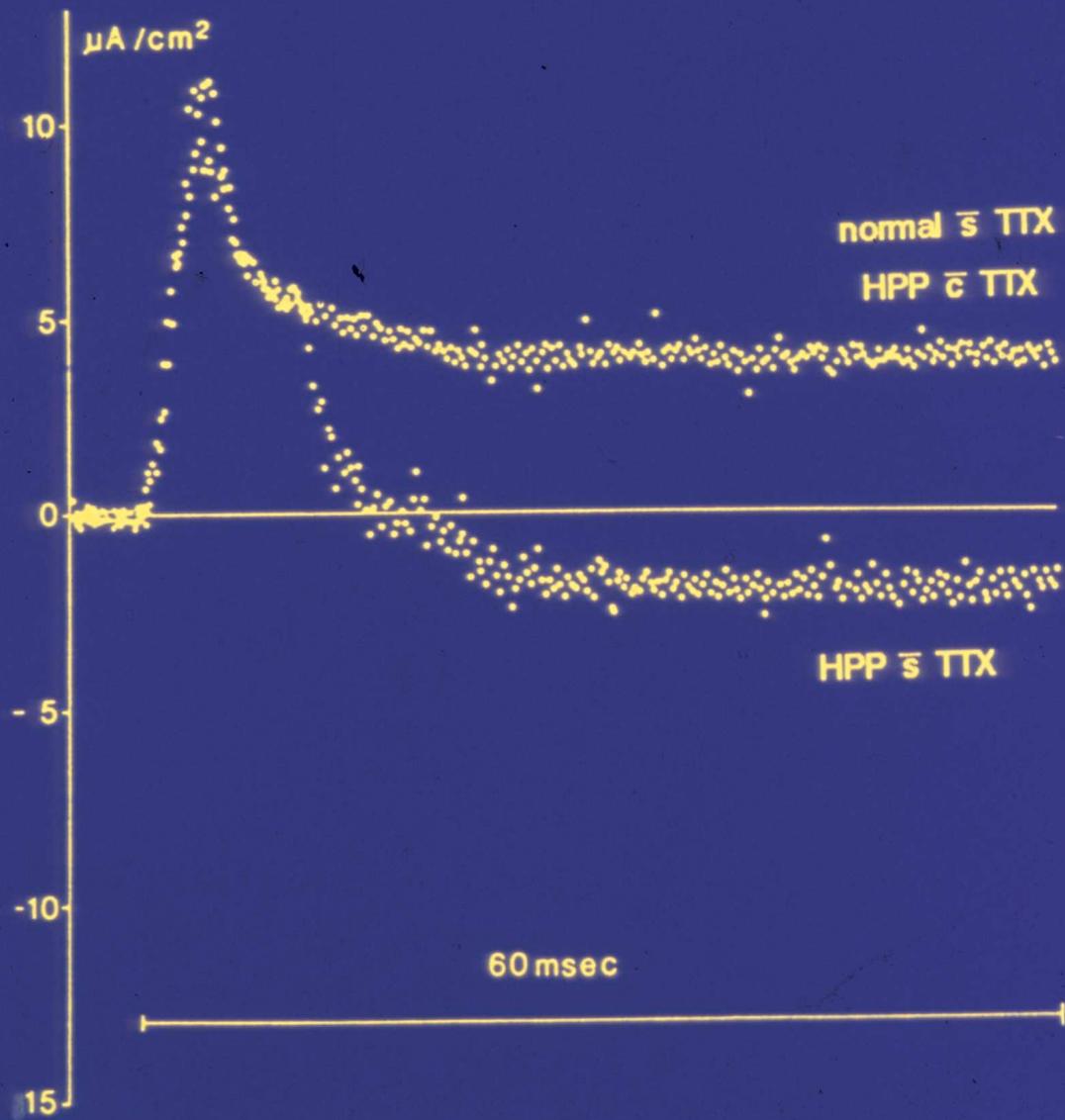
Normal



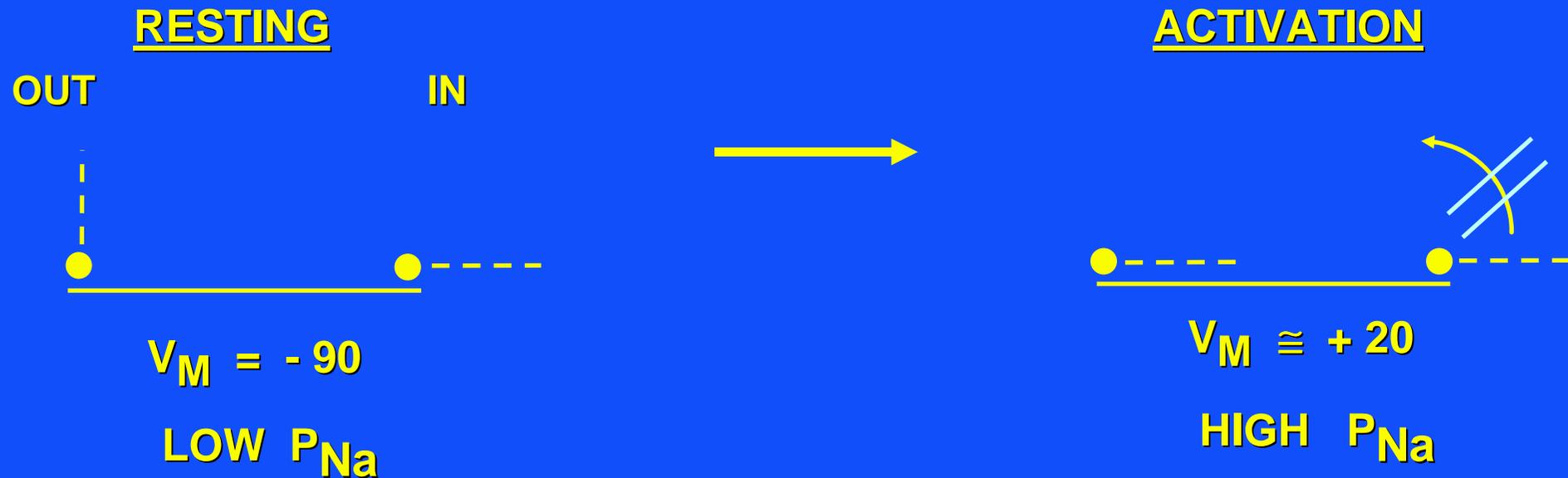
HPP



# HUMAN HPP



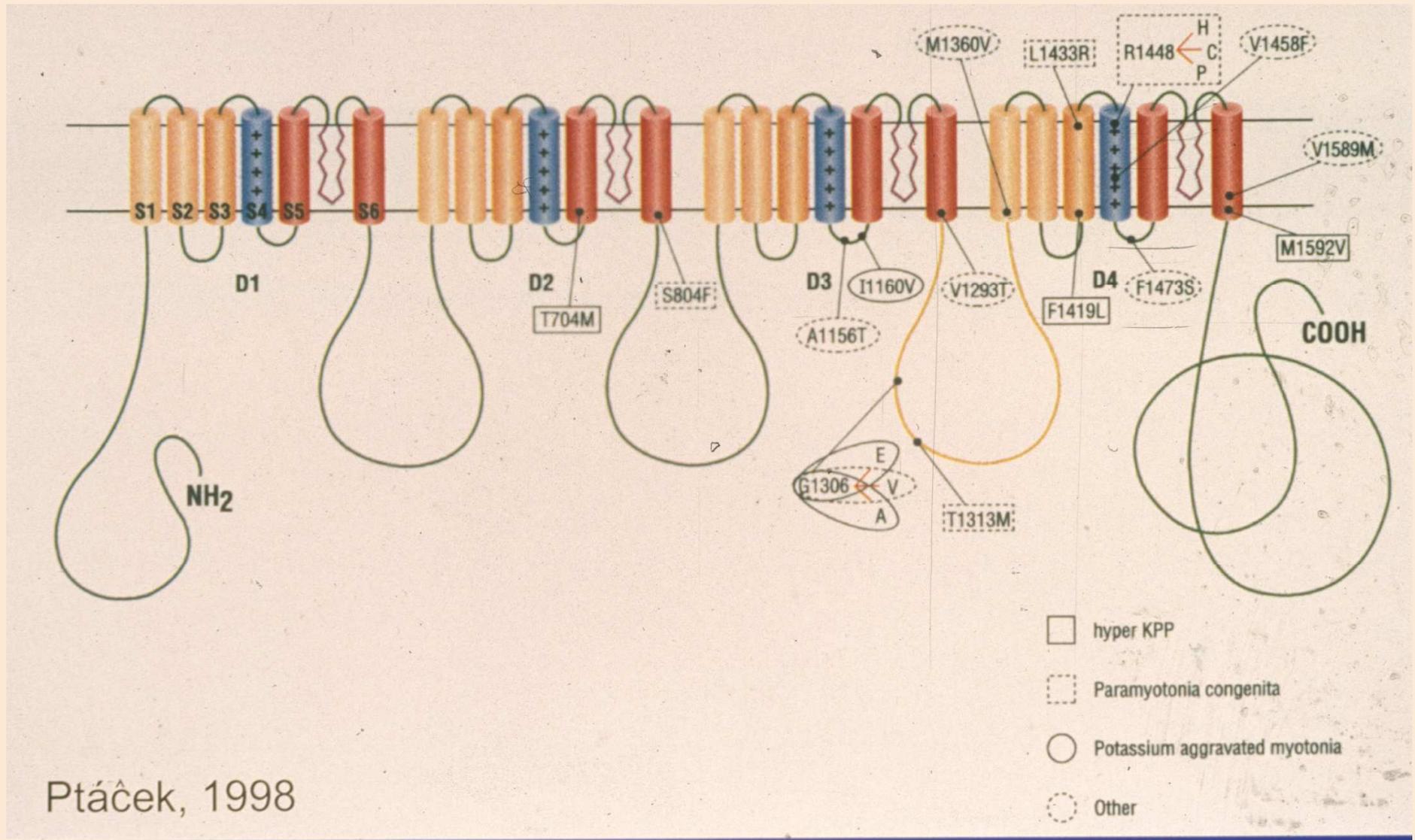
# SODIUM CHANNEL ACTIVITY: HPP



HPP : TTX - SENSITIVE MUSCLE FIBERS

1. FAILURE OF INACTIVATION GATES TO CLOSE
2. PERSISTENT TTX - SENSITIVE  $i_{Na}$

# Na<sup>+</sup> CHANNEL DEFECT IN HPP

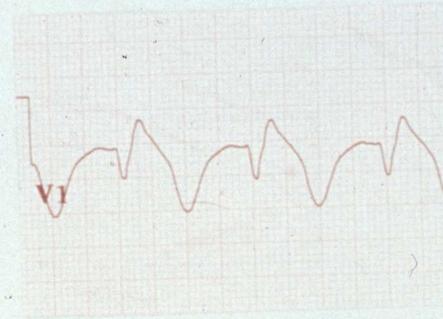


Ptáček, 1998

# TWO KINDS OF HYPERKALEMIC SYNDROMES

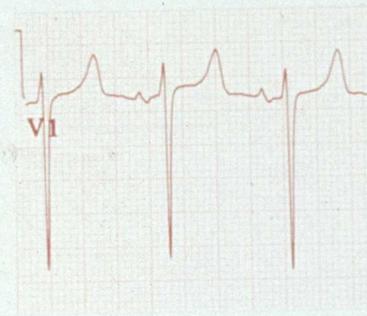
<u>Fiber</u>	<u>Activation Threshold</u>	<u>Disorder</u>
Skeletal muscle <i>TTX - sensitive</i>	- 60	{ periodic paralysis heart generally unaffected
Myocardium <i>TTX - insensitive</i>	- 75	{ cardiac standstill rare skeletal muscle paralysis

05-Nov-93  
00:39



K+9.9

06-Nov-93  
09:24



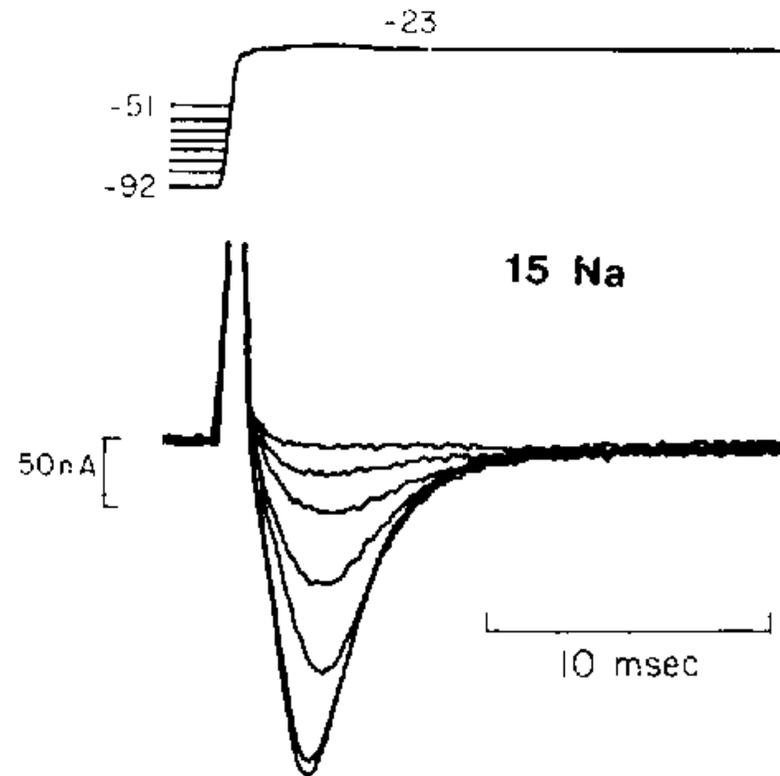
K+4.8

09-Nov-93  
05:24



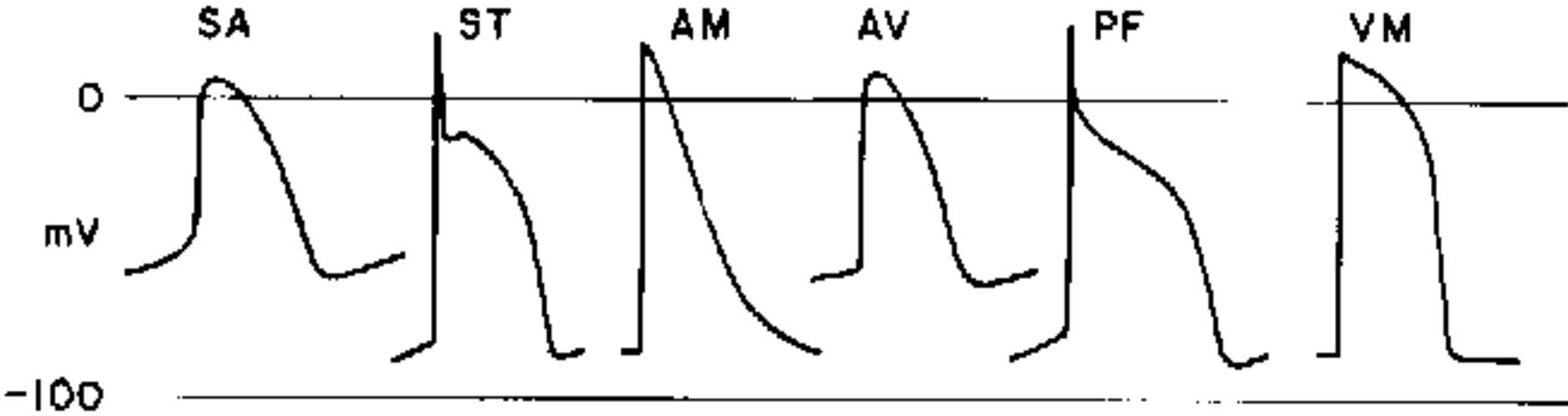
K+4.6

# PARTIAL DEPOLARIZATION INACTIVATES CARDIAC ACTION POTENTIAL



TSIEN & HESS, 1986

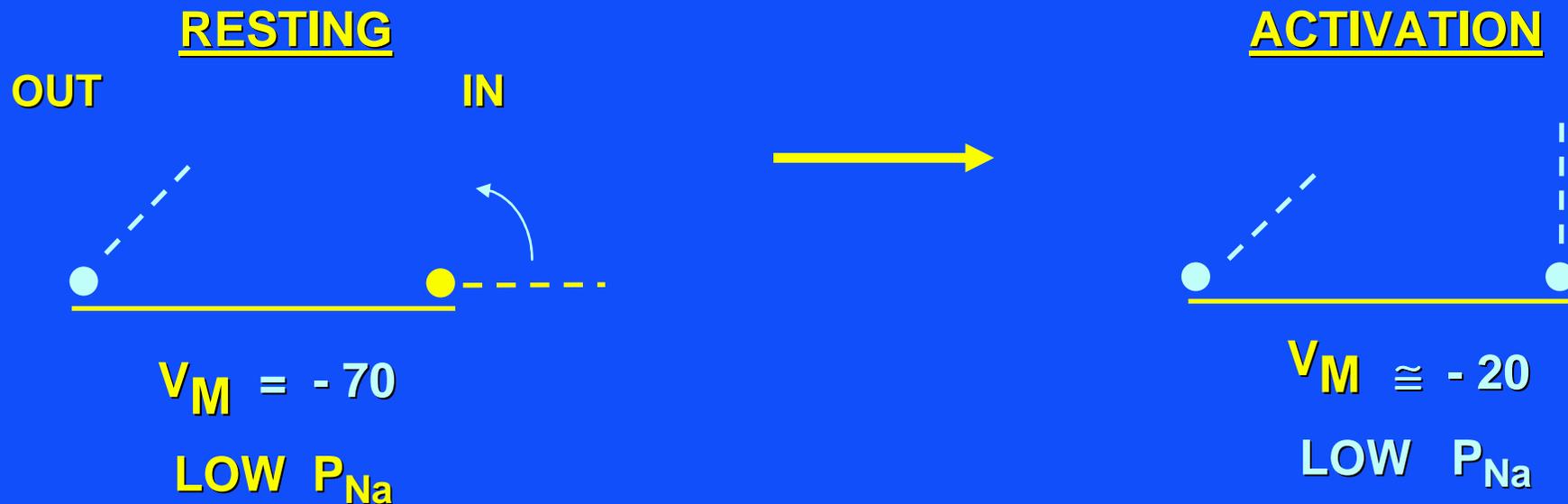
# THE CARDIAC ACTION POTENTIALS



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

TSIEN & HESS, 1986

# SODIUM CHANNEL ACTIVITY: HYPERKALEMIA



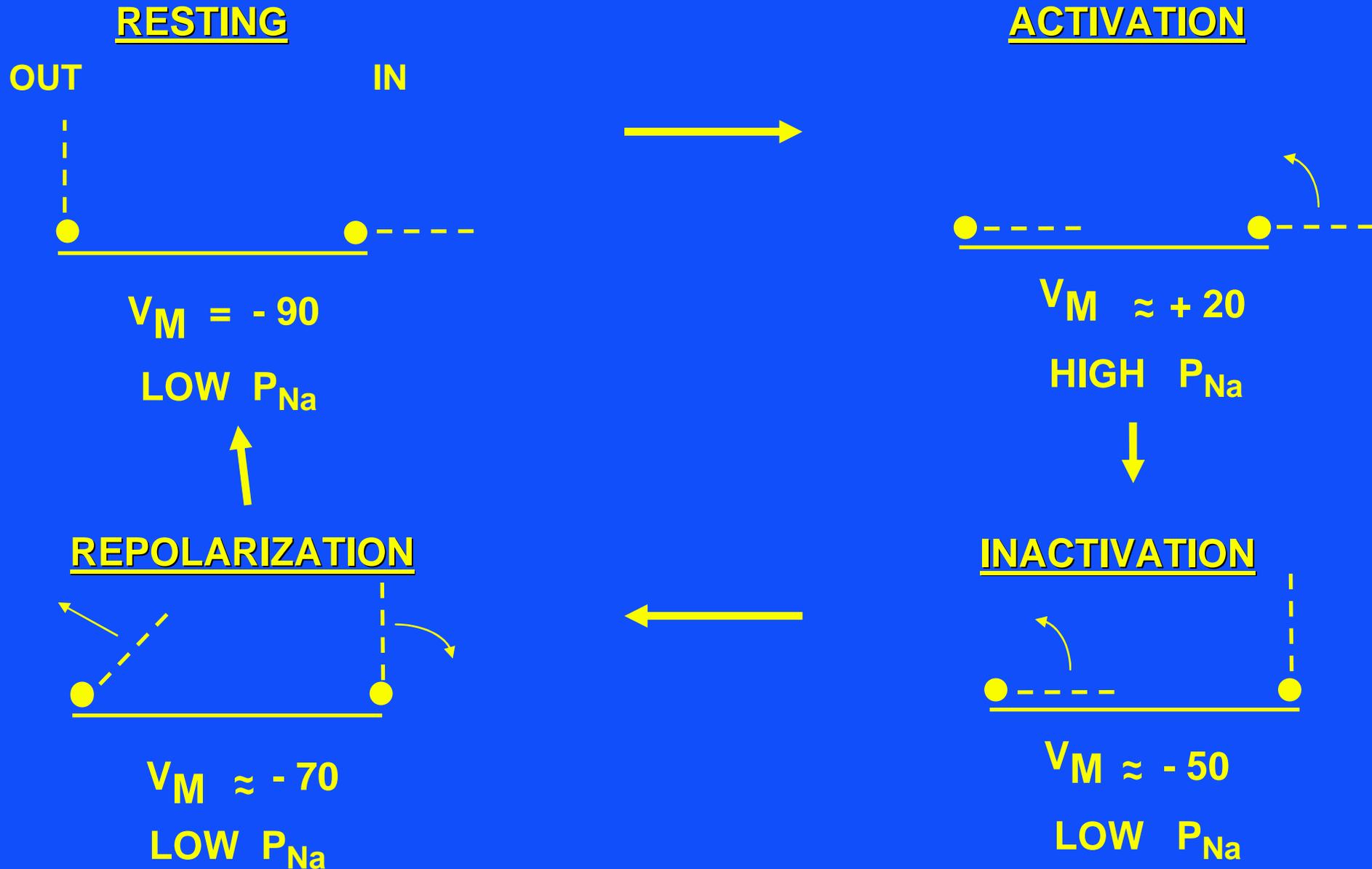
## CARDIOTOXICITY

- 1 .  $\uparrow K^+$  DEPOLARIZES  $V_M$
- 2 . ACTIVATION GATES PARTIALLY OPEN
- 3 . INACTIVATION GATES CLOSED
- 4 .  $i_{Na}$  BLOCKED

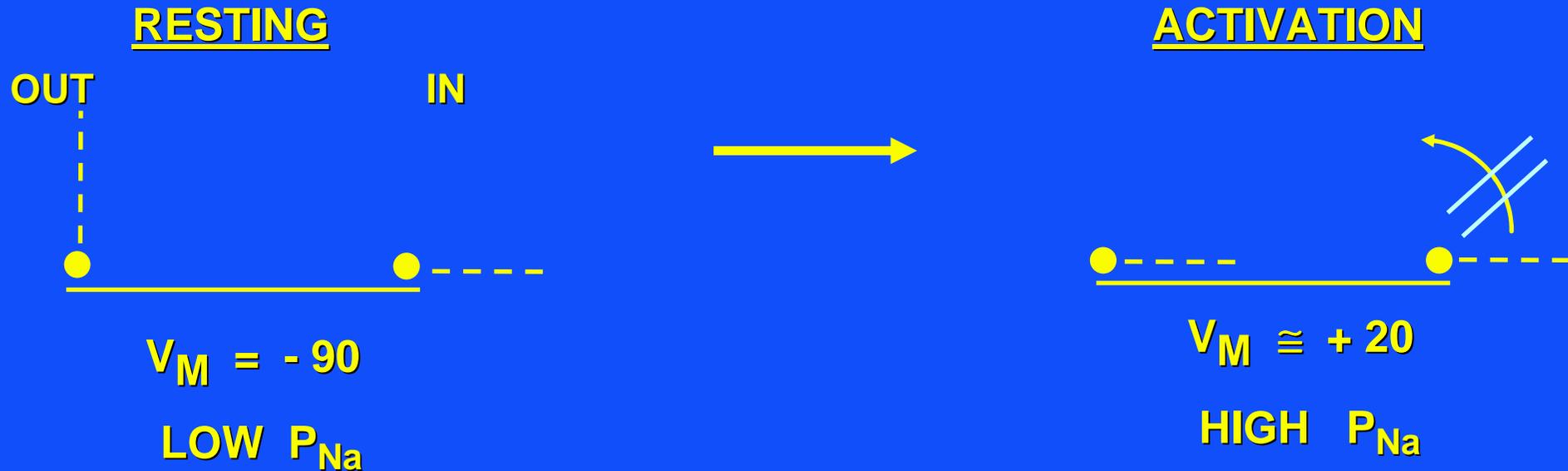
# Na<sup>+</sup> CHANNELS

<hr/>	<u>SKELTAL MUSCLE</u>	<u>CARDIAC</u>
TTX	SENSITIVE	INSENSITIVE
CHANNEL ACTIVATION	LOW VOLTAGE	HIGH VOLTAGE

# SODIUM CHANNEL ACTIVITY: NORMAL



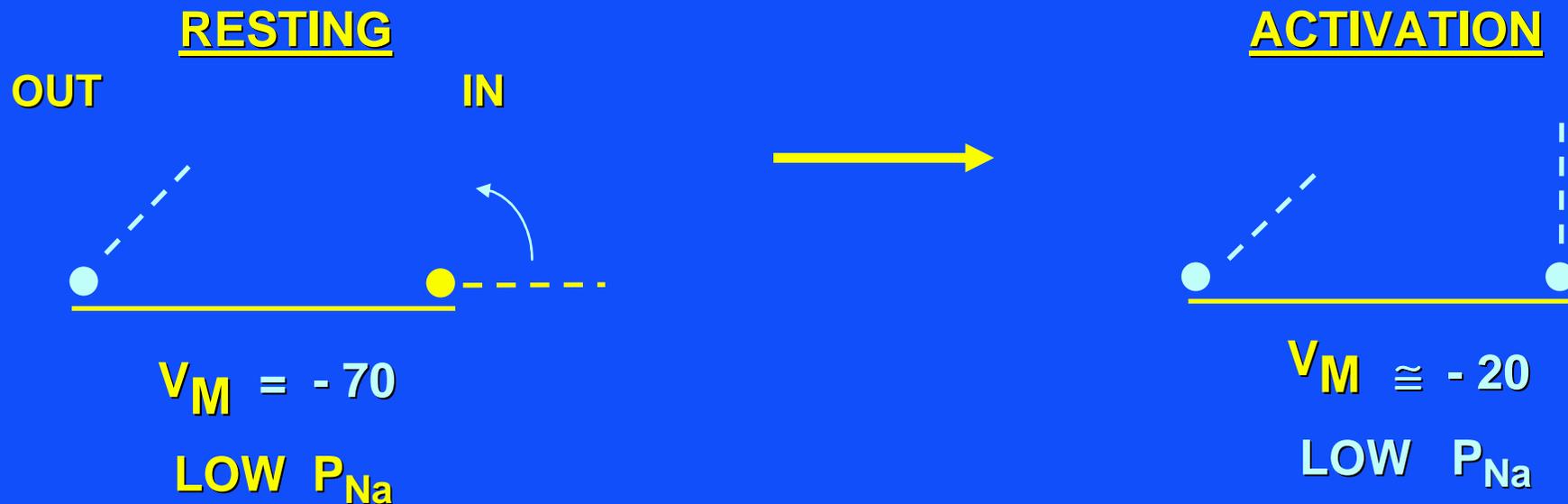
# SODIUM CHANNEL ACTIVITY: HPP



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# SODIUM CHANNEL ACTIVITY: HYPERKALEMIA



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