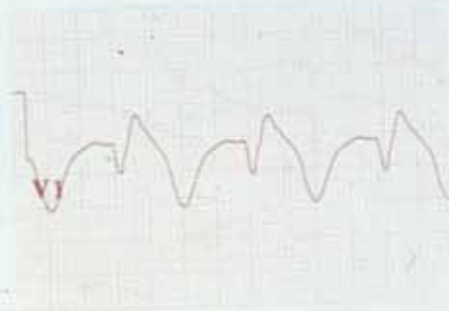


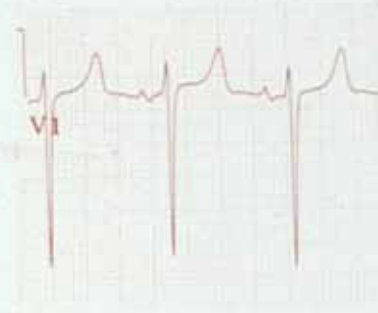
THE HYPERKALEMIC SYNDROMES

05-Nov-93
00:39



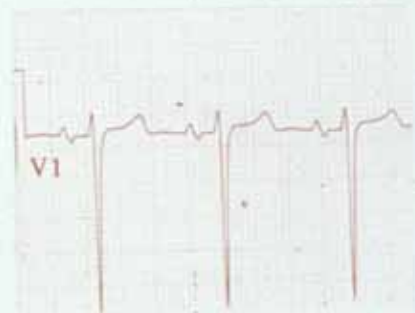
K+9.9

06-Nov-93
09:24



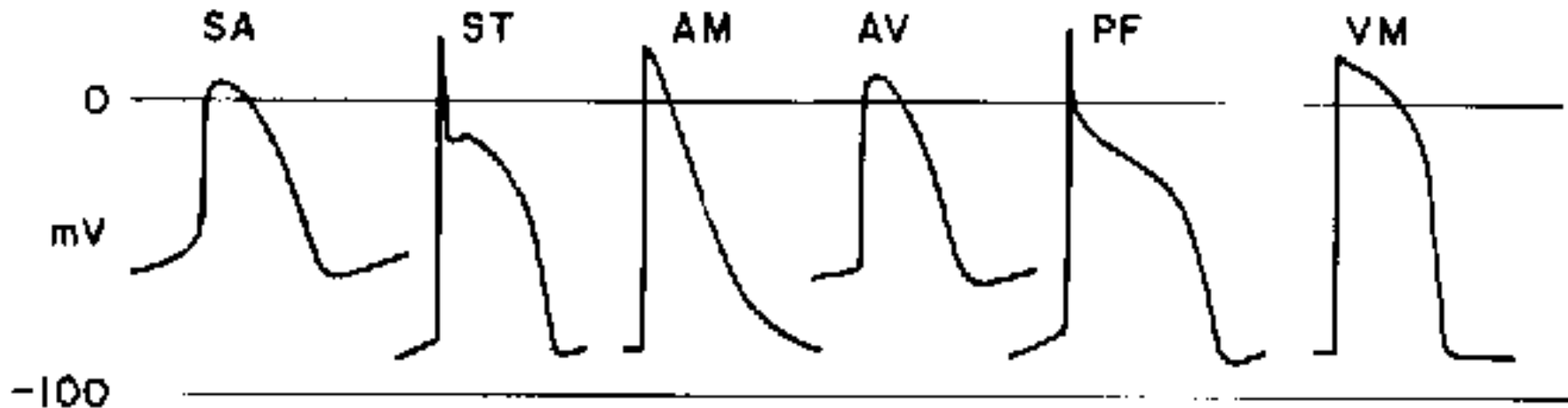
K+4.8

09-Nov-93
05:24



K+4.6

THE CARDIAC ACTION POTENTIALS



GATING

Ca⁺⁺

Na⁺

Na⁺

Ca⁺⁺

Na⁺

Na⁺

TSIEN & HESS, 1986

TWO KINDS OF HYPERKALEMIC SYNDROMES

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

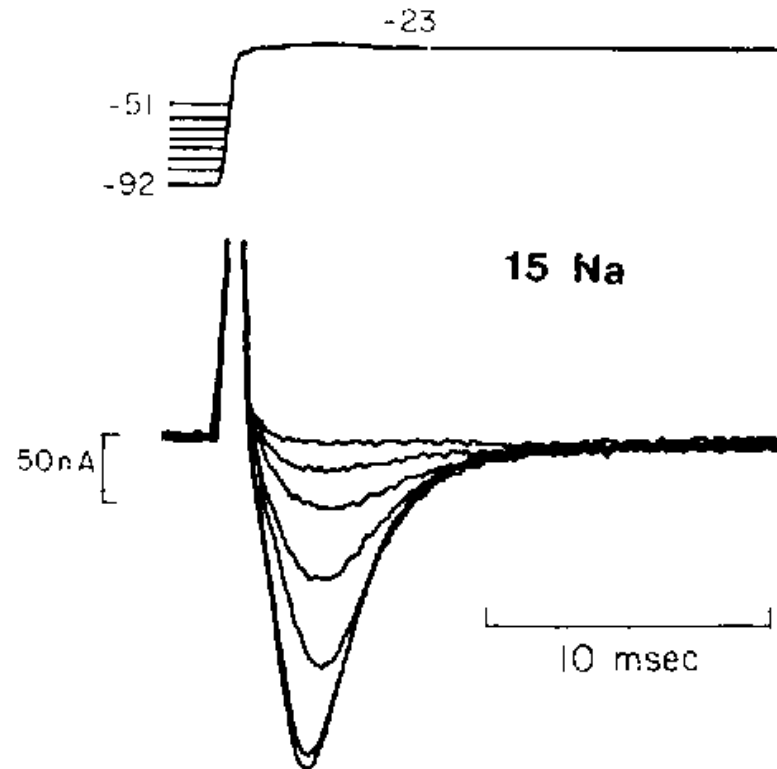
THE RESTING CARDIAC MEMBRANE VOLTAGE

$$V_M = 60 \log \frac{K_i}{K_o}$$

$$K_o = 4 : \quad K_i / K_o = 30; \quad V_M \approx 89 \text{ mV}$$

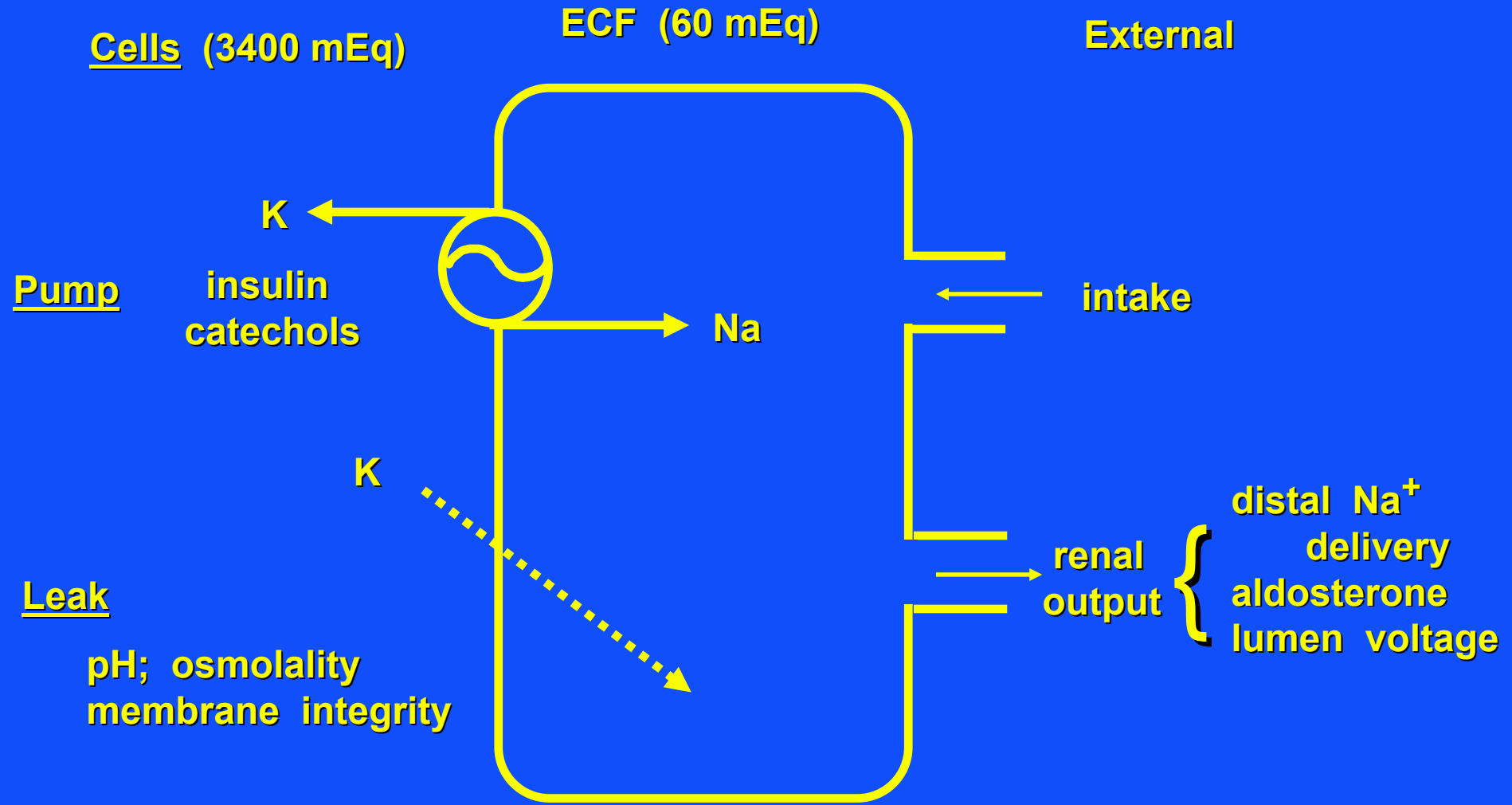
$$K_o = 8 : \quad K_i / K_o = 17; \quad V_M = 70 \text{ mV}$$

PARTIAL DEPOLARIZATION INACTIVATES CARDIAC ACTION POTENTIAL



TSIEN & HESS, 1986

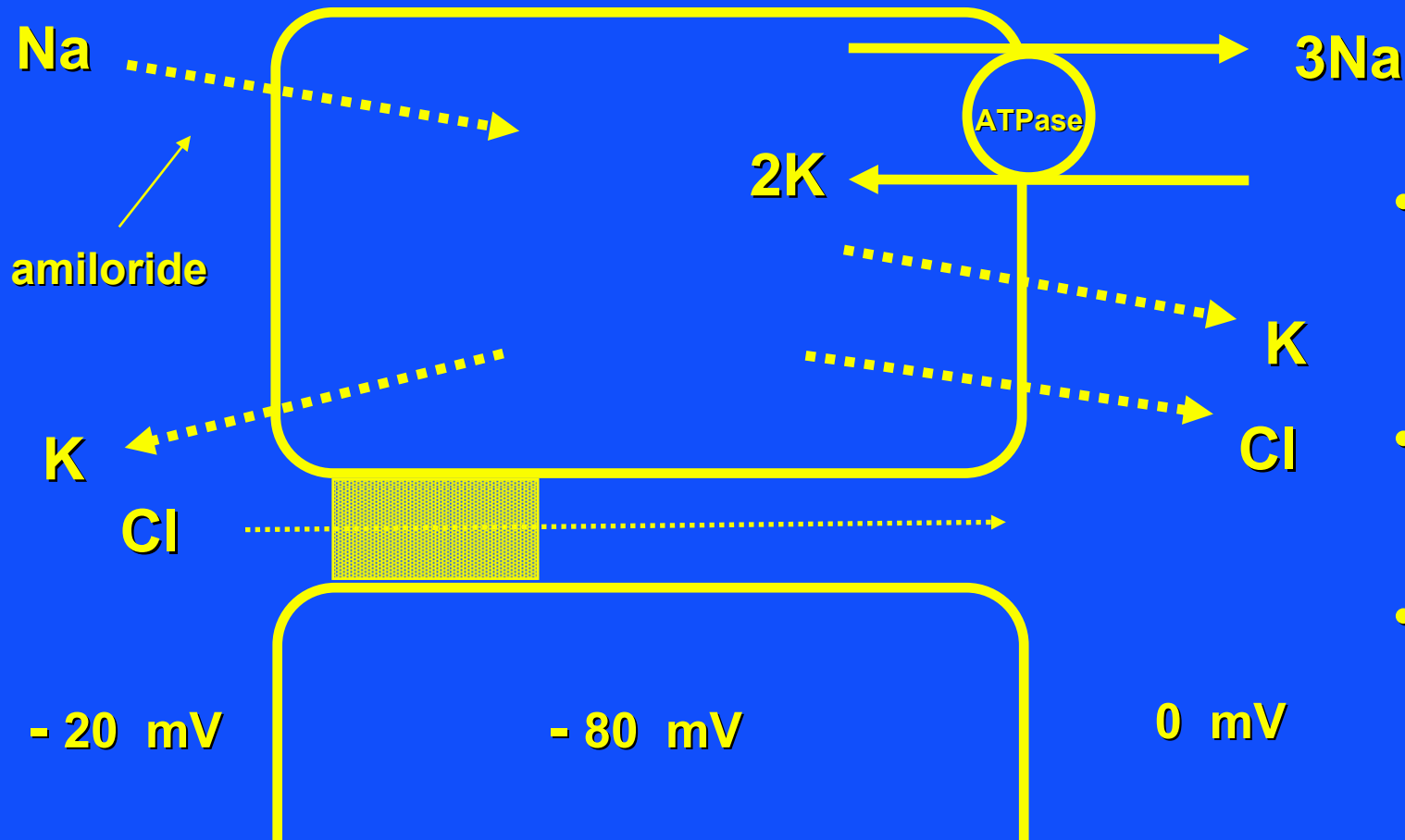
K⁺ BALANCE



RENAL HANDLING OF K^+

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

THE CCD PRINCIPAL CELL

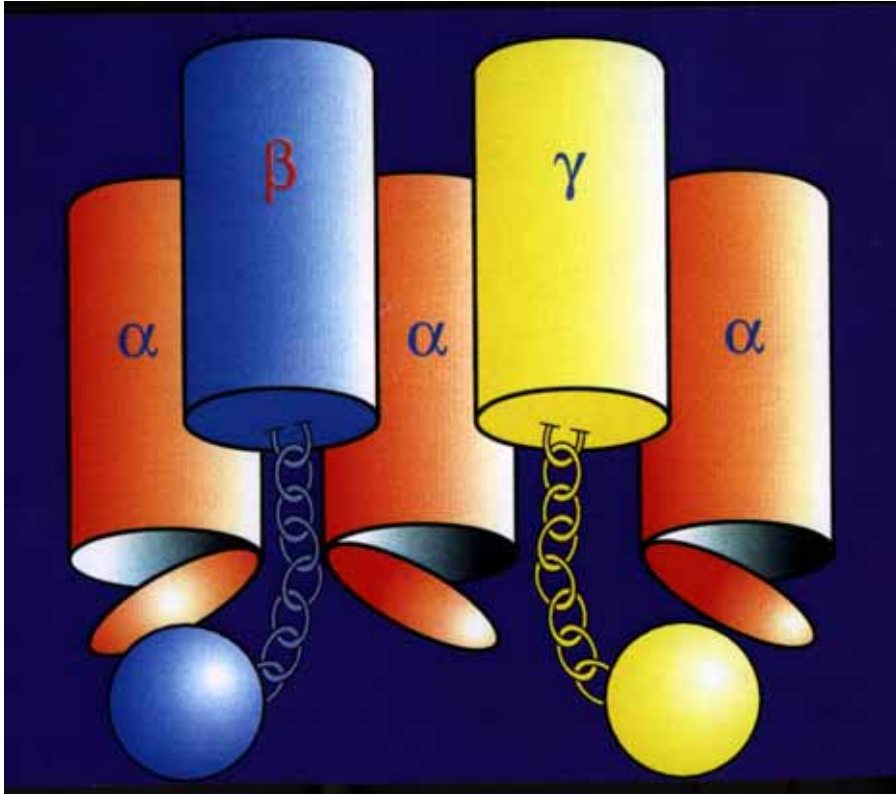


- Predominant in late DCT and CCT
- Aldosterone-responsive
- Sensitive to:
 - amiloride
 - triamterene
 - spironolactone

ENaC

Epithelial Na Channel

- Each α subunit :
amiloride-sensitive Na channel
- β and γ subunits:
 \uparrow *surface delivery of ENaC*
- Liddle's syndrome:
 β subunit mutation
- pseudohypoaldosteronism I:
 α or β subunit mutation
- ARDS :
 α subunit mutation



MAJOR CAUSES OF HYPERKALEMIA

I. Diminished Renal Excretion

Reduced GFR

ATN

ESRD

Reduced Tubular Secretion

Addison's disease

Principal cell disease

Potassium - sparing diuretics

II. Transcellular Shifts

Acidosis

Cell destruction

HPP

Diabetic hyperglycemia

Insulin - dependence

plus aldosterone lack

Depolarizing muscle

paralysis

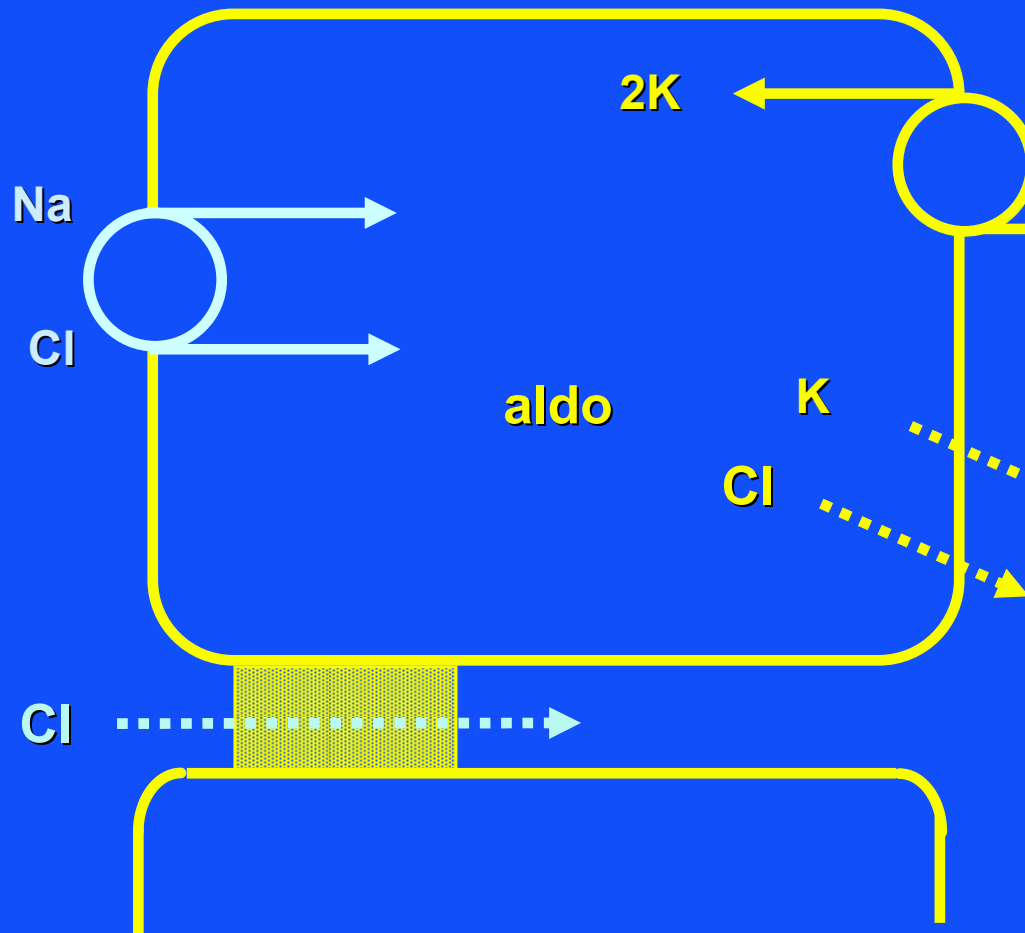
HYPERKALEMIC RTA SYNDROMES

PRINCIPAL CELL DISORDERS

DISORDER	PRINCIPAL DEFECT	PRINCIPAL FEATURES
Gordon's syndrome	Activated NaCl cotransporter High shunt conductance	↑ K ⁺ ; Na ⁺ avid
Pseudohypoaldosteronism I	Closed Na ⁺ channel	↑ K ⁺ ; Na ⁺ wasting; RTA
Interstitial disease	Hyporeninemic hypoaldosteronism	↑ K ⁺ ; Na ⁺ wasting; RTA

DISTAL CONVOLUTED TUBULE DISEASE

GORDON'S SYNDROME (PSEUDOHYPOALDOSTERONISM II)

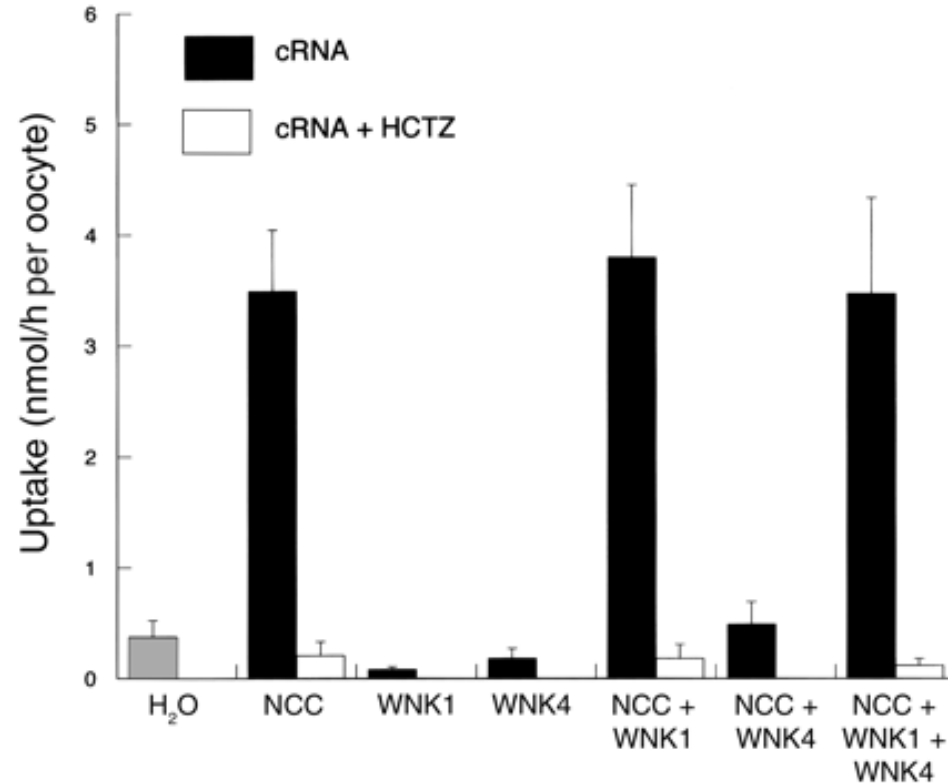


WNK 1, 4 mutations activate thiazide-sensitive NaCl transporter

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

GORDON'S SYNDROME

A DCT DISEASE

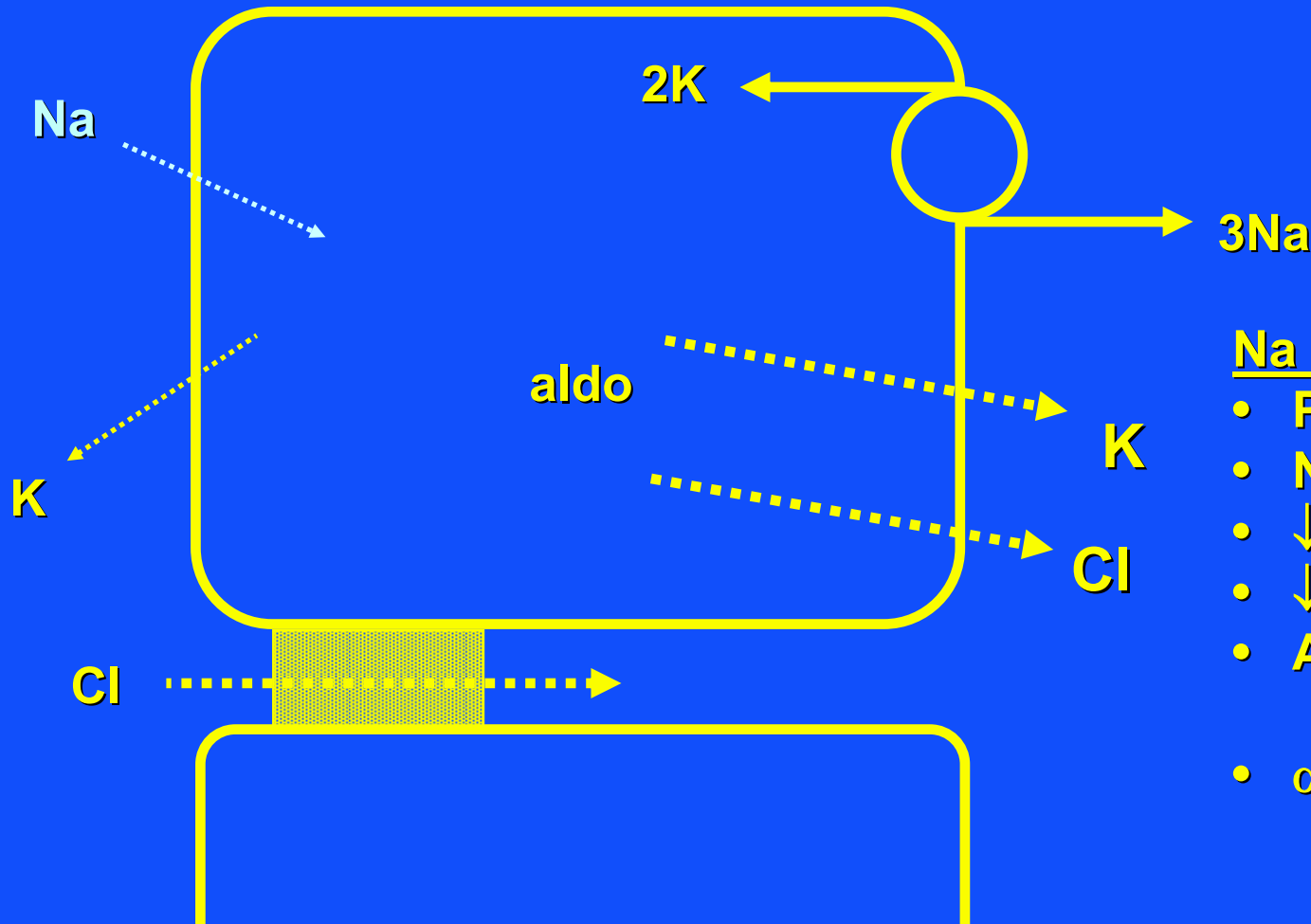


WNK: with no lysine
WNK I: ↑ NCC activity
WNK IV: function unknown

Yang *et al.*
JCI 111:1039, 2003

PRINCIPAL CELL DISEASES

Na^+ CHANNEL BLOCKADE (PSEUDOHYPOALDOSTERONISM I)

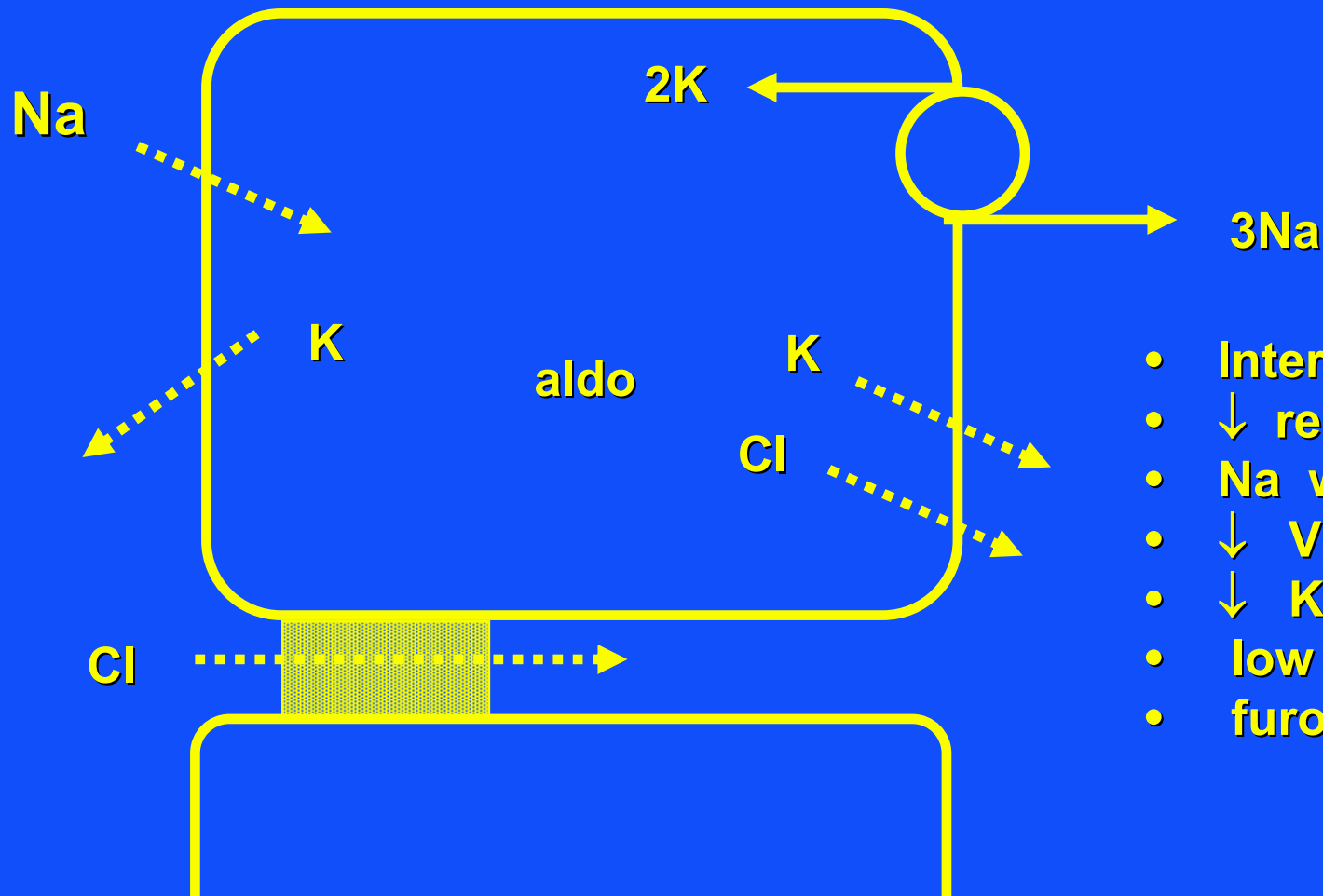


Na Channel Blockade:

- Prototype: amiloride Rx
- Na wasting
- $\downarrow V_M$
- \downarrow K, H secretion
- Aldosterone unresponsive
- α or β 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⁺ 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:

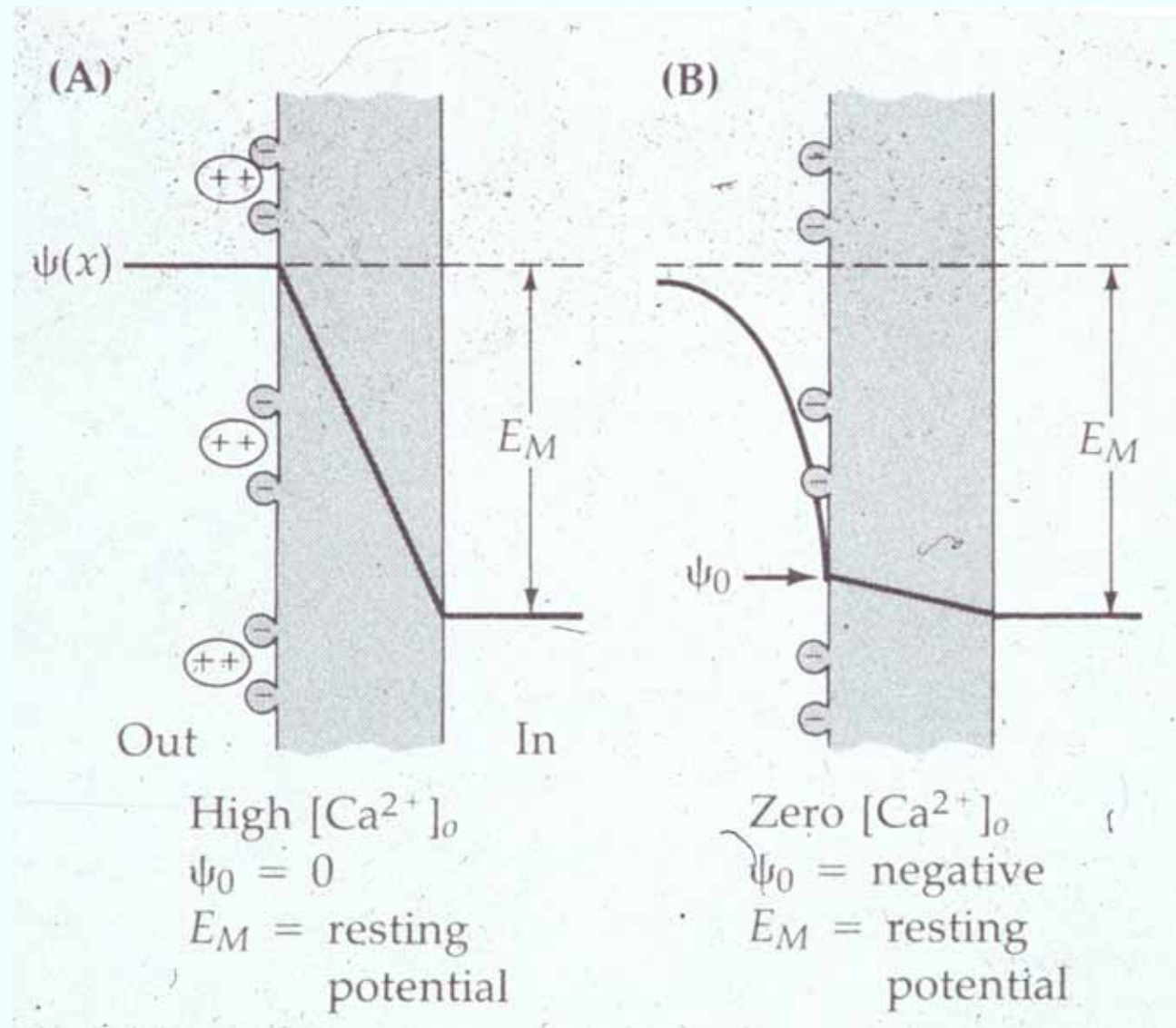
0.5 mEq K⁺ / 25 Gm GLUCOSE

ALBUTEROL (β - AGONIST):

BY INHALATION

CARDIAC PROTECTION IN HYPERKALEMIA

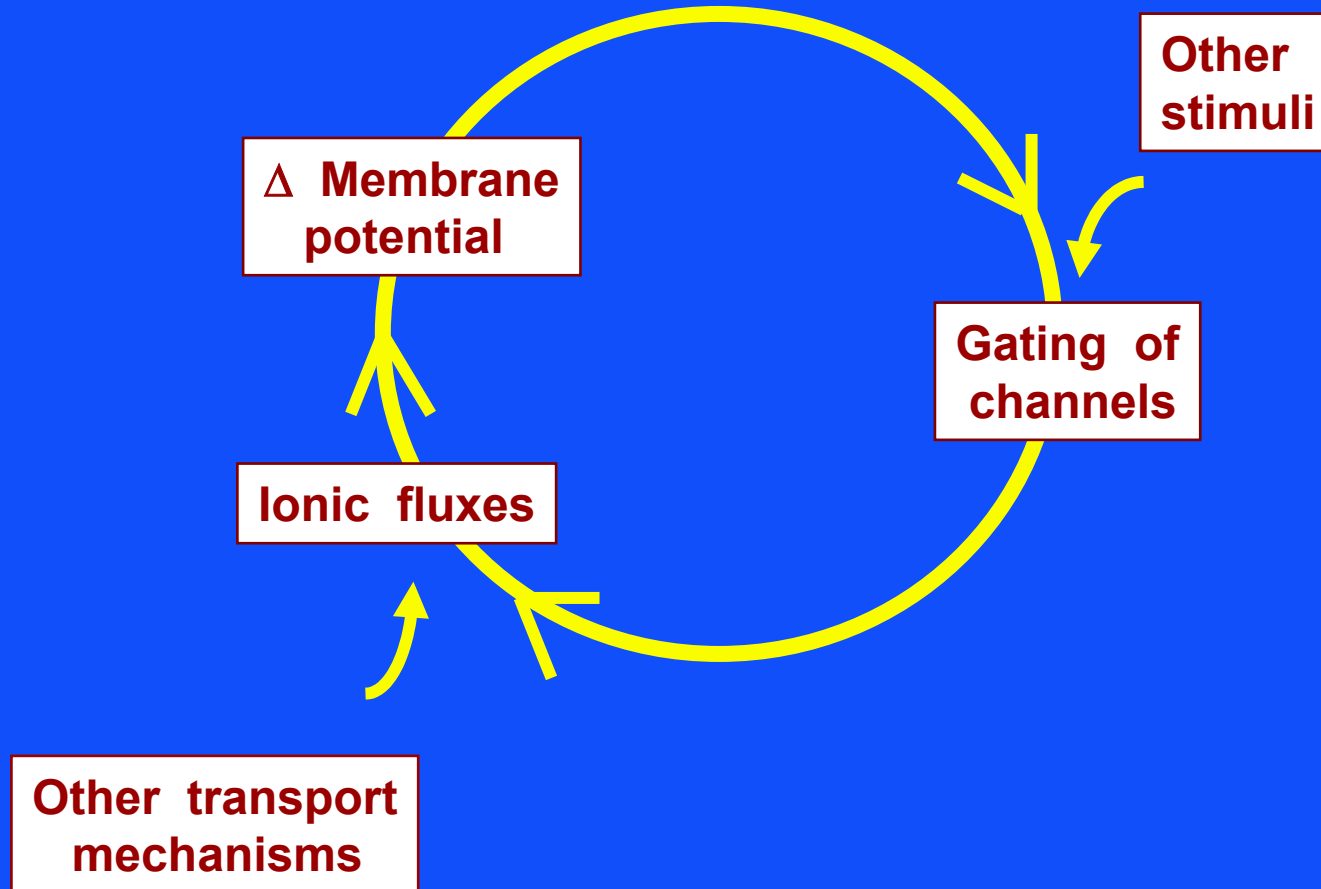
Ca^{++} SCREENING OF SURFACE POTENTIAL



TWO KINDS OF HYPERKALEMIC SYNDROMES

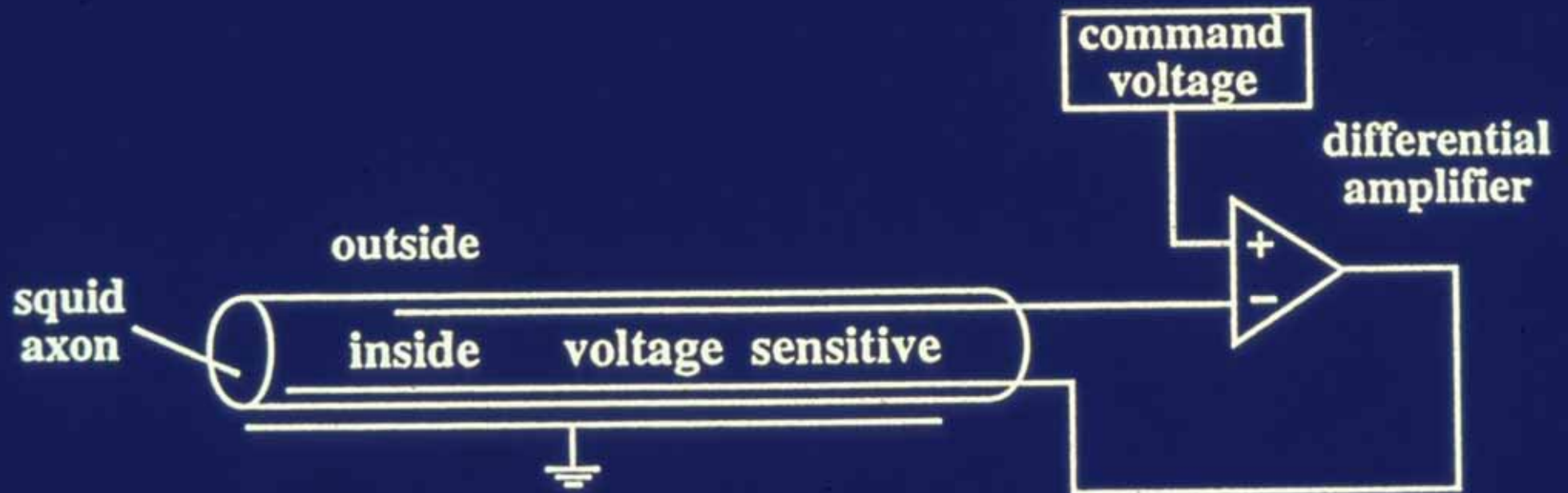
<u>Fiber</u>	<u>Activation Threshold</u>	<u>Disorder</u>
Skeletal muscle <i>TTX - sensitive</i>	- 60	{ periodic paralysis heart generally unaffected
Myocardium <i>TTX - insensitive</i>	- 75	{ cardiac standstill rare skeletal muscle paralysis

THE GREAT HODGKIN-HUXLEY CONTRIBUTION

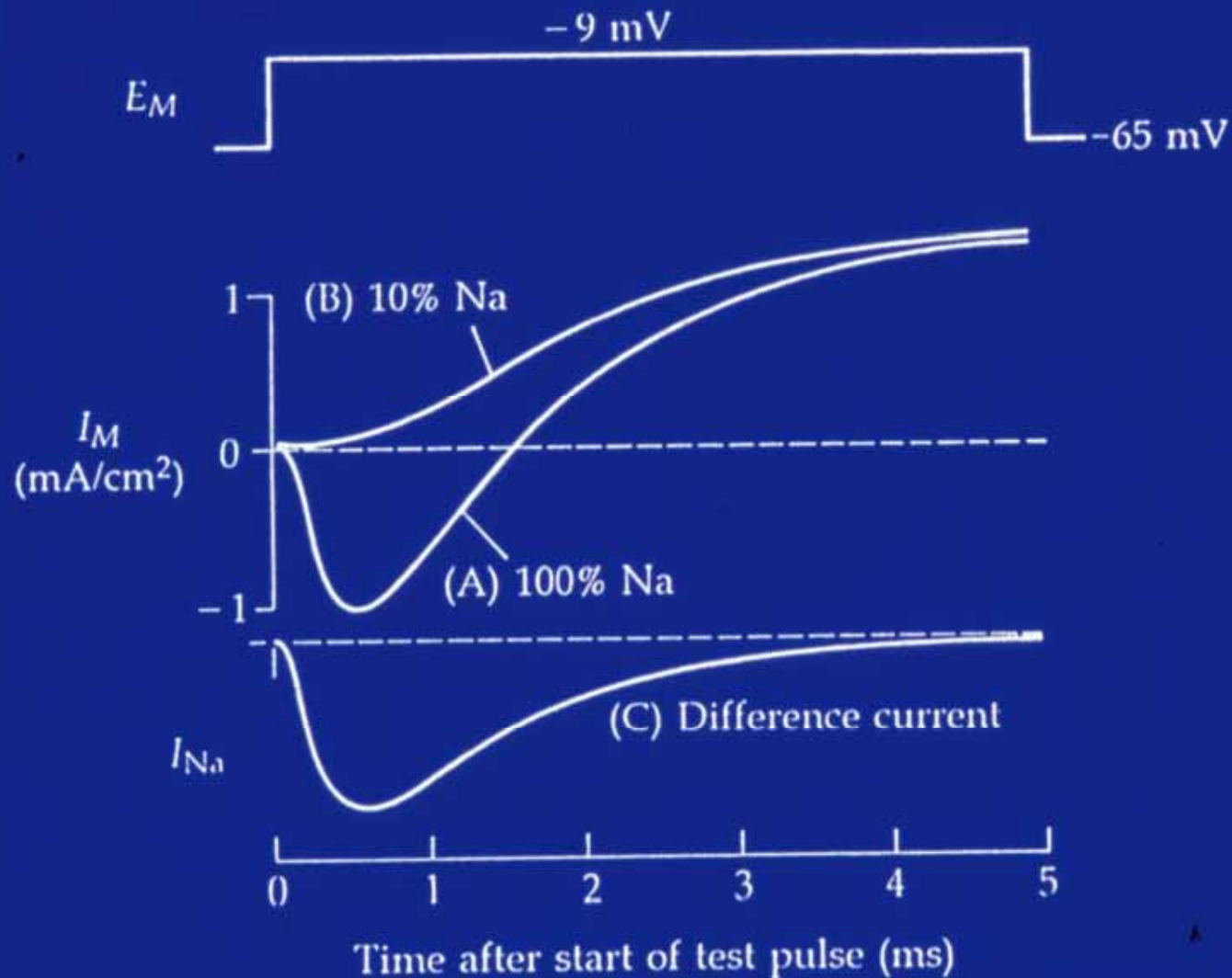


CLASSICAL CYCLE OF ELECTRICAL EXCITATION

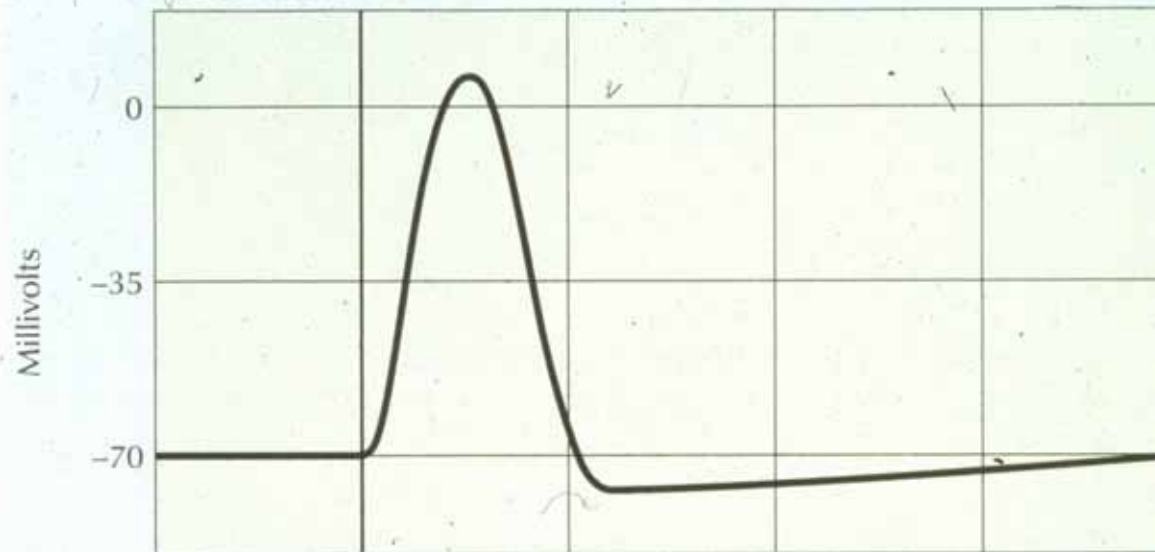
The Voltage Clamp Technique



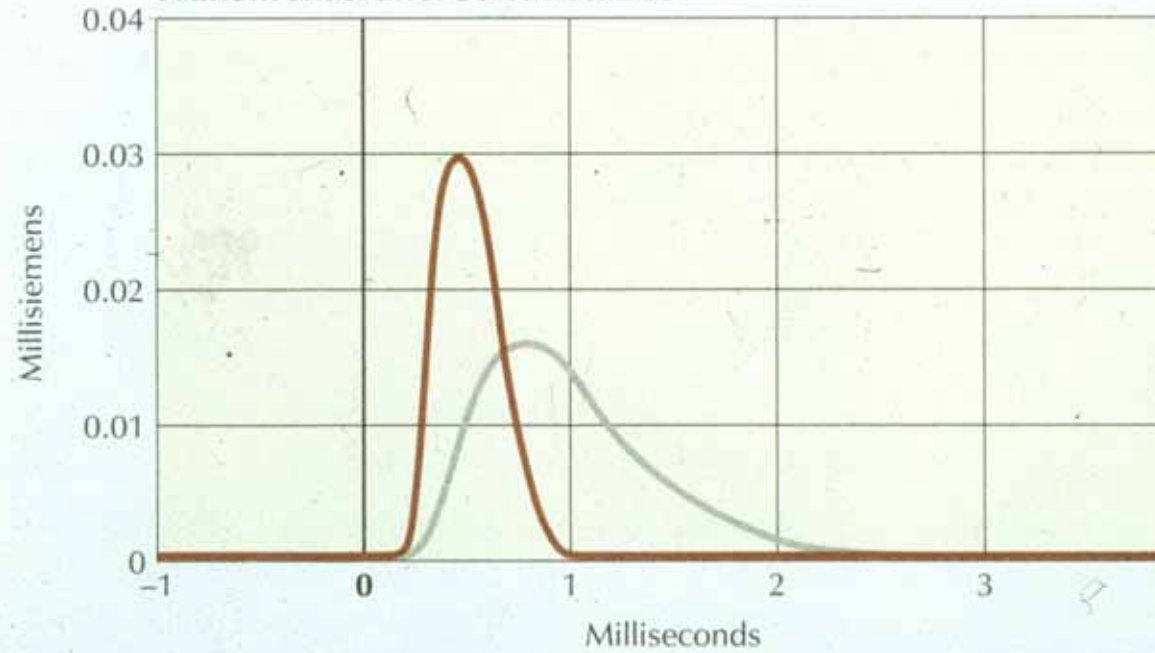
THE HODGKIN-HUXLEY EXPERIMENTAL STRATEGY



Action Potential



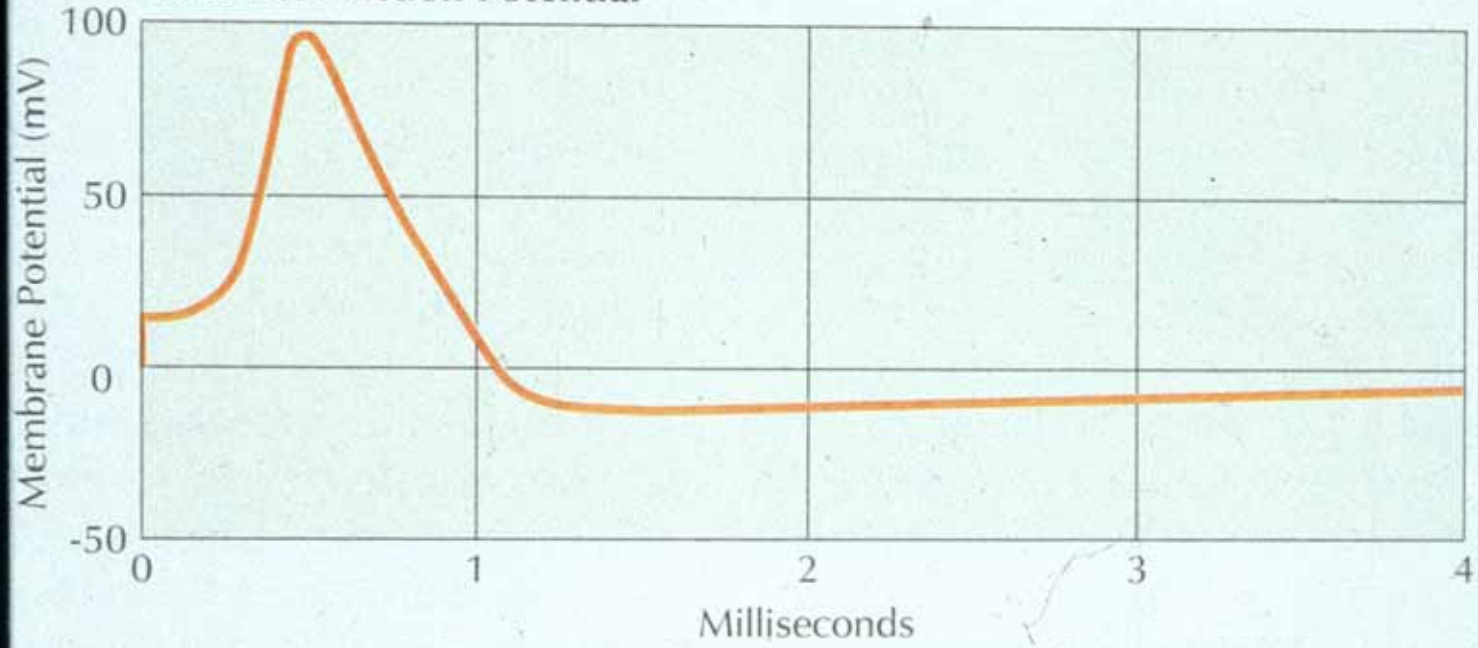
Transmembrane Conductance



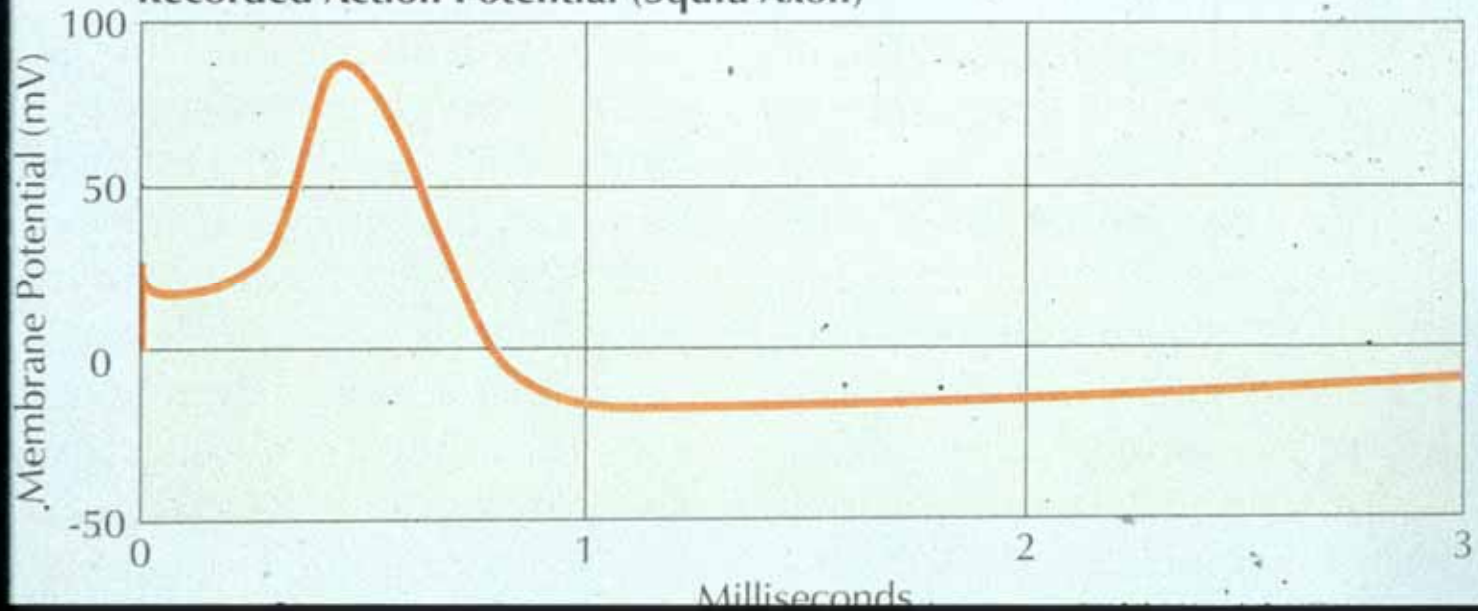
— Sodium

— Potassium

Calculated Action Potential

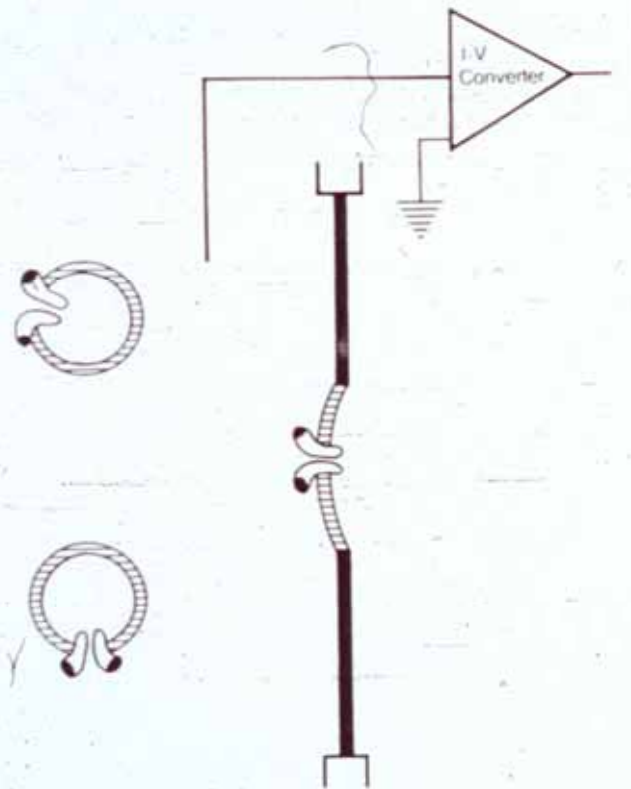


Recorded Action Potential (Squid Axon)



ELECTROPHYSIOLOGIC APPROACHES

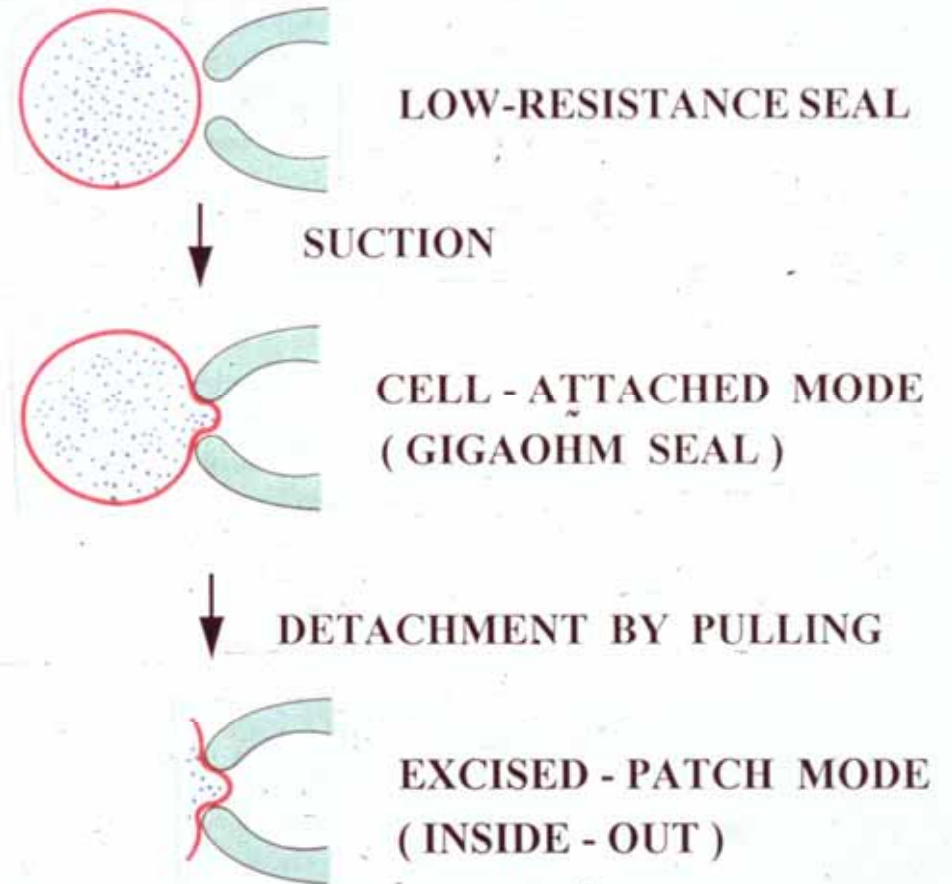
VESICLE FUSION INTO BILAYERS



320mM KCl
Cis

50 mM KCl
Trans

EXCISED PATCH TECHNIQUE



LOW-RESISTANCE SEAL

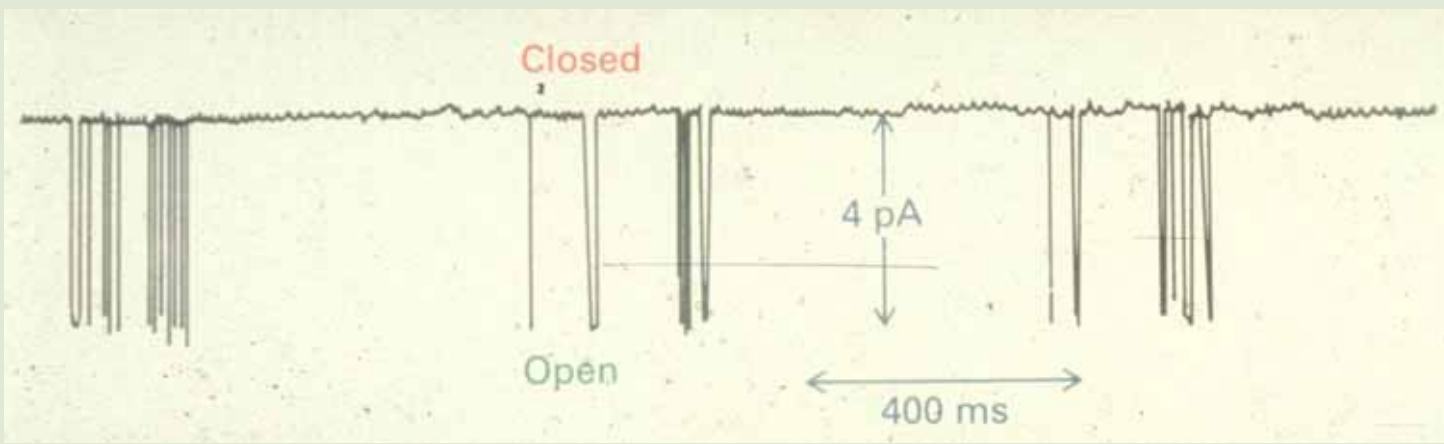
SUCTION

CELL - ATTACHED MODE
(GIGAOHM SEAL)

DETACHMENT BY PULLING

EXCISED - PATCH MODE
(INSIDE - OUT)

(STRYER, 1988)

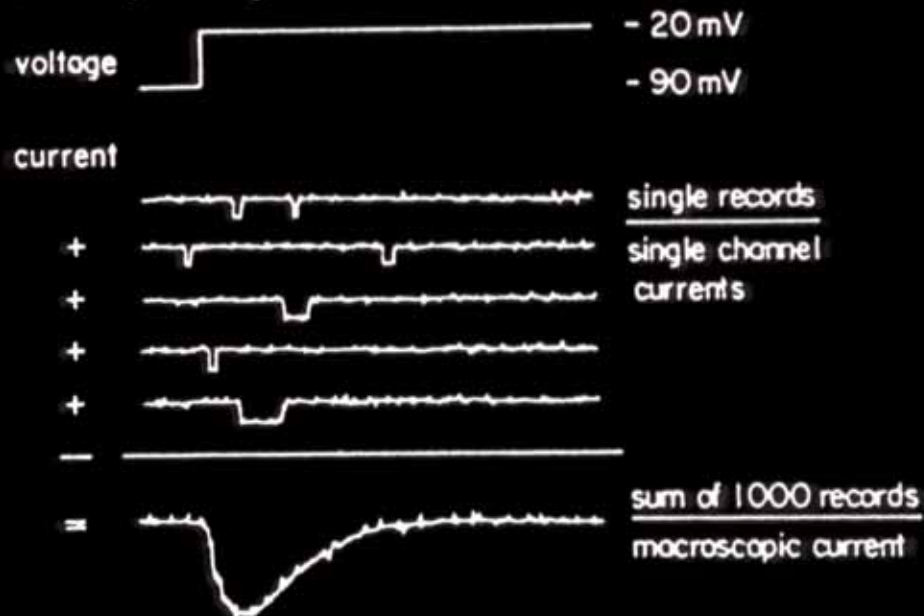


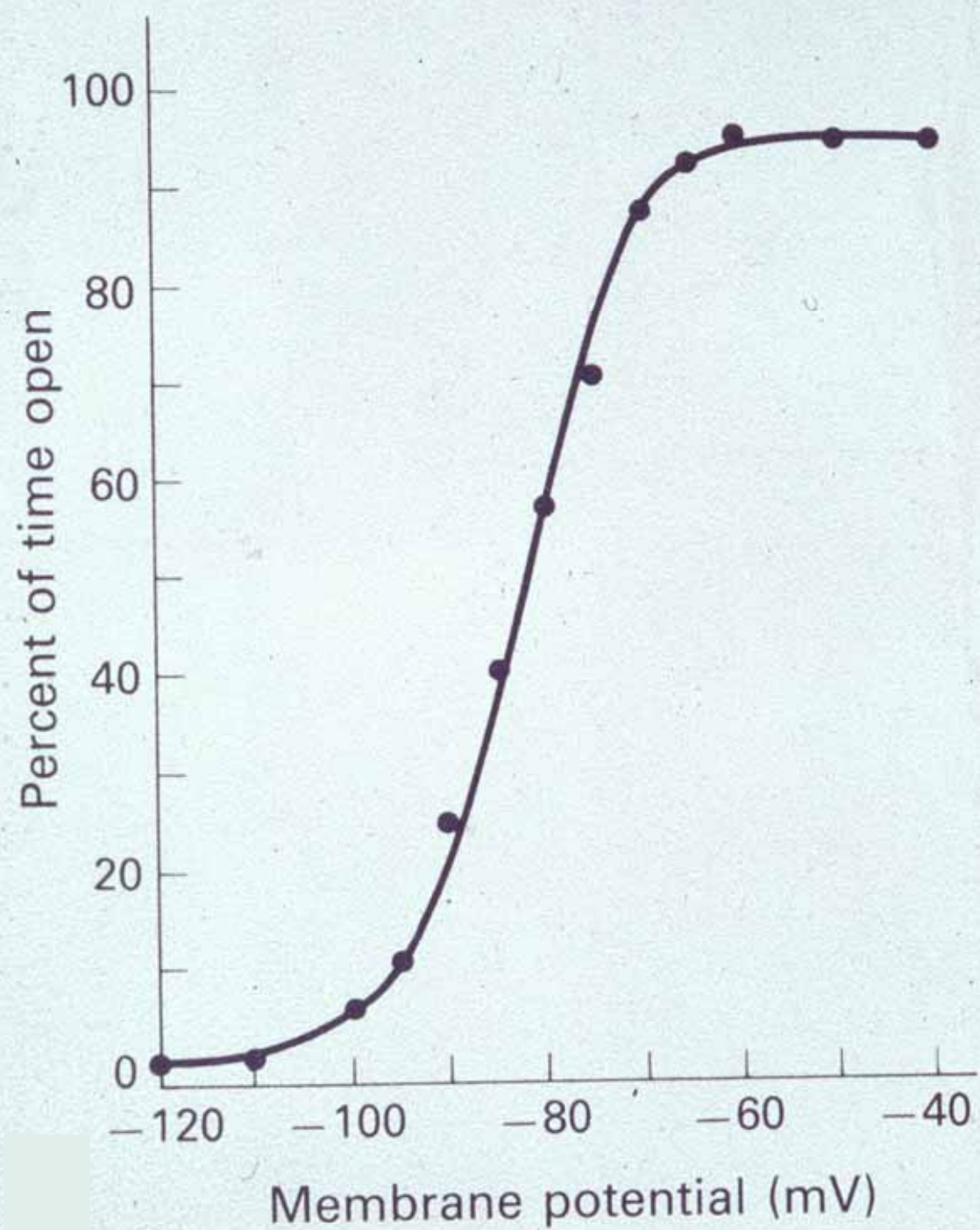
MACROSCOPIC AND SINGLE Na⁺ CHANNEL BEHAVIOR

A. Traditional voltage clamp - Large membrane area

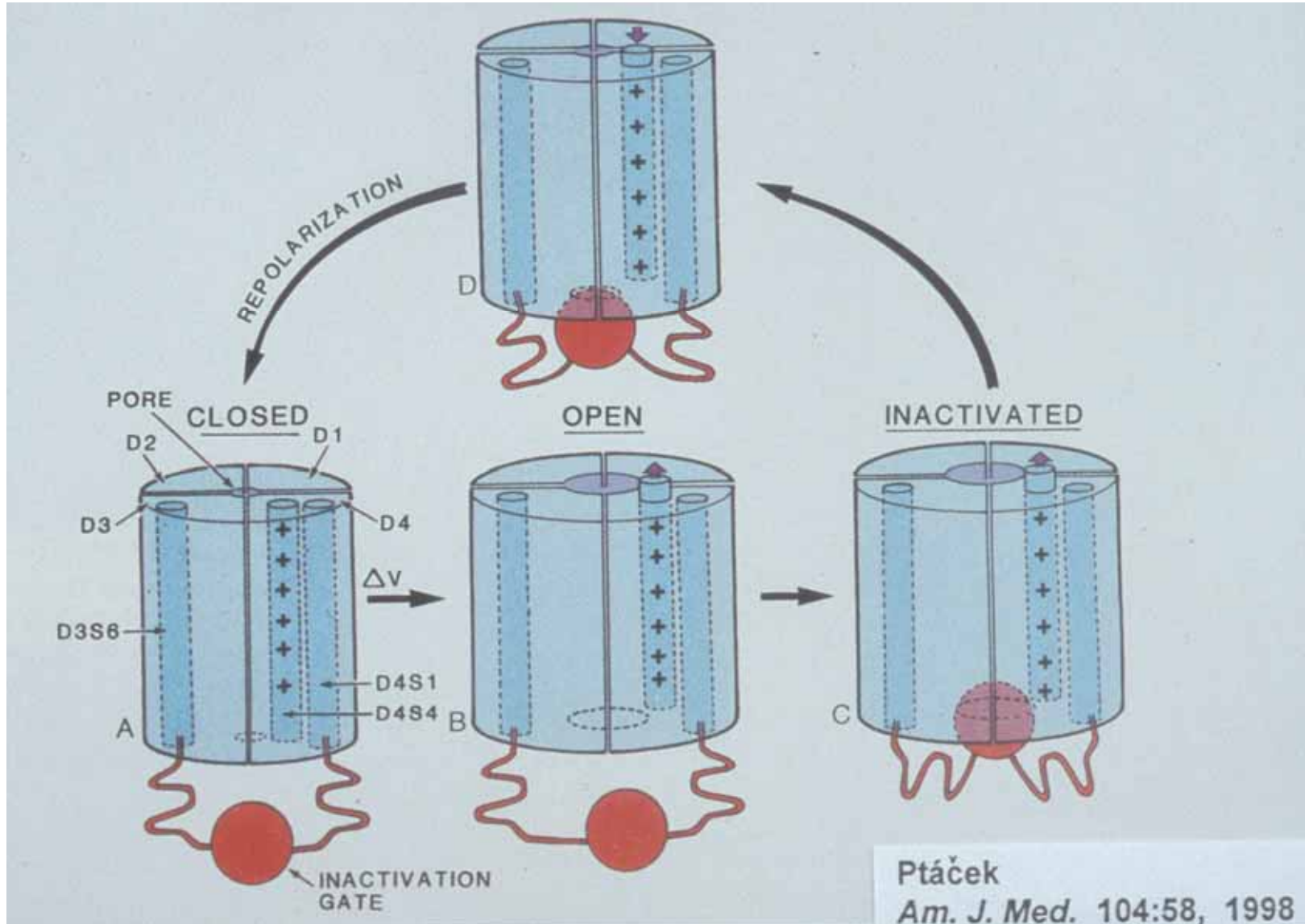


B. Patch Clamp Very small membrane area





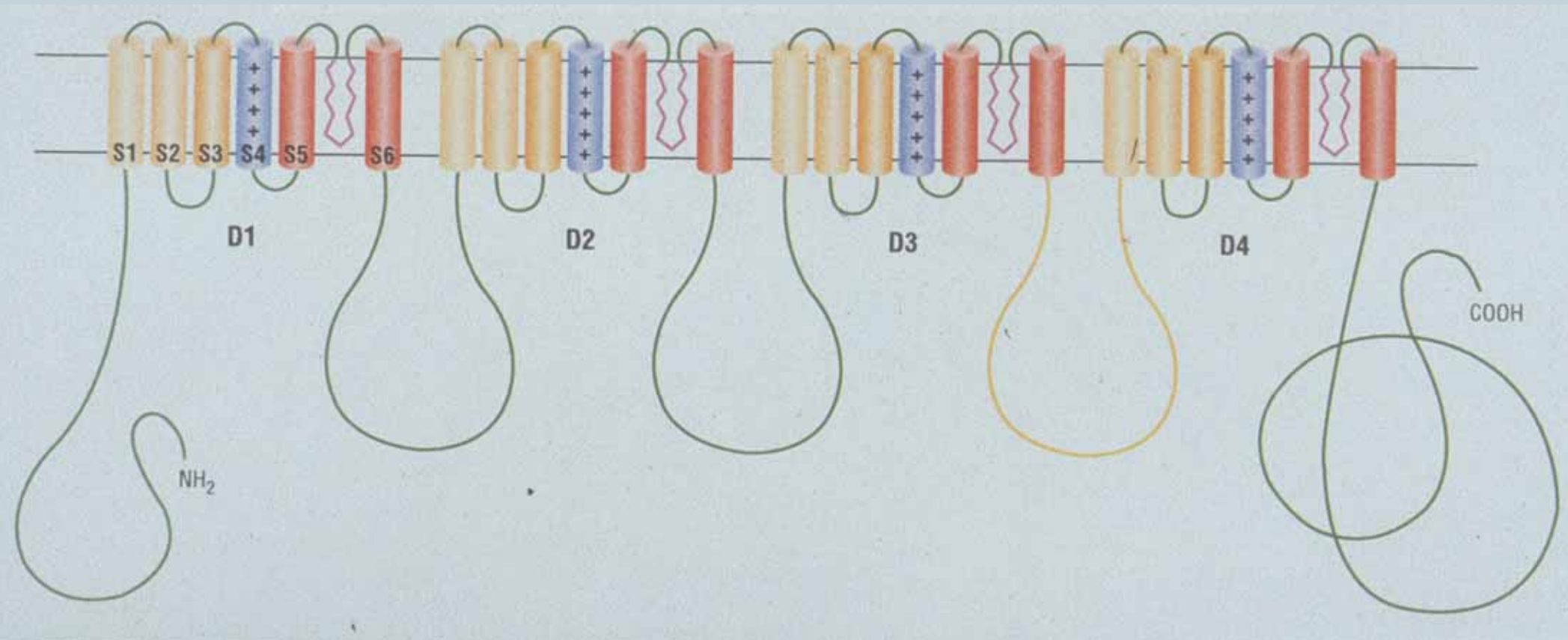
CATION CHANNEL KINETICS



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**

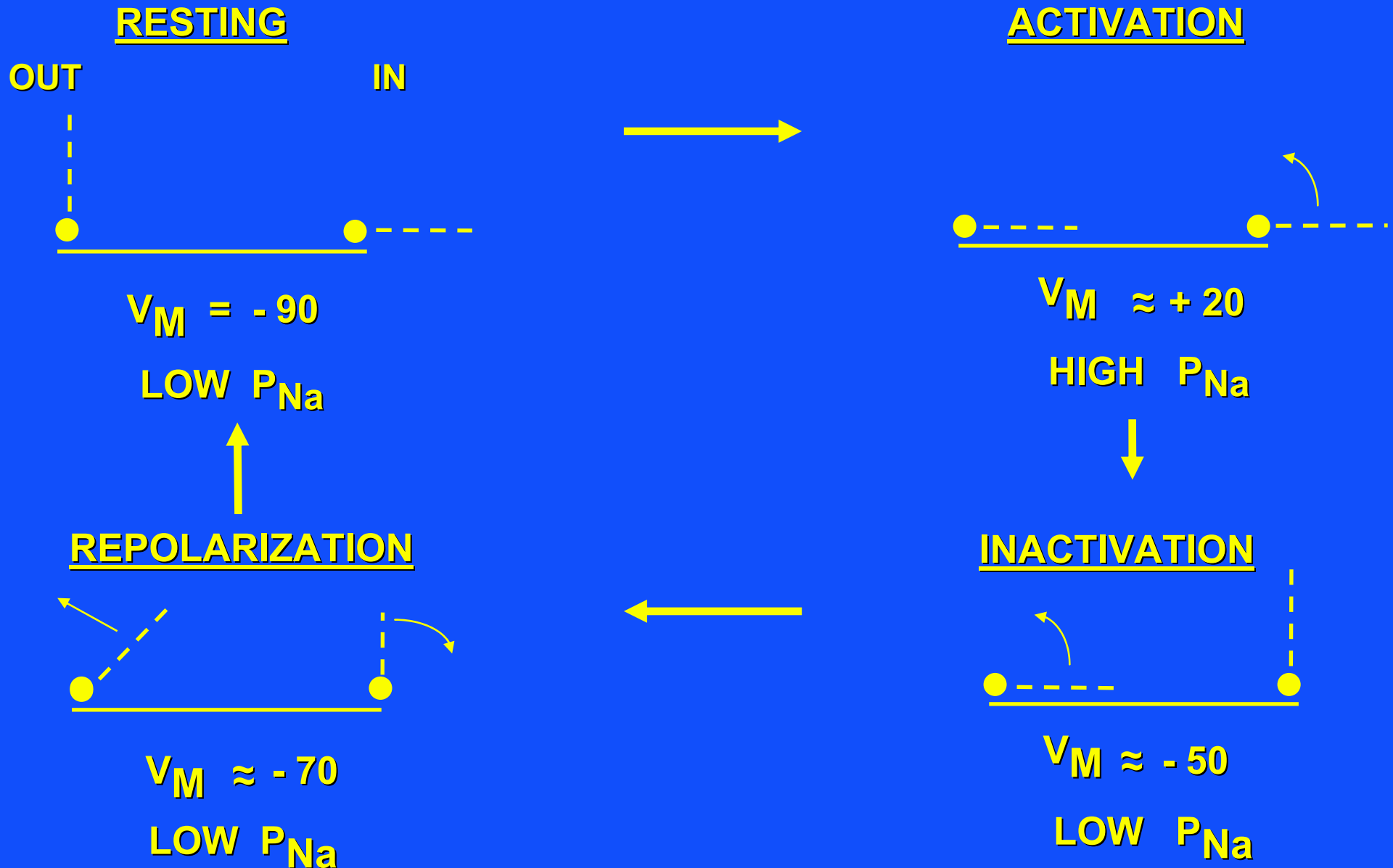
VOLTAGE-GATED CATION CHANNELS



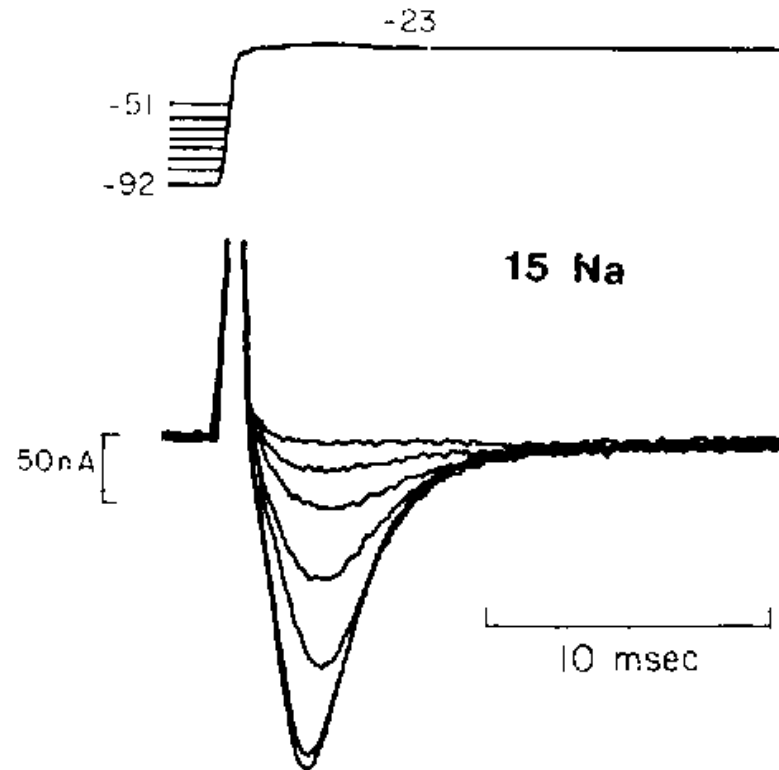
Ptáček

Am. J. Med. 104:58, 1998

SODIUM CHANNEL ACTIVITY: NORMAL

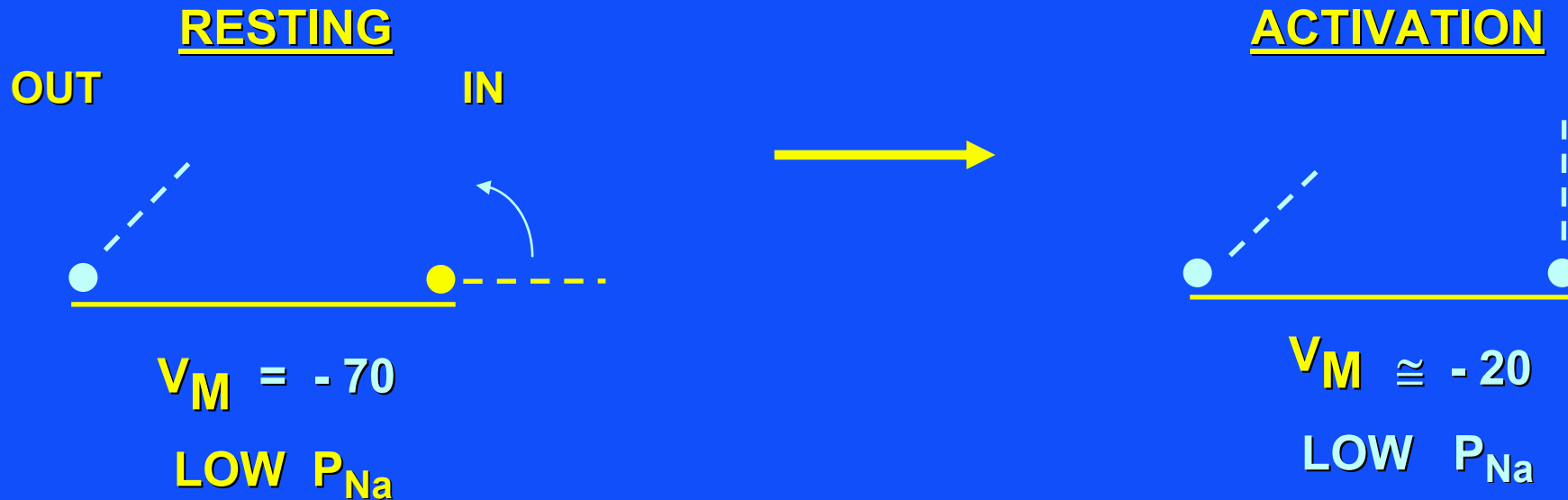


PARTIAL DEPOLARIZATION INACTIVATES CARDIAC ACTION POTENTIAL



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

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⁺ 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



Scientific American May, 1991

Pillars of the **STUD BOOK** James Weatherby, 1791

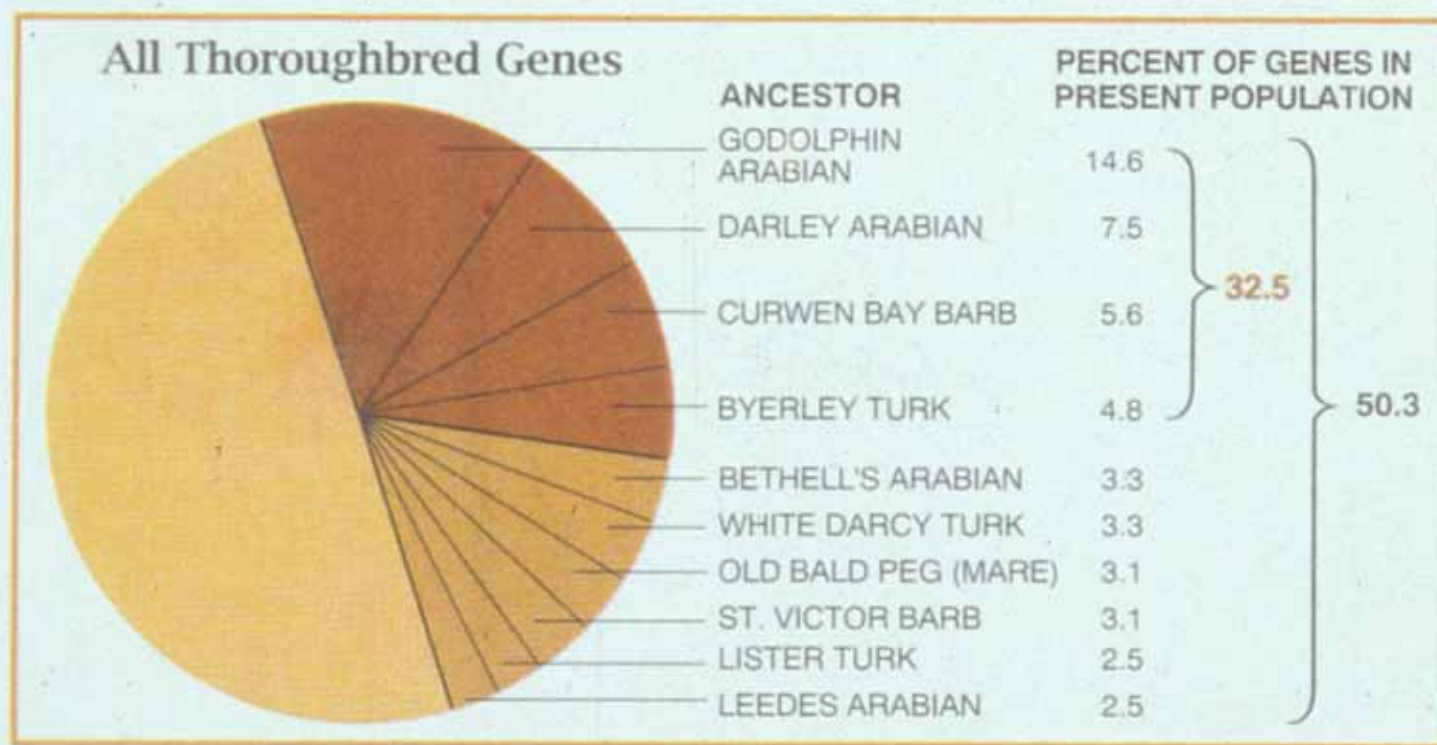


Godolphin Arabian
1725

Darley Arabian
1688

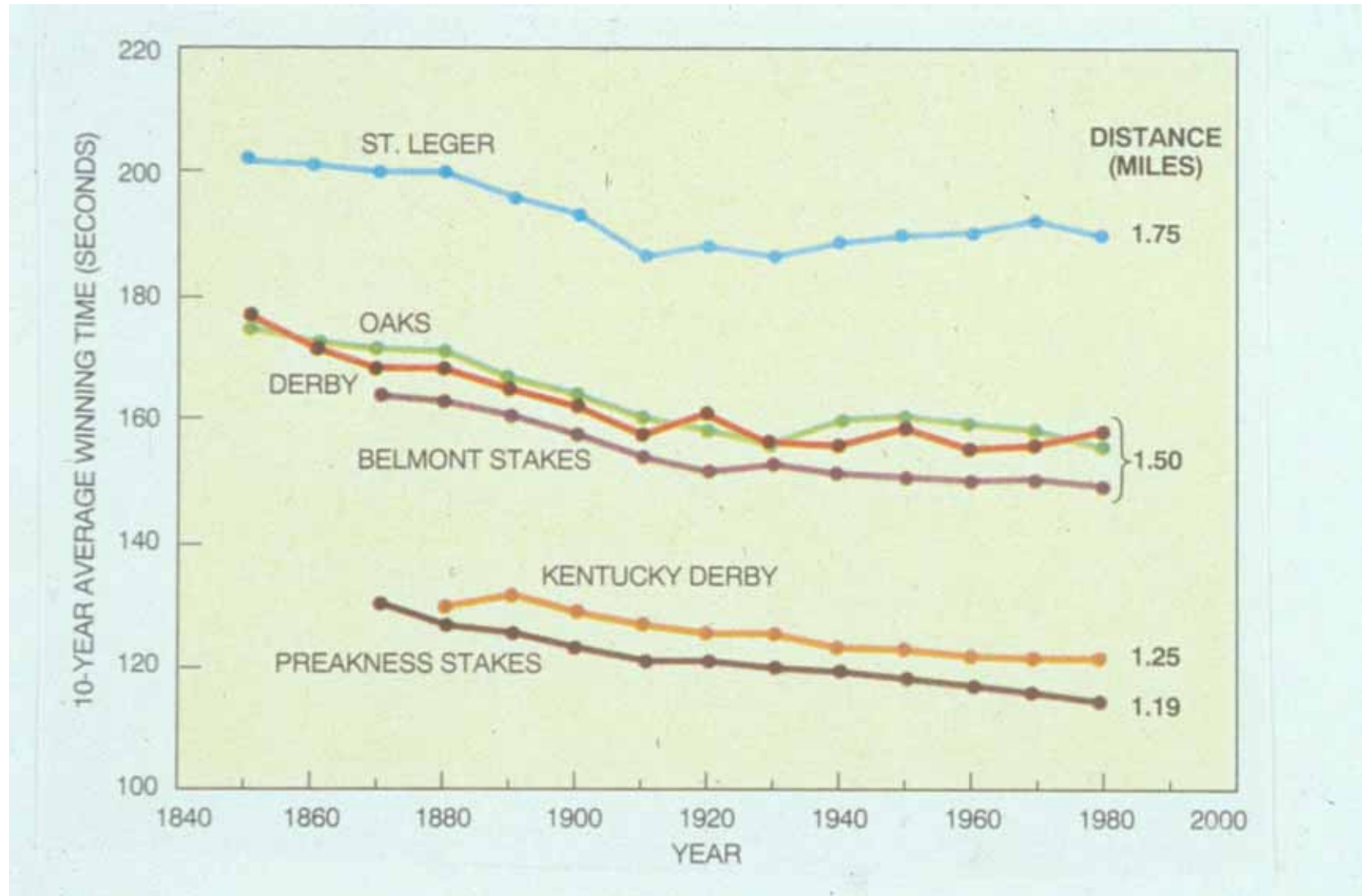
Byerley Turk
1690

PILLARS OF THE *STUD BOOK*



SCIENTIFIC AMERICAN MAY, 1991

THE GREAT RACES



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

Stallion Manager

Mark Faulkner

Faulkner Quarter Horses

Route 4 - Box 770 - Interstate 35 and Waterloo

Edmond, Oklahoma 73034 Ext 146

Allen E. Faulkner • (405) 341-8626



Attending Veterinarian

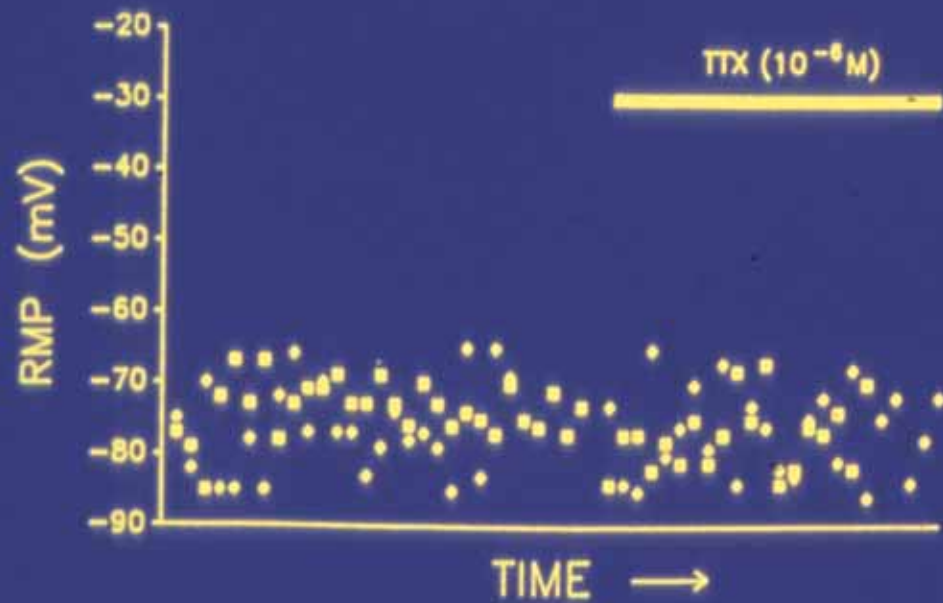
DR. MIKE JOHNSTON

Trainer

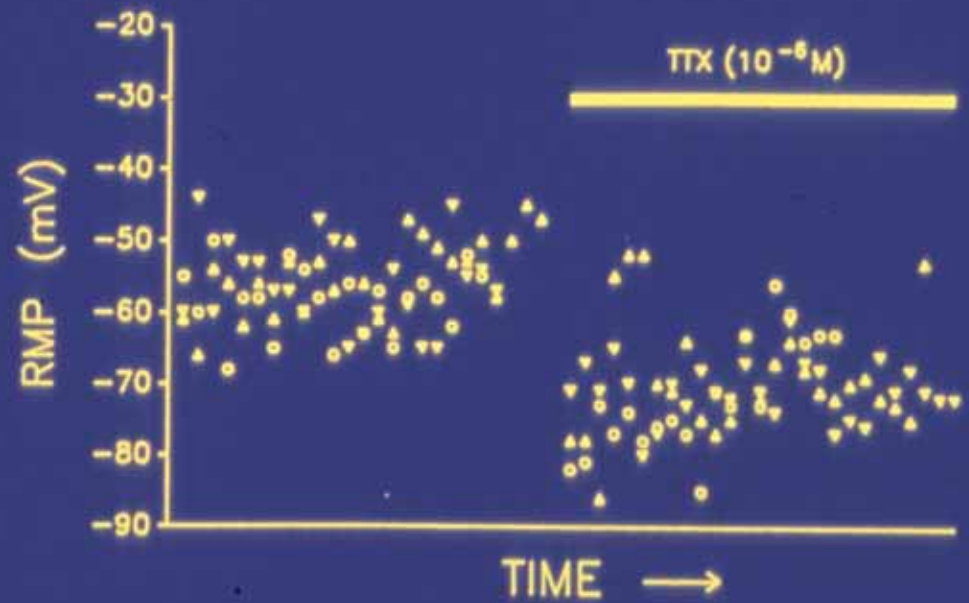
Jeff LaGrow

HPP IN HORSES

Normal

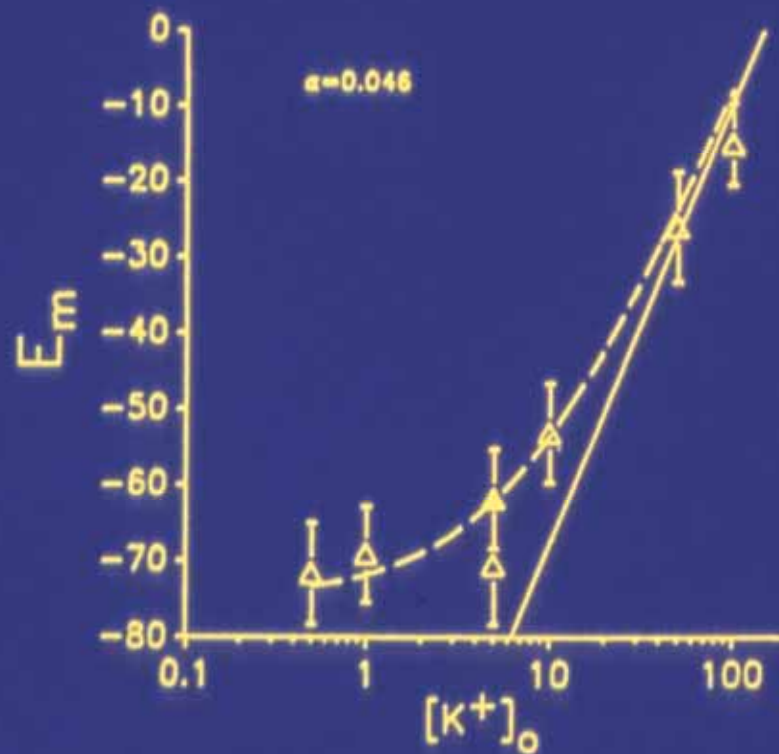


HPP

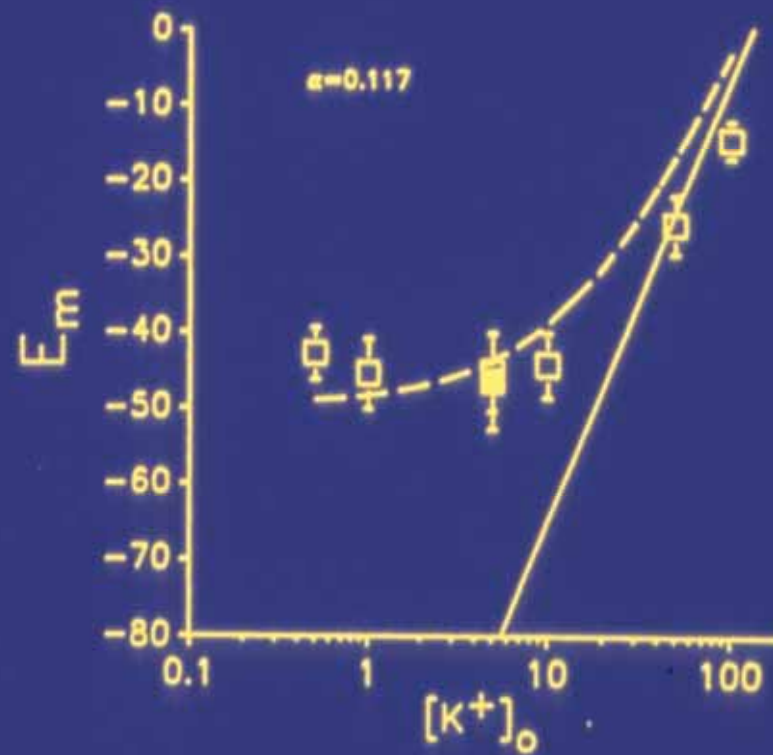


HPP IN HORSES

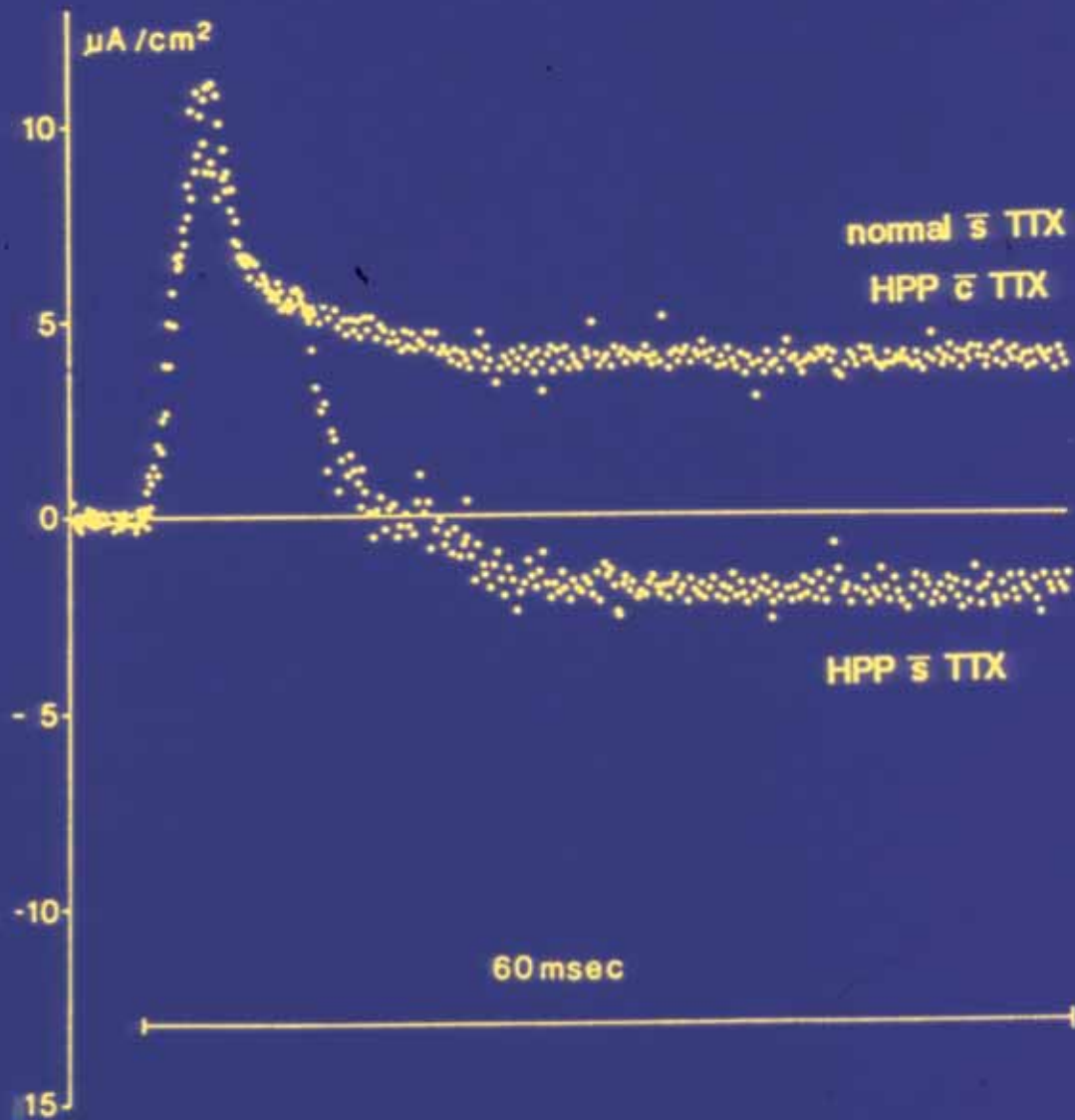
Normal



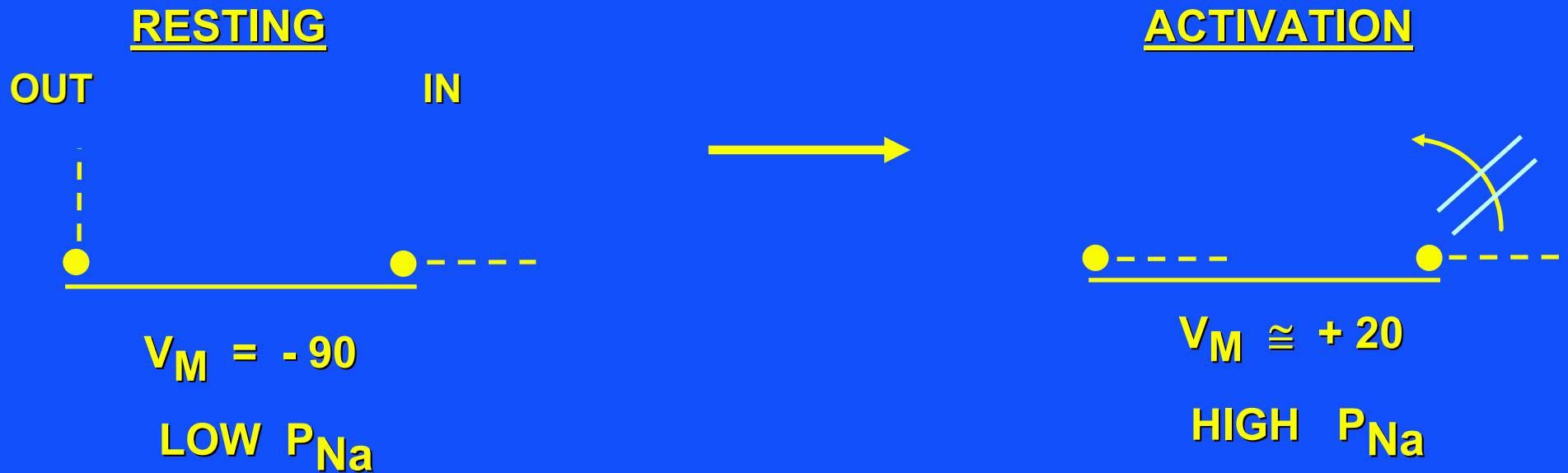
HPP



HUMAN HPP



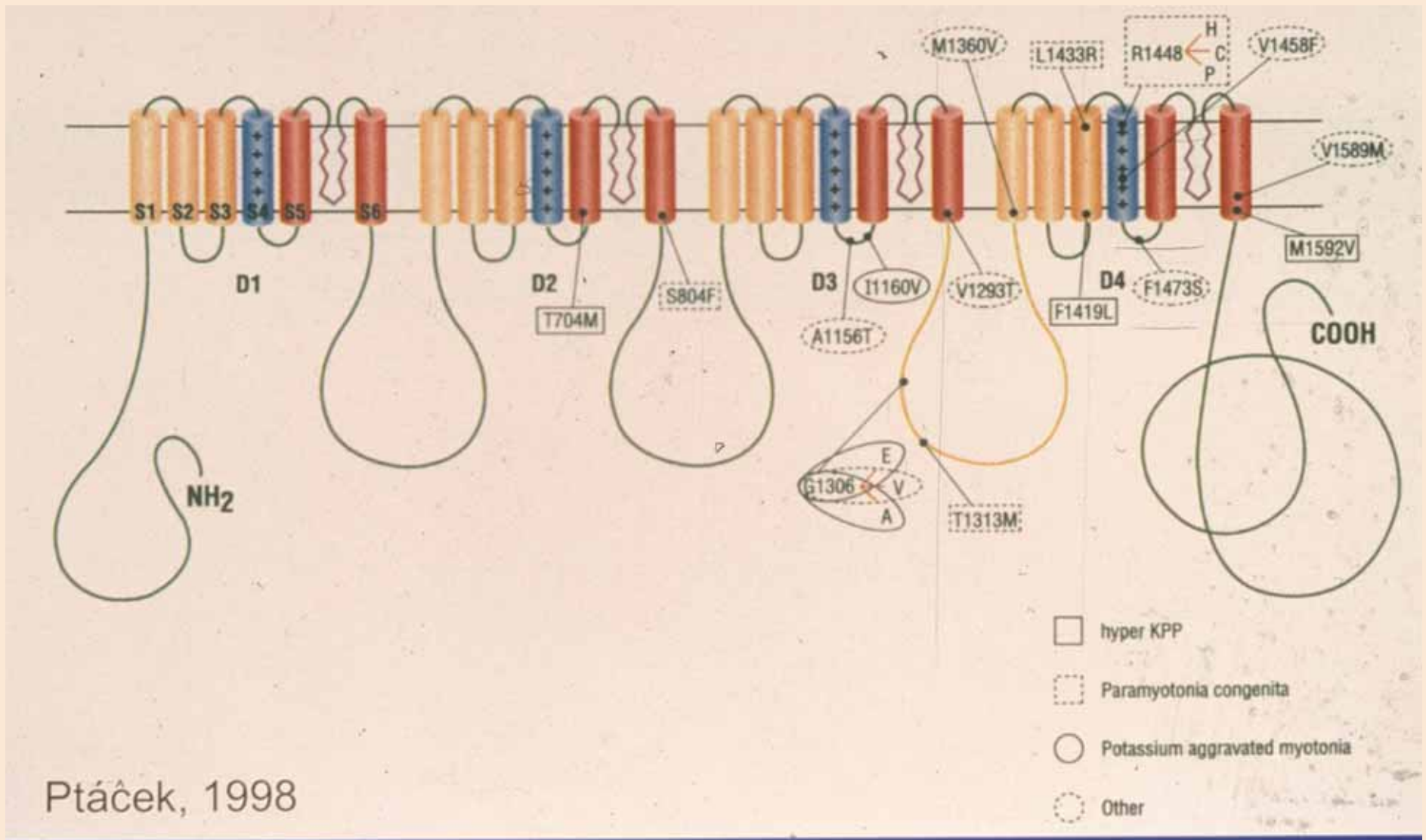
SODIUM CHANNEL ACTIVITY: HPP



HPP : TTX - SENSITIVE MUSCLE FIBERS

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

Na⁺ CHANNEL DEFECT IN HPP



Na⁺ CHANNELS

SKELTAL
MUSCLE

CARDIAC

TTX

SENSITIVE

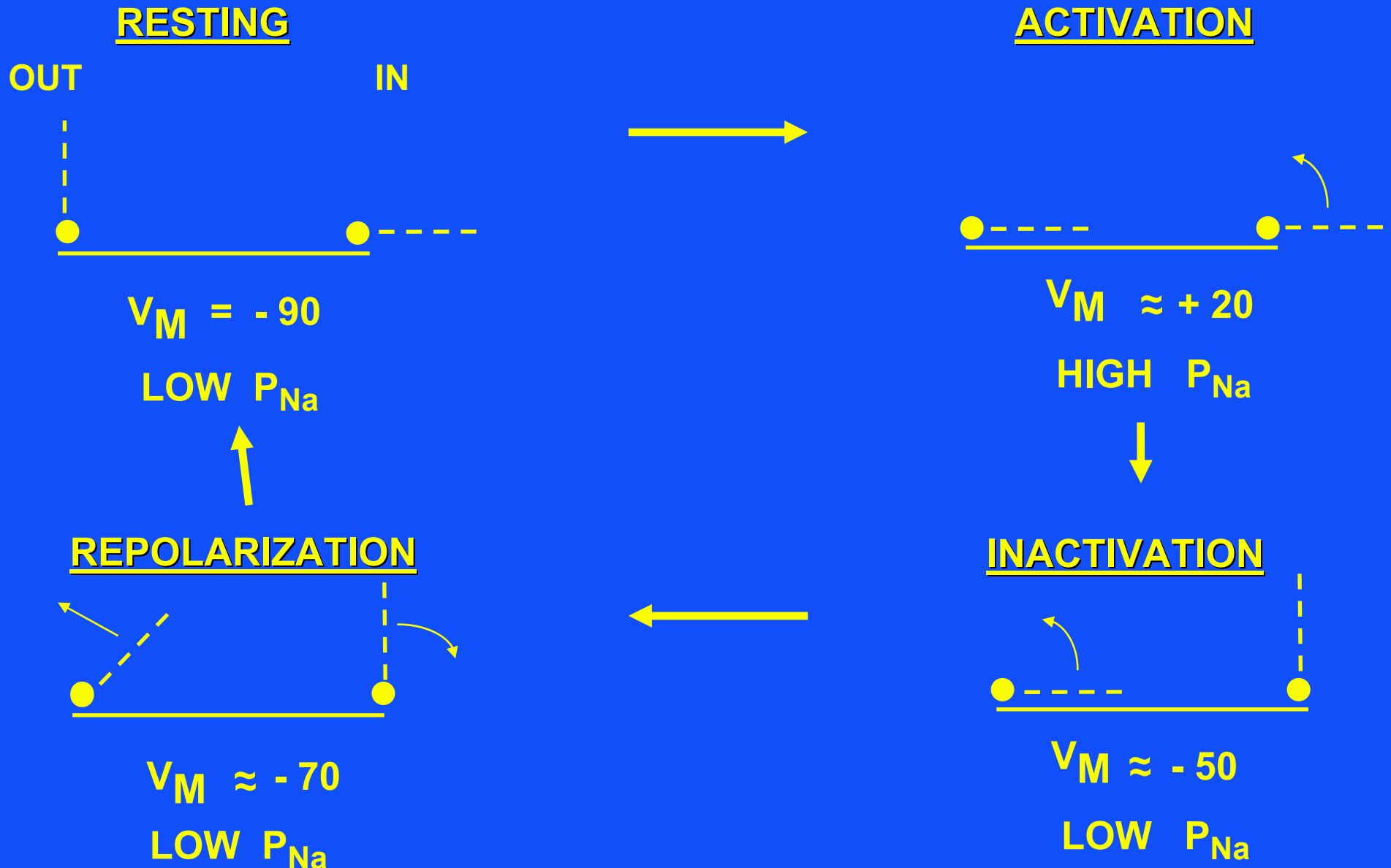
INSENSITIVE

CHANNEL
ACTIVATION

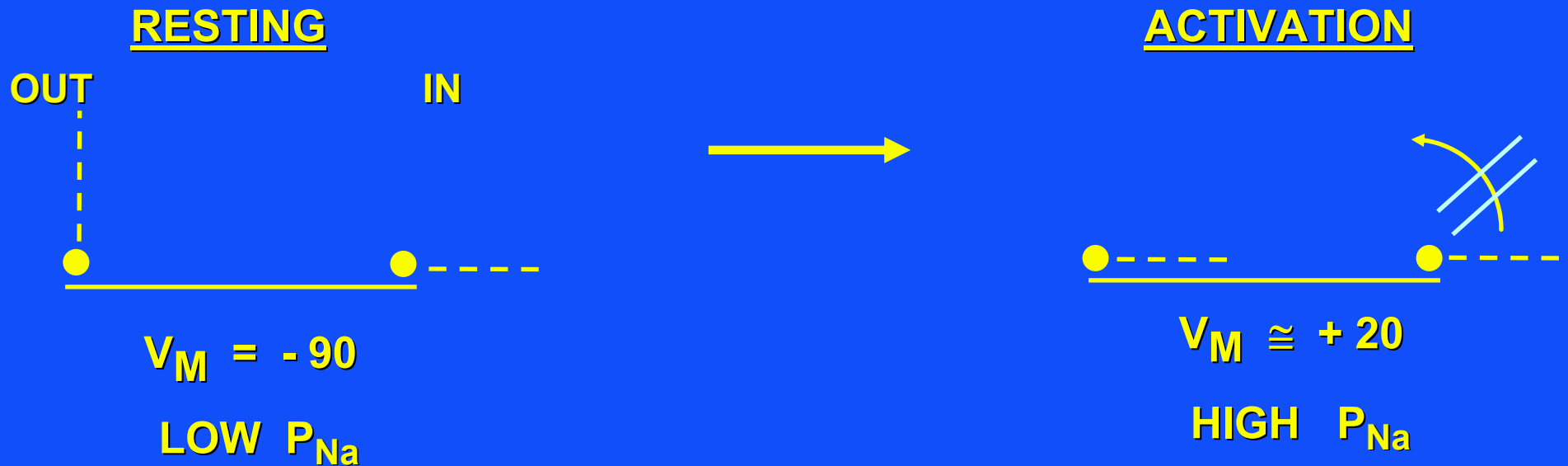
LOW
VOLTAGE

HIGH
VOLTAGE

SODIUM CHANNEL ACTIVITY: NORMAL



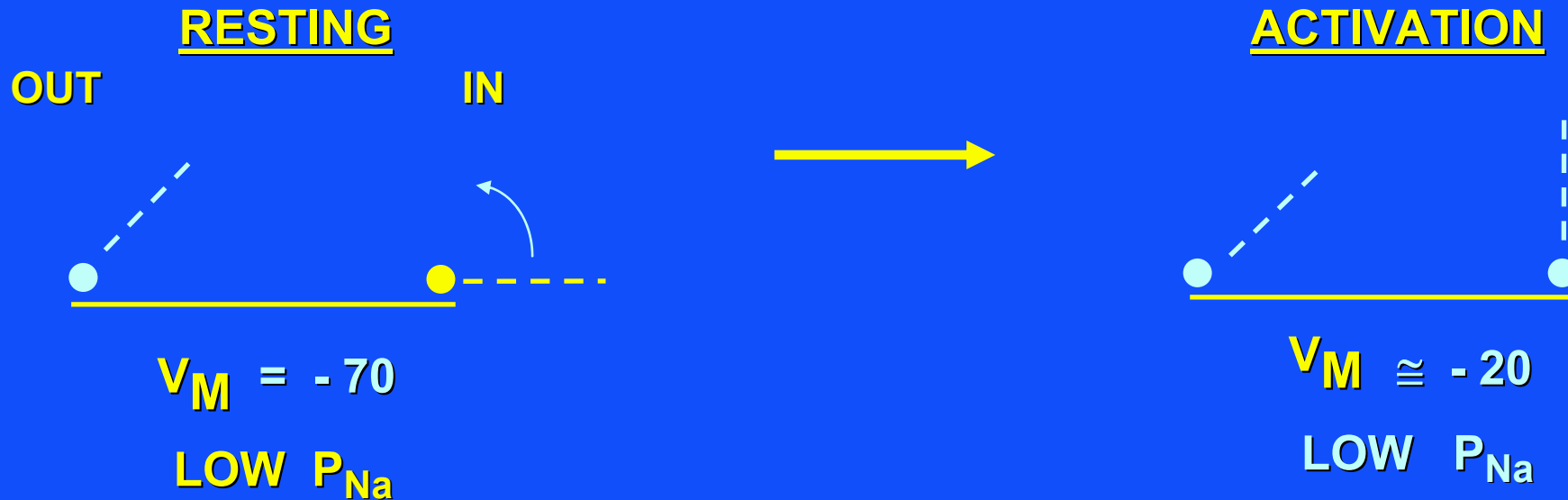
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