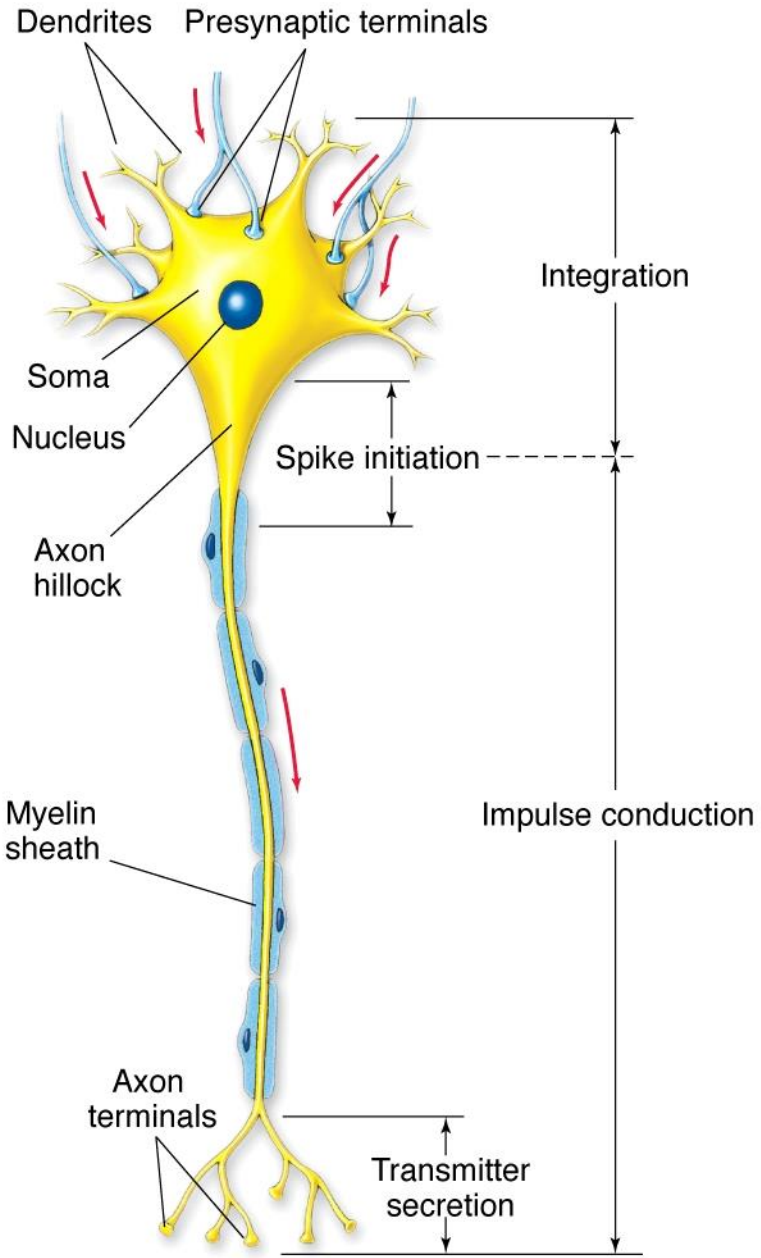
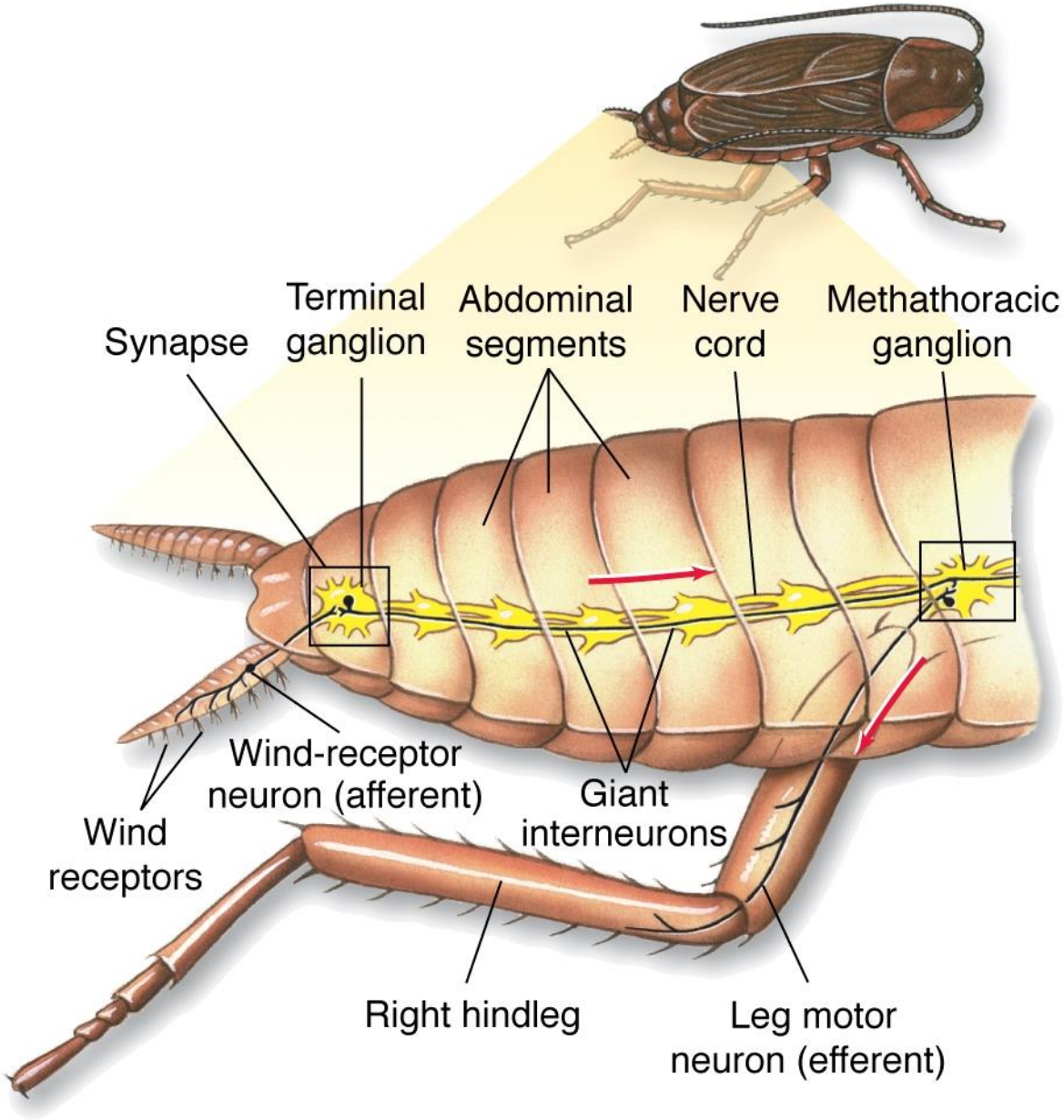
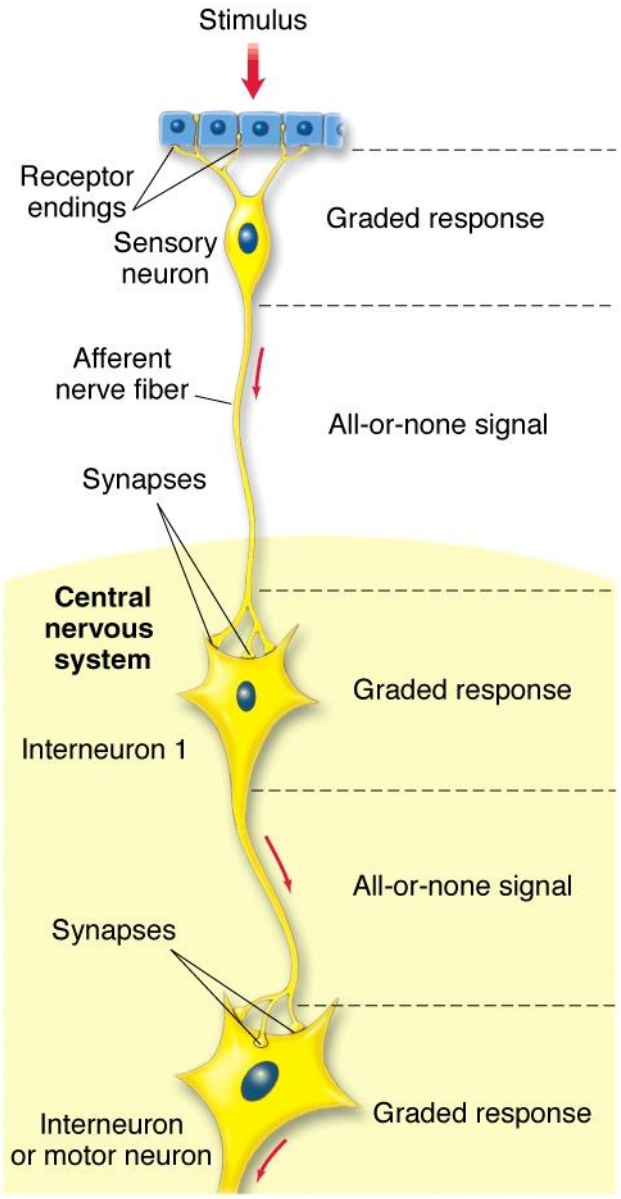
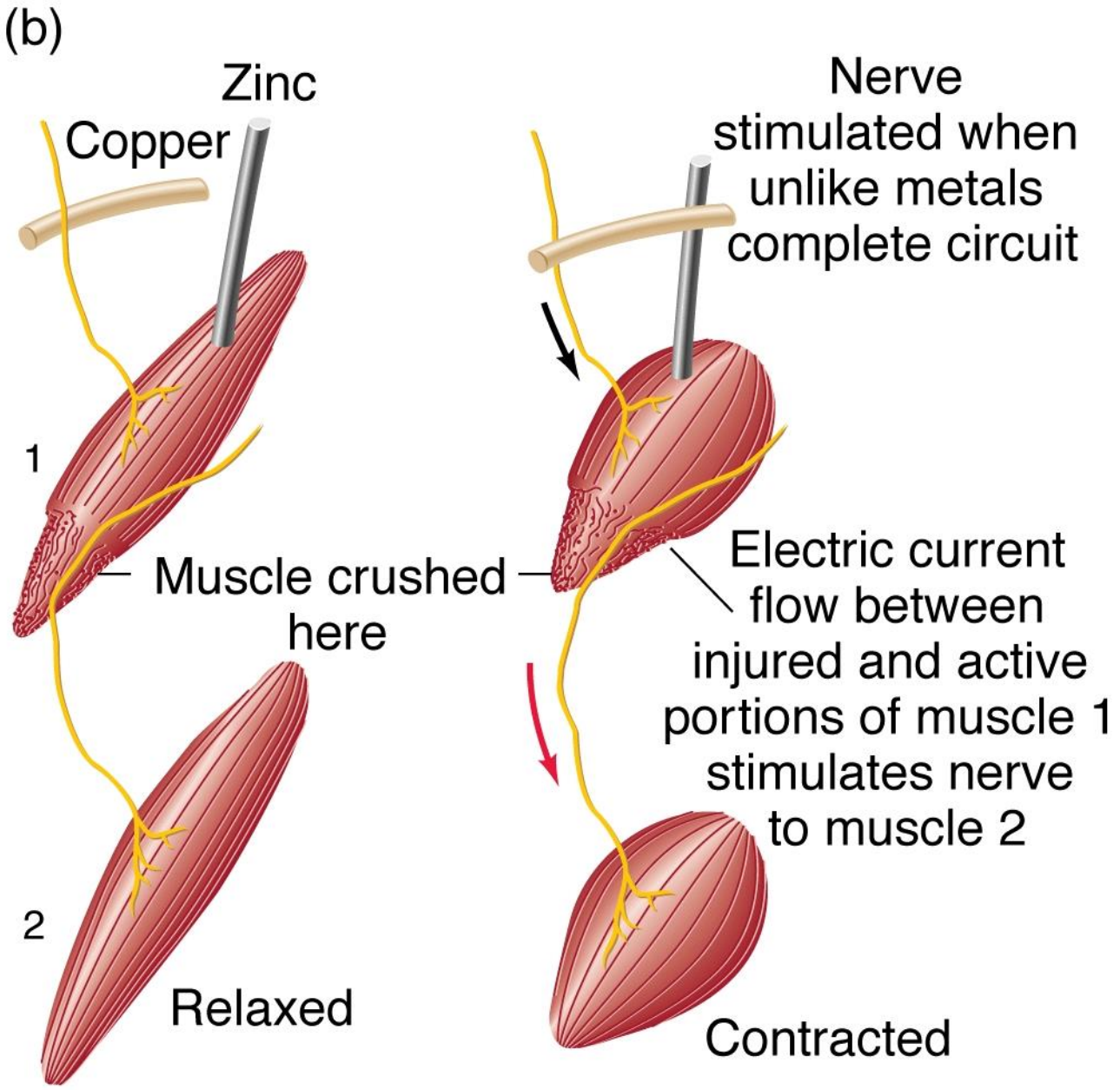
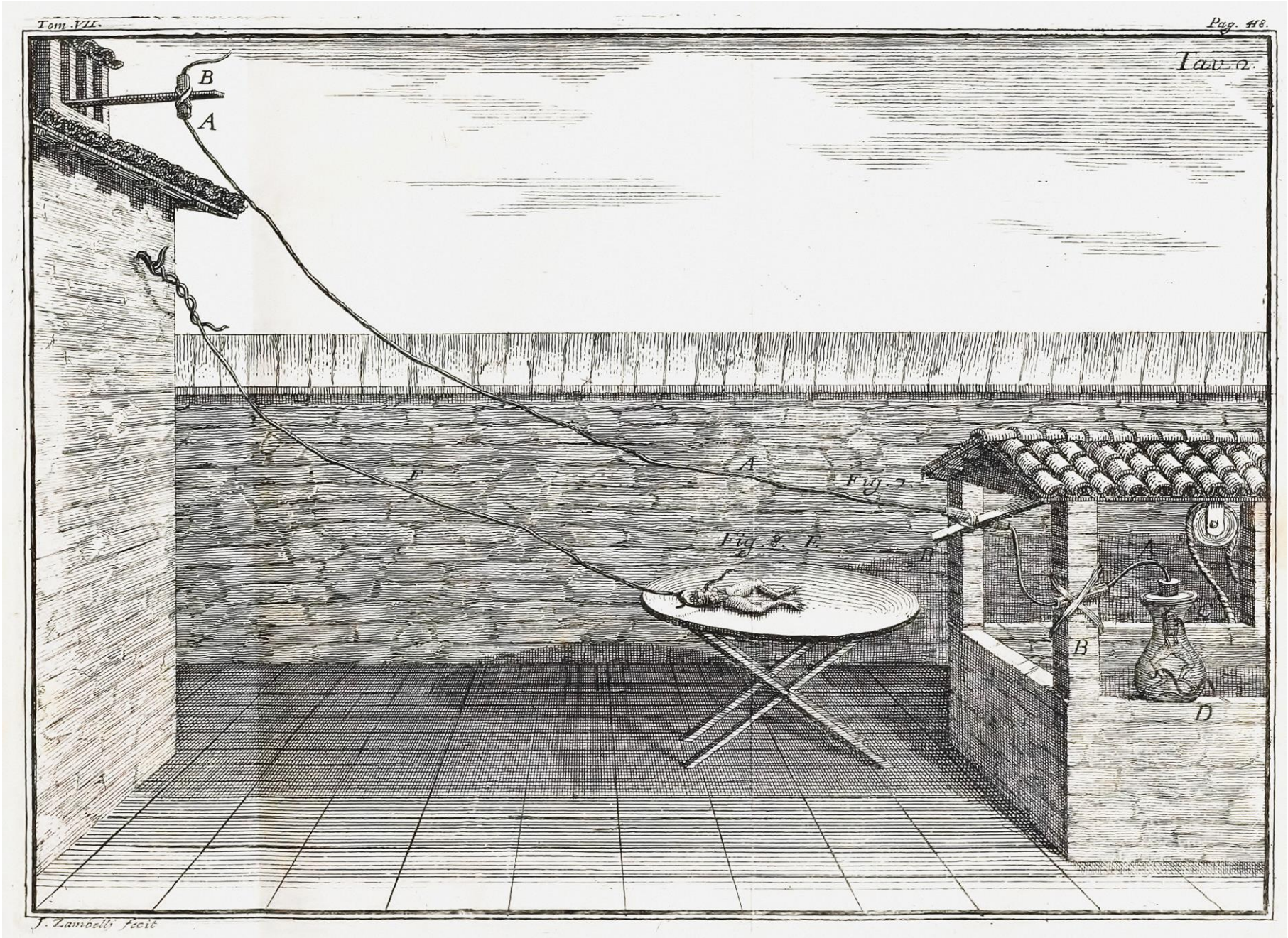
Neuronal function


Dendrites
Presynaptic terminals
Integration
Soma
Nucleus
Spike initiation
Axon hillock
Myelin sheath
Impulse conduction
Axon terminals
Transmitter secretion

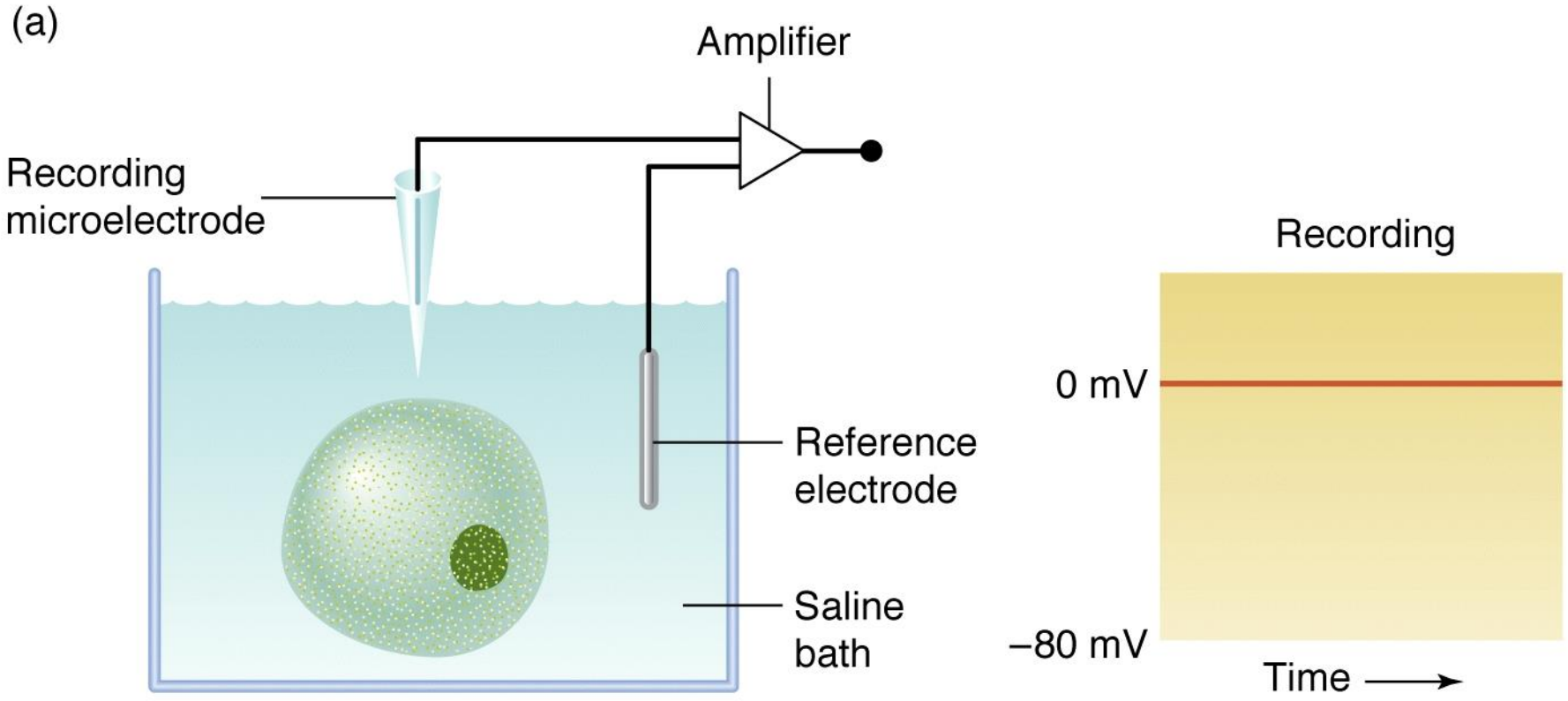

Synapse
Terminal ganglion
Abdominal segments
Nerve cord
Methathoracic ganglion
Wind-receptor neuron (afferent)
Giant interneurons
Wind receptors
Right hindleg
Leg motor neuron (efferent)


Stimulus
Receptor endings
Sensory neuron
Graded response
Afferent nerve fiber
All-or-none signal
Synapses
Central nervous system
Graded response
Interneuron 1
All-or-none signal
Synapses
Interneuron or motor neuron
Graded response

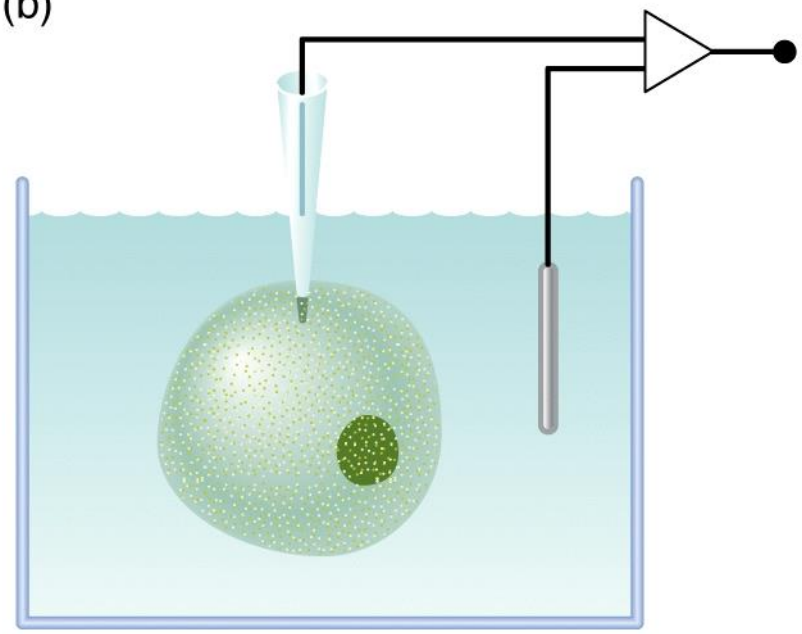

(b)
Zinc
Copper
Nerve stimulated when unlike metals complete circuit
1
Muscle crushed here
Electric current flow between injured and active portions of muscle 1 stimulates nerve to muscle 2
2
Relaxed
Contracted

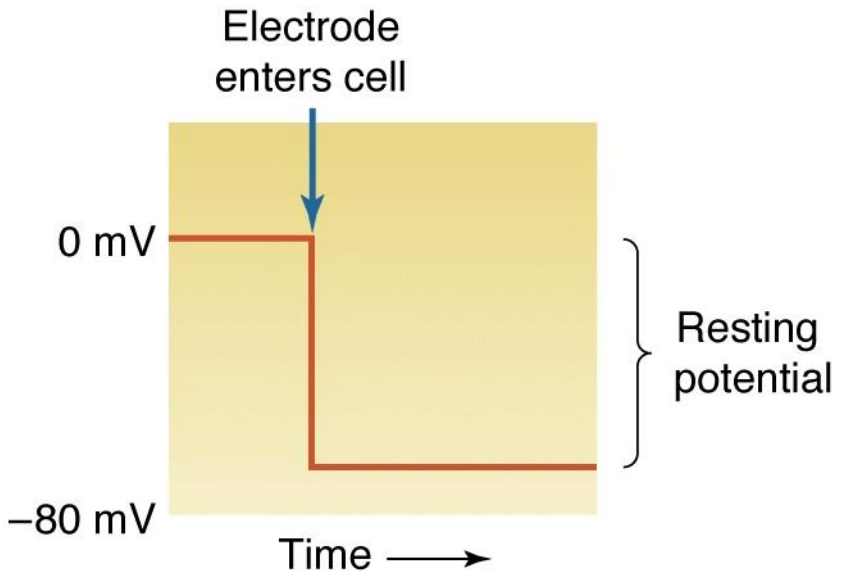


https://upload.wikimedia.org/wikipedia/commons/8/82/Galvani_frog_legs_experiment_setup.png


(a)
Amplifier
Recording microelectrode
Reference electrode
Saline bath
Recording
0 mV
−80 mV
Time

(b)





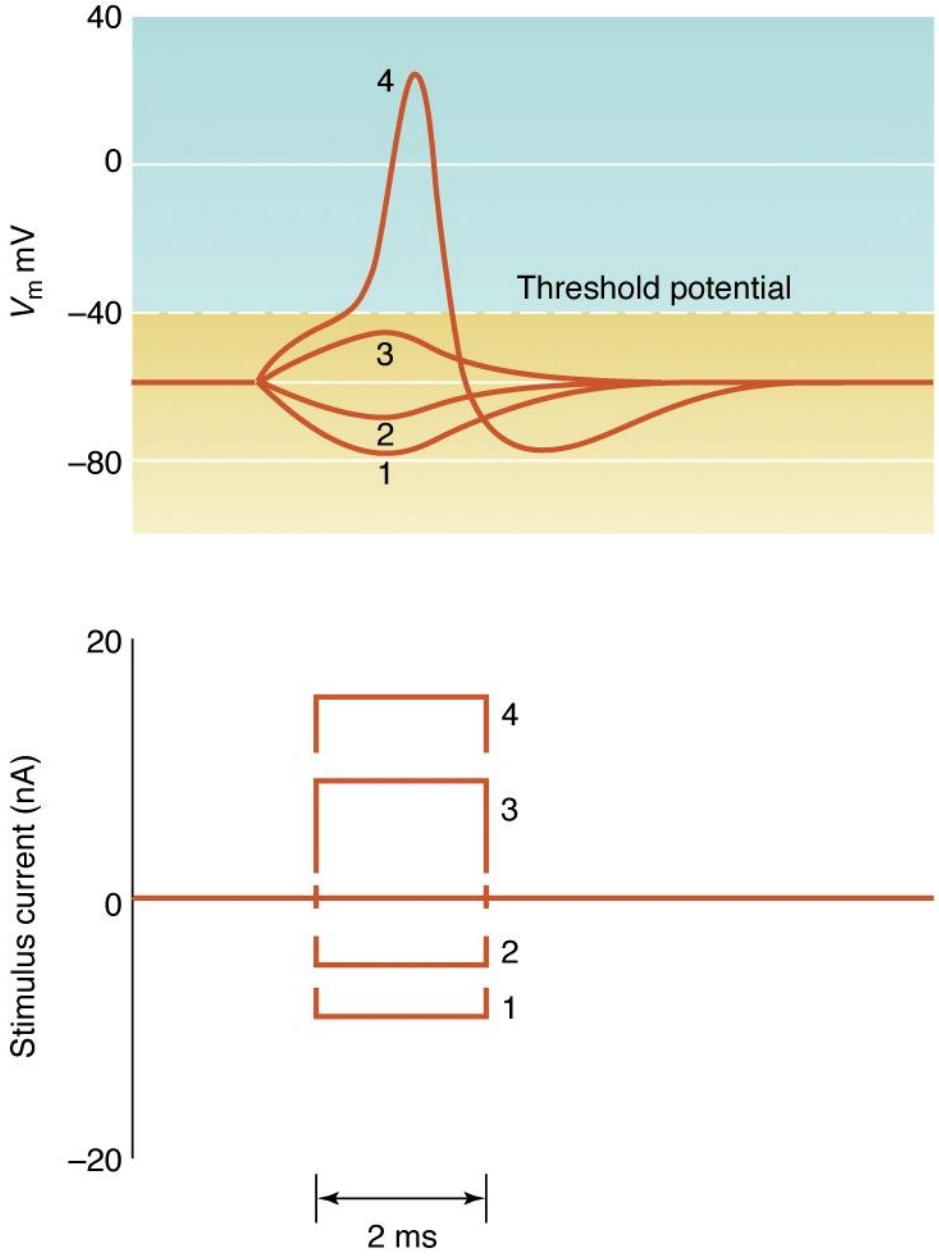
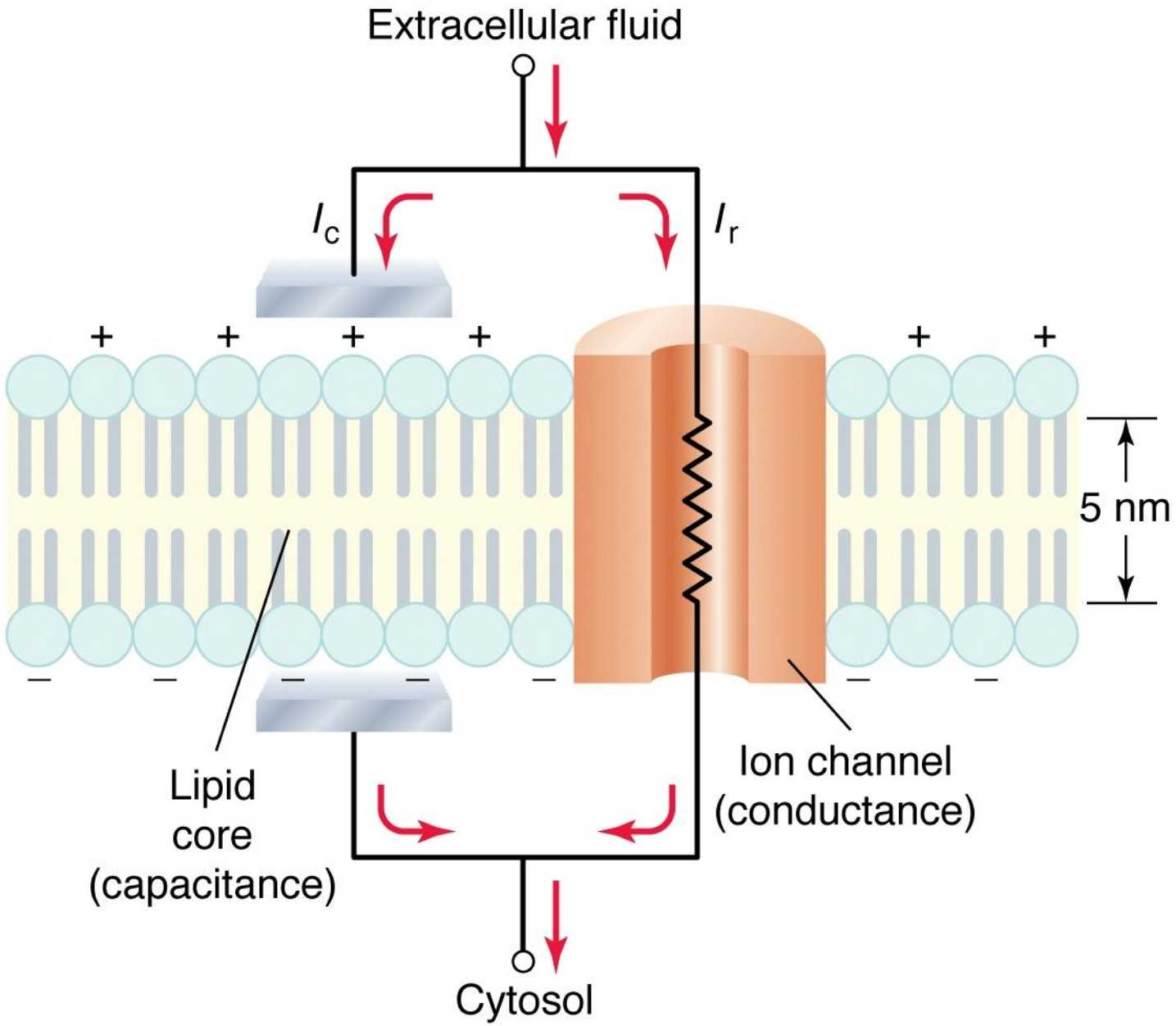
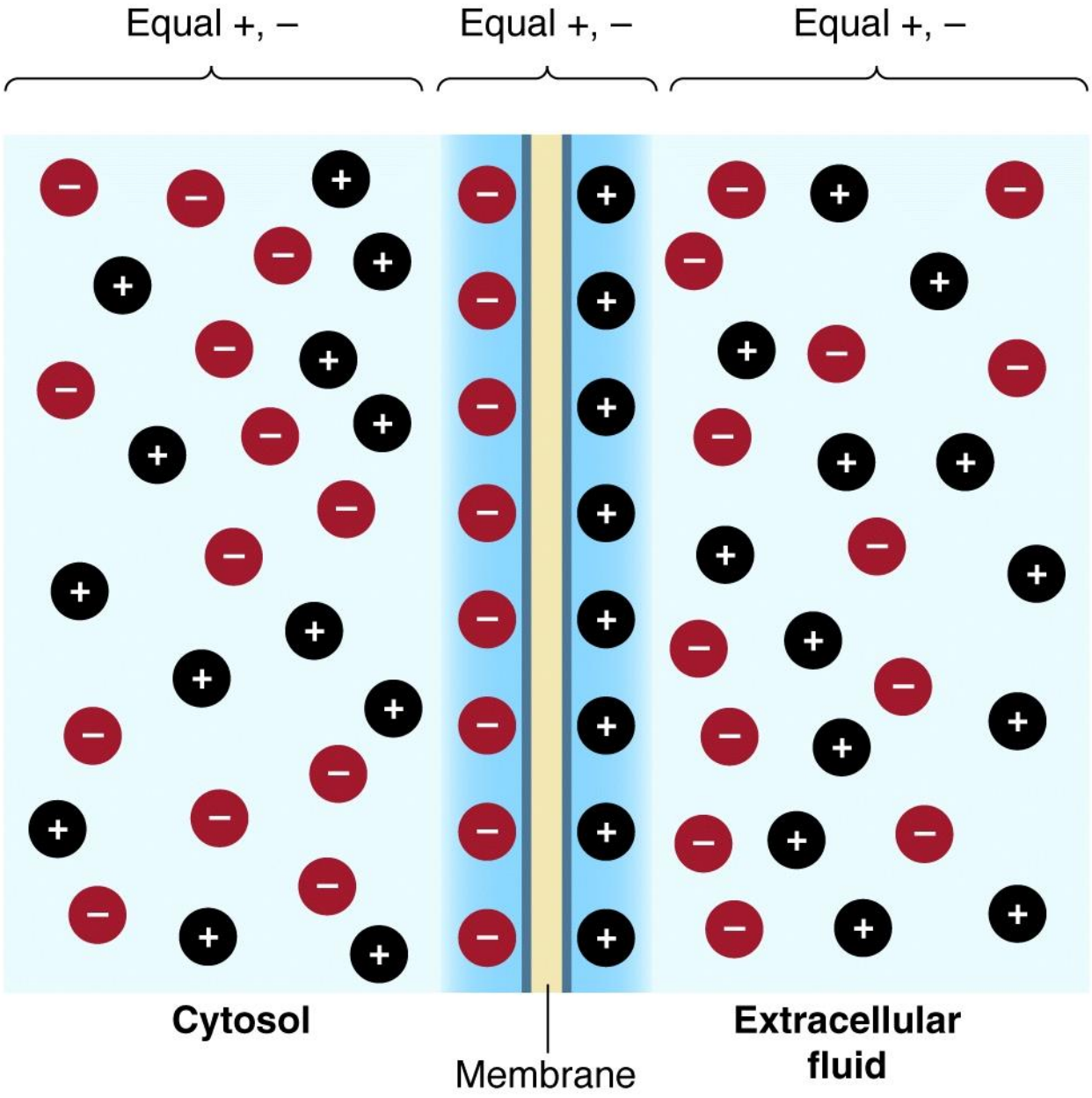
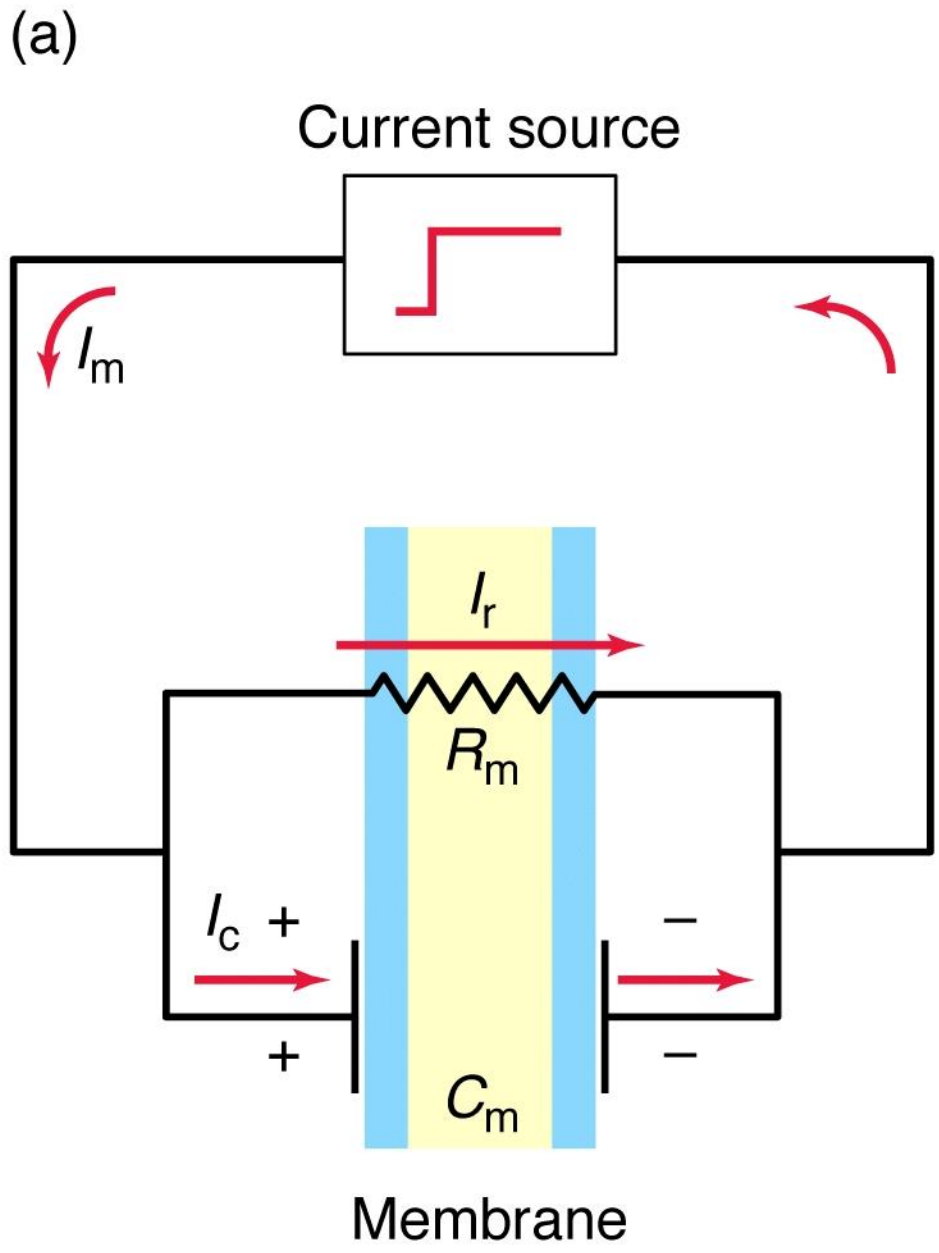

40
0
−40
−80
V_m mV
Threshold potential
4
3
2
1
20
0
−20
Stimulus current (nA)
4
3
2
1
2 ms

Table 5-1 **Examples of ion channels found in axons**

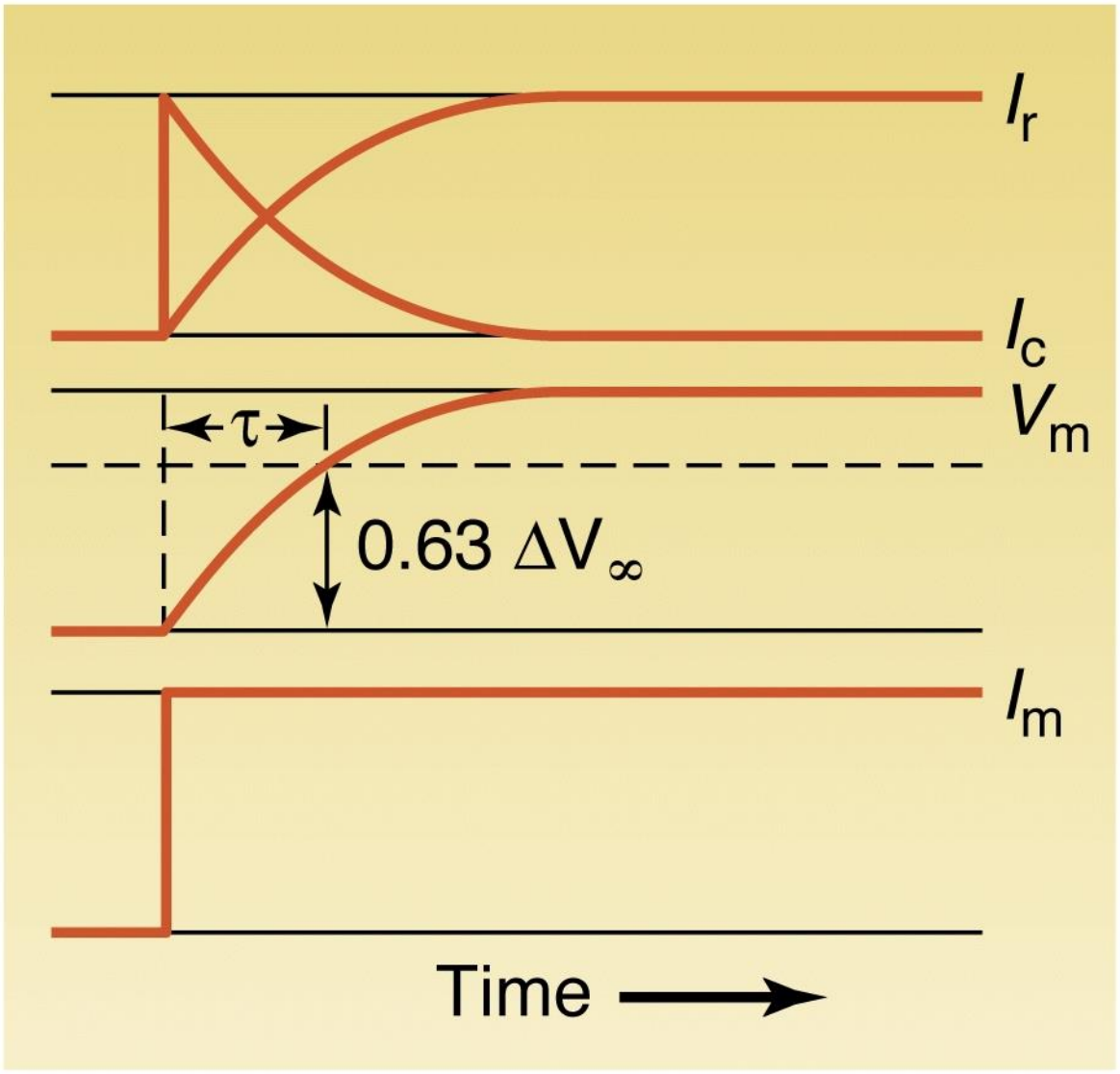
Channel	Current through channel	Characteristics	Selected blockers	Function
Leak channel (open in resting axon)	I_K (leak)	Produces relatively high P_K of resting cell	Partially blocked by tetraethylammonium (TEA)	Largely responsible for V_{rest}
Voltage-gated Na^+ channel	I_{Na}	Rapidly activated by depolarization; becomes inactivated even if V_m remains depolarized	Tetrodotoxin (TTX)	Produces rising phase of AP
Voltage-gated Ca^{2+} channel	I_{Ca}	Activated by depolarization but more slowly than Na^+ channel; inactivated as function of cytoplasmic $[Ca^{2+}]$ or V_m	Verapamil, D600, Co^{2+}, Cd^{2+}, Mn^{2+}, Ni^{2+}, La^{3+}	Produces slow depolarization; allows Ca^{2+} to enter cell, where it can act as second messenger
Voltage-gated K^+ channel ("delayed rectifier")	$I_{K(V)}$	Activated by depolarization but more slowly than Na^+ channel; inactivated slowly and not completely if V_m remains depolarized	Intra- and extracellular TEA, amino pyridines	Carries current that rapidly repolarizes the membrane to terminate an AP
Ca^{2+}-dependent K^+ channel	$I_{K(Ca)}$	Activated by depolarization plus elevated cytoplasmic $[Ca^{2+}]$; remains open as long as cytoplasmic $[Ca^{2+}]$ is higher than normal	Extracellular TEA	Carries current that repolarizes the cell following APs based on either Na^+ or Ca^{2+} and that balances I_{Ca}, thus limiting depolarization by I_{Ca}


Extracellular fluid
I_c
I_r
+ + + + + +
− − − − − − −
5 nm
Lipid
core
(capacitance)
Ion channel
(conductance)
Cytosol

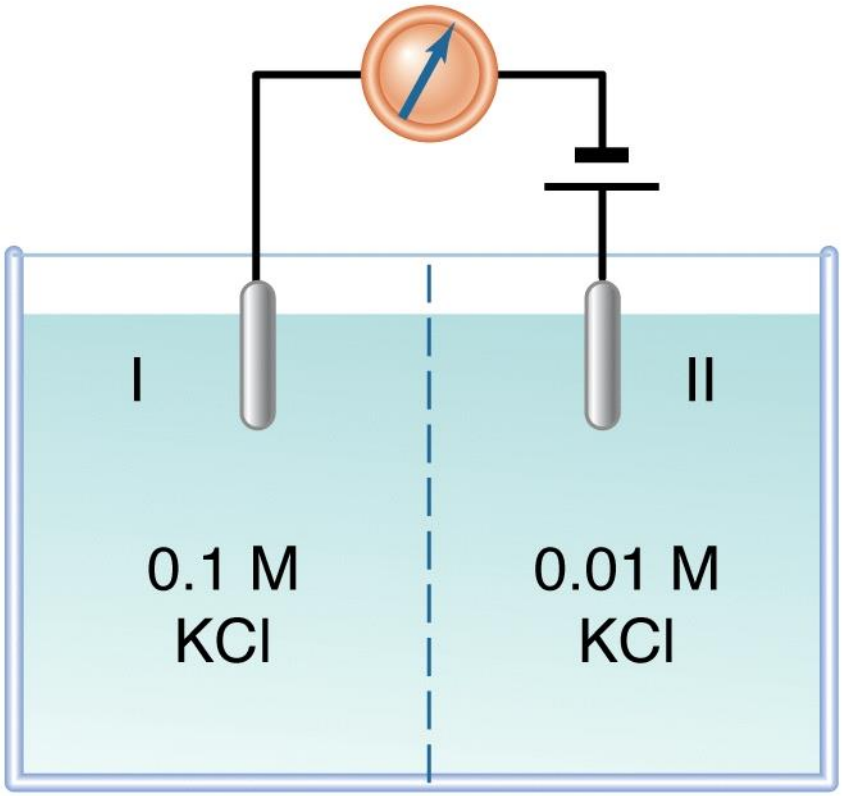

Equal +, –
Equal +, –
Equal +, –
Cytosol
Membrane
Extracellular fluid

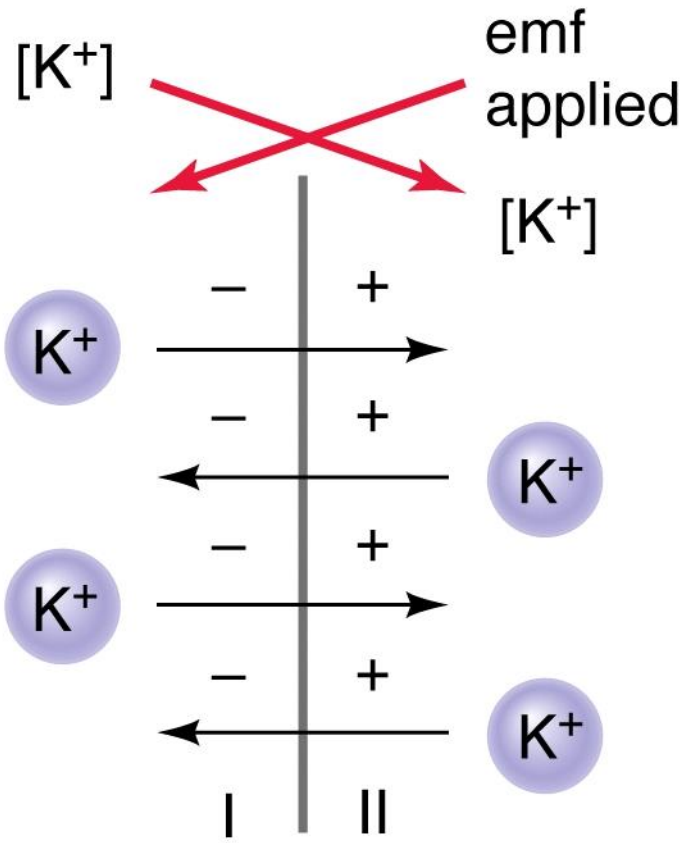

(a)
Current source
I_m
I_r
R_m
I_c +
+
–
–
C_m
Membrane

(b)



(c)

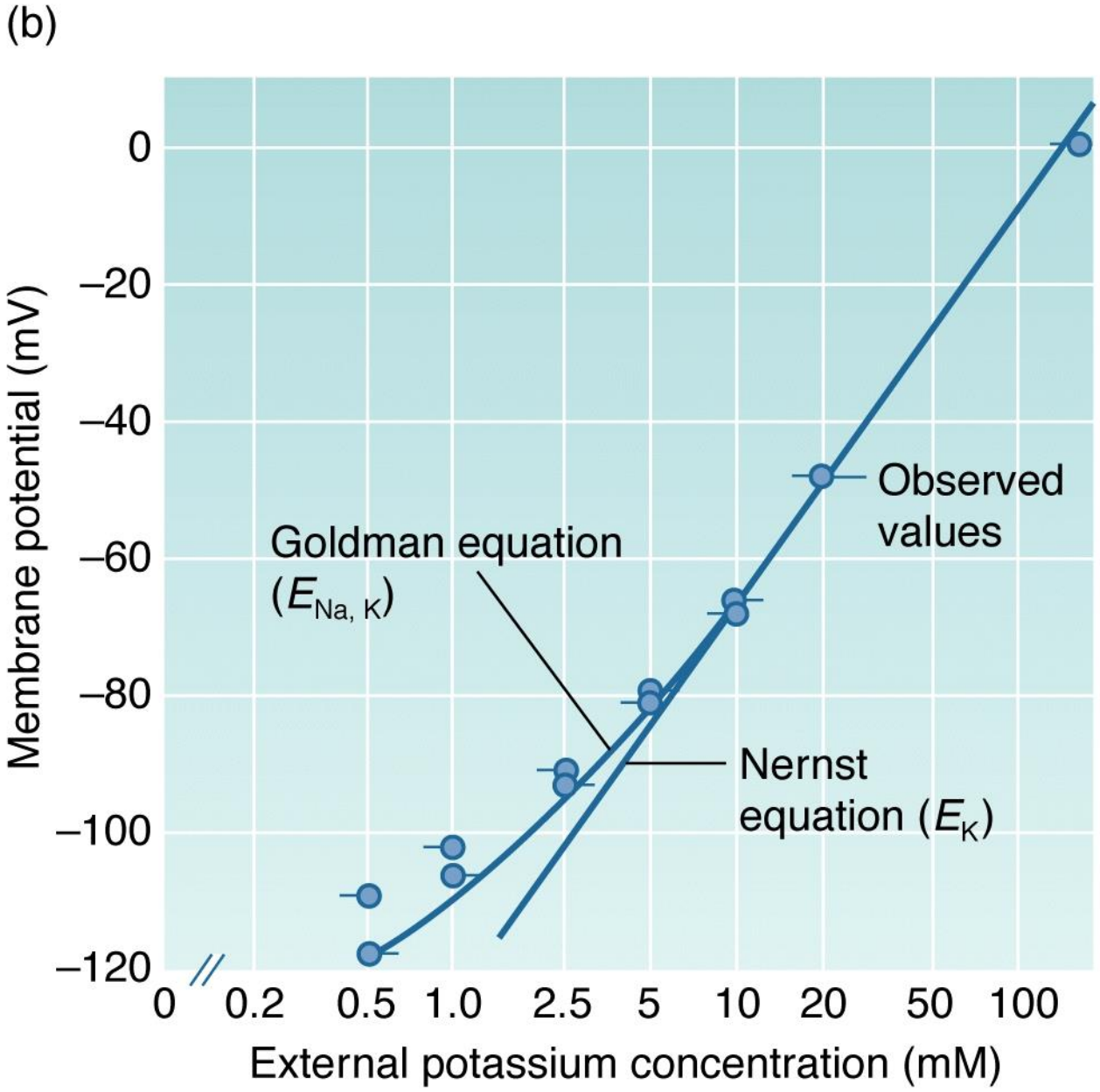


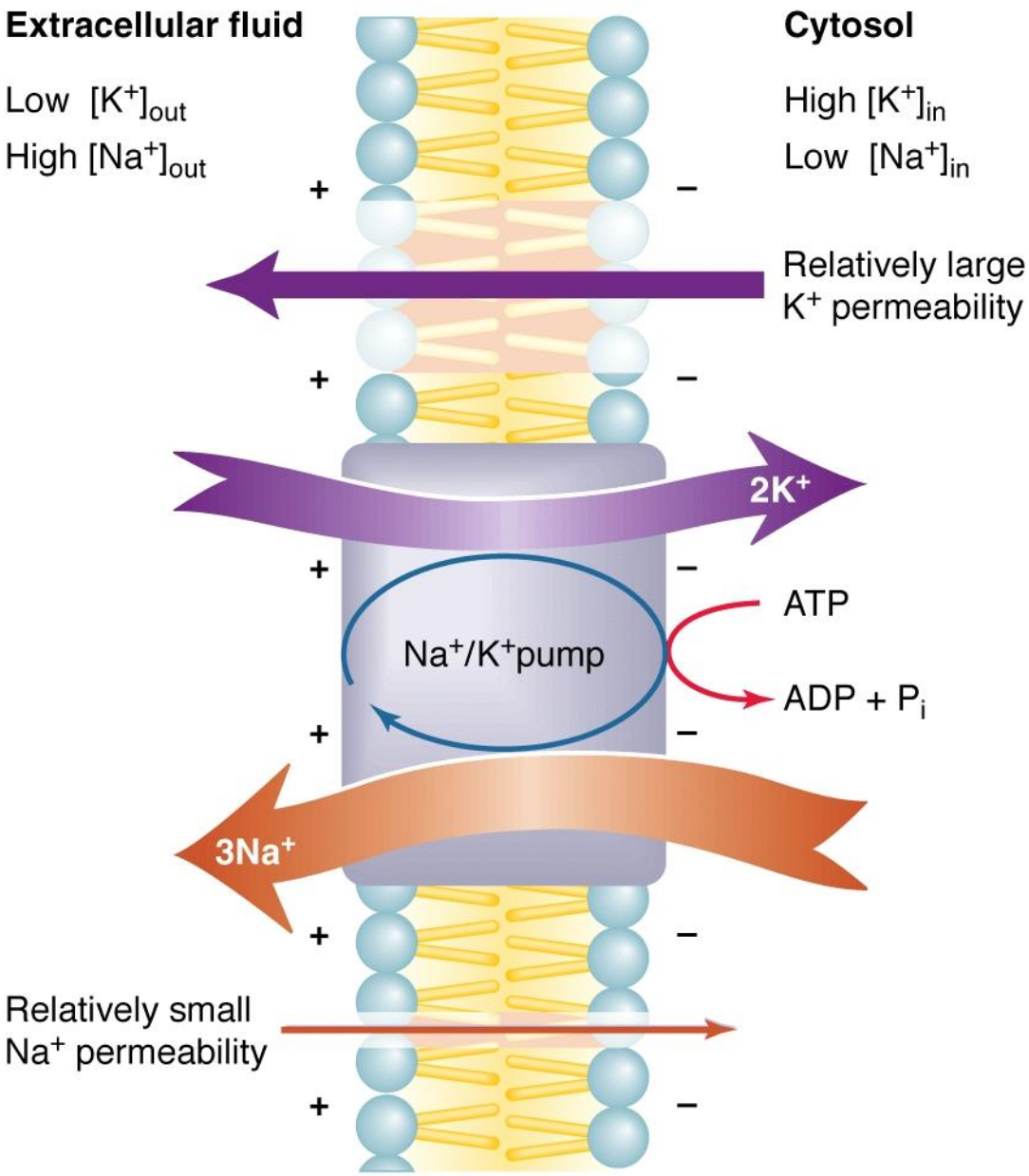


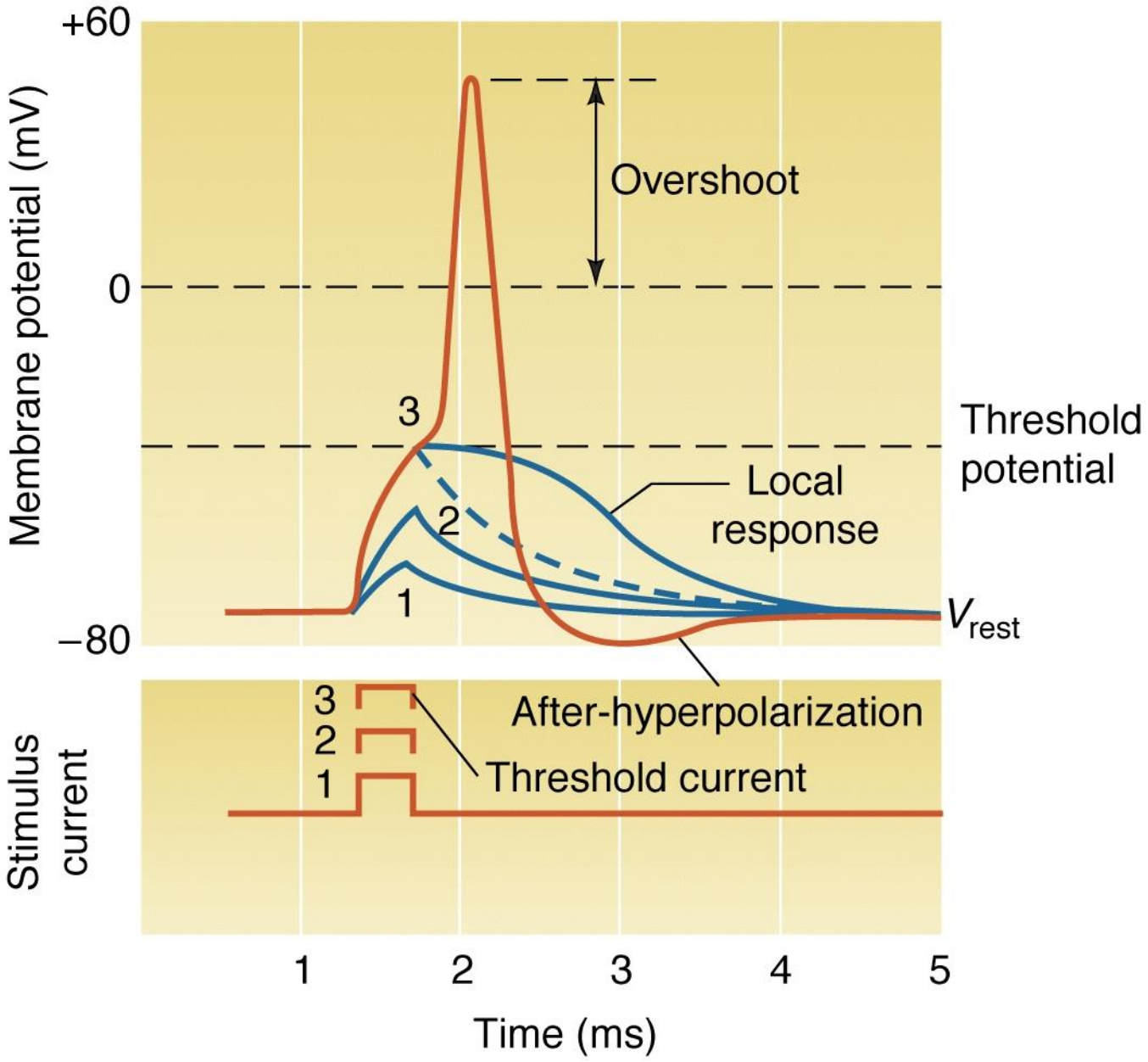
Nernst equation: 1864 – 1941. **Walther Nernst**

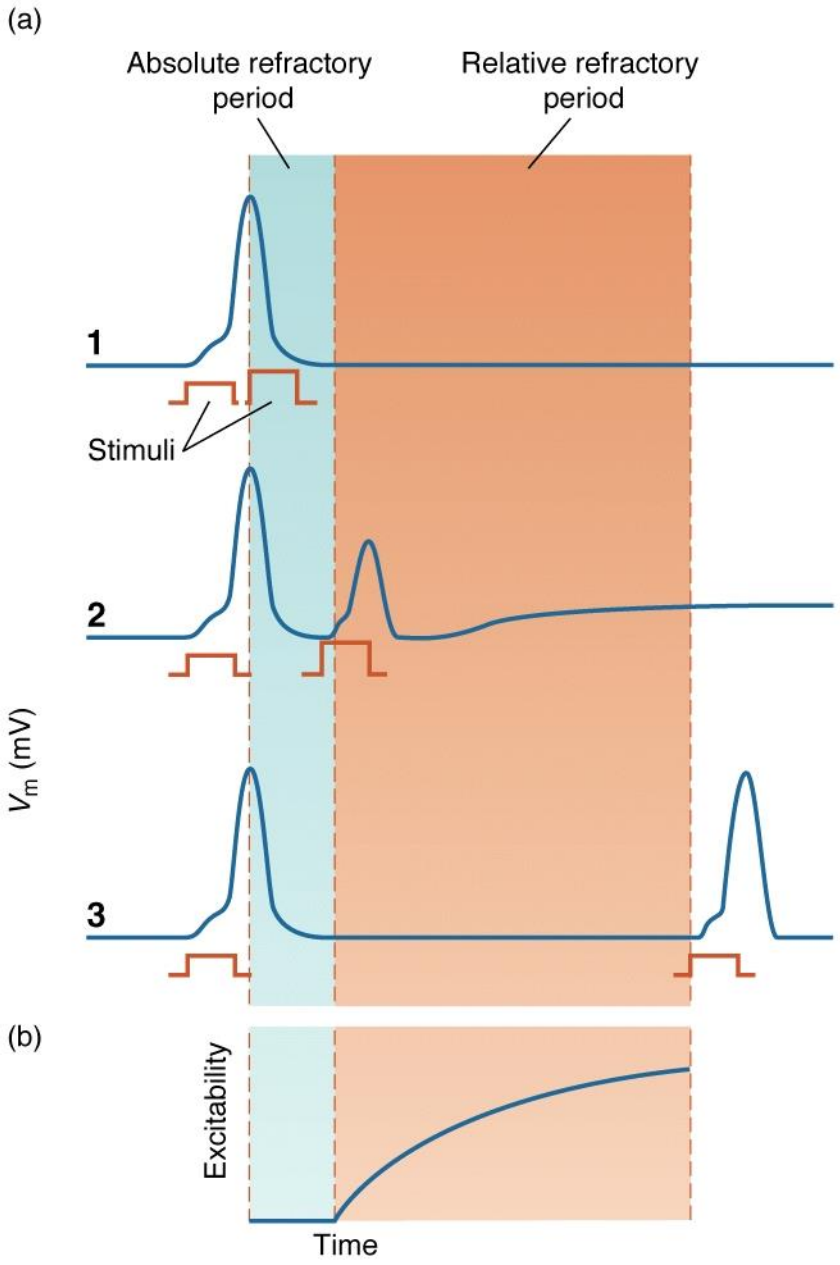
$$E = \frac{RT}{zF} \ln \frac{[\text{ion outside cell}]}{[\text{ion inside cell}]} = 2.3026 \frac{RT}{zF} \log_{10} \frac{[\text{ion outside cell}]}{[\text{ion inside cell}]}.$$

At room temperature (25 °C), $\frac{RT}{F}$ may be treated like a constant and replaced by 25.693 mV for cells.

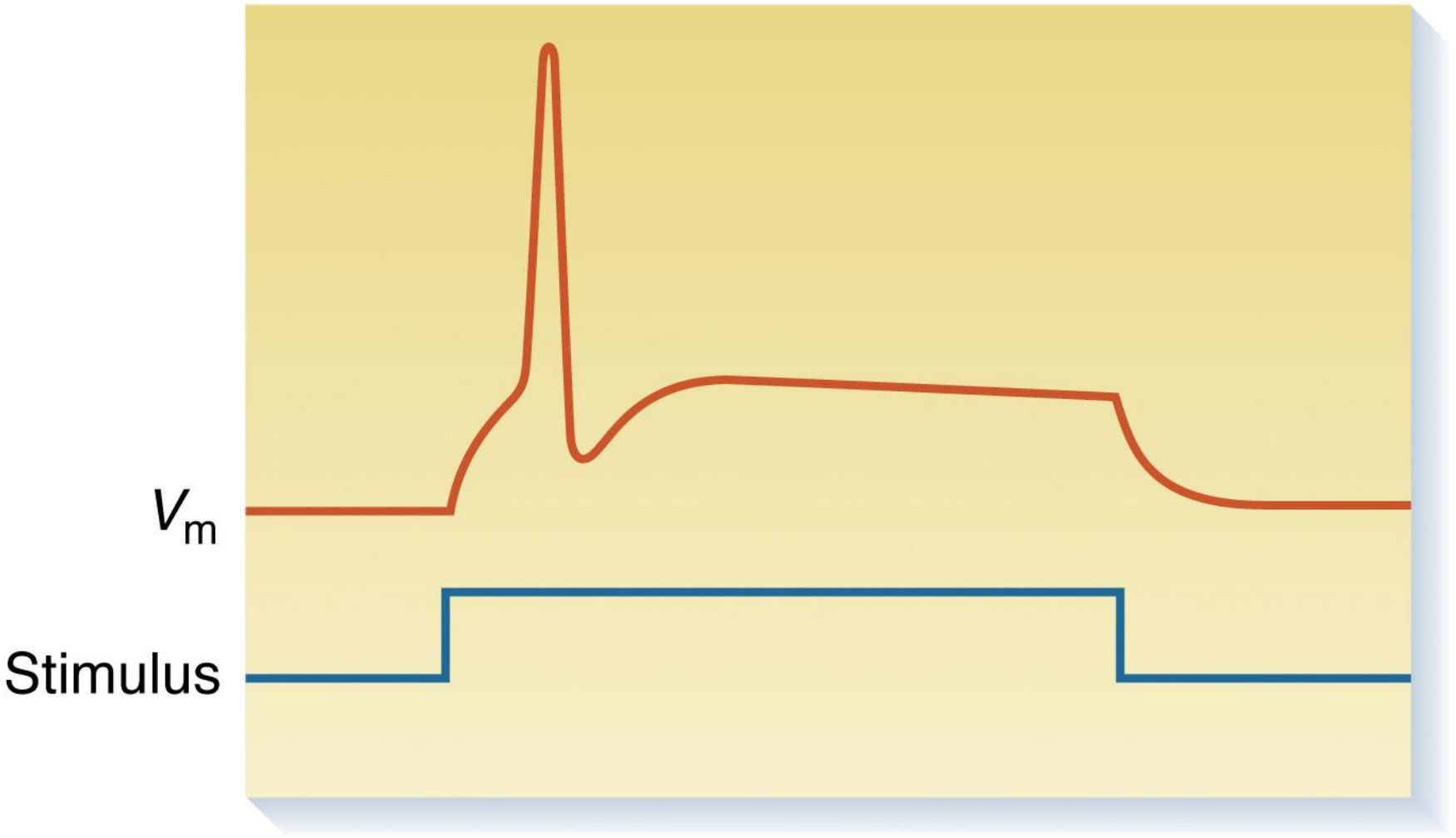

(b)
Membrane potential (mV)
0
–20
–40
–60
–80
–100
–120
0
0.2
0.5
1.0
2.5
5
10
20
50
100
External potassium concentration (mM)
Goldman equation
($E_{Na, K}$)
Nernst
equation (E_K)
Observed
values


Extracellular fluid
Low $[K^+]_{out}$
High $[Na^+]_{out}$
Cytosol
High $[K^+]_{in}$
Low $[Na^+]_{in}$
Relatively large K^+ permeability
$2K^+$
Na^+/K^+pump
ATP
ADP + P_i
$3Na^+$
Relatively small Na^+ permeability
+
−

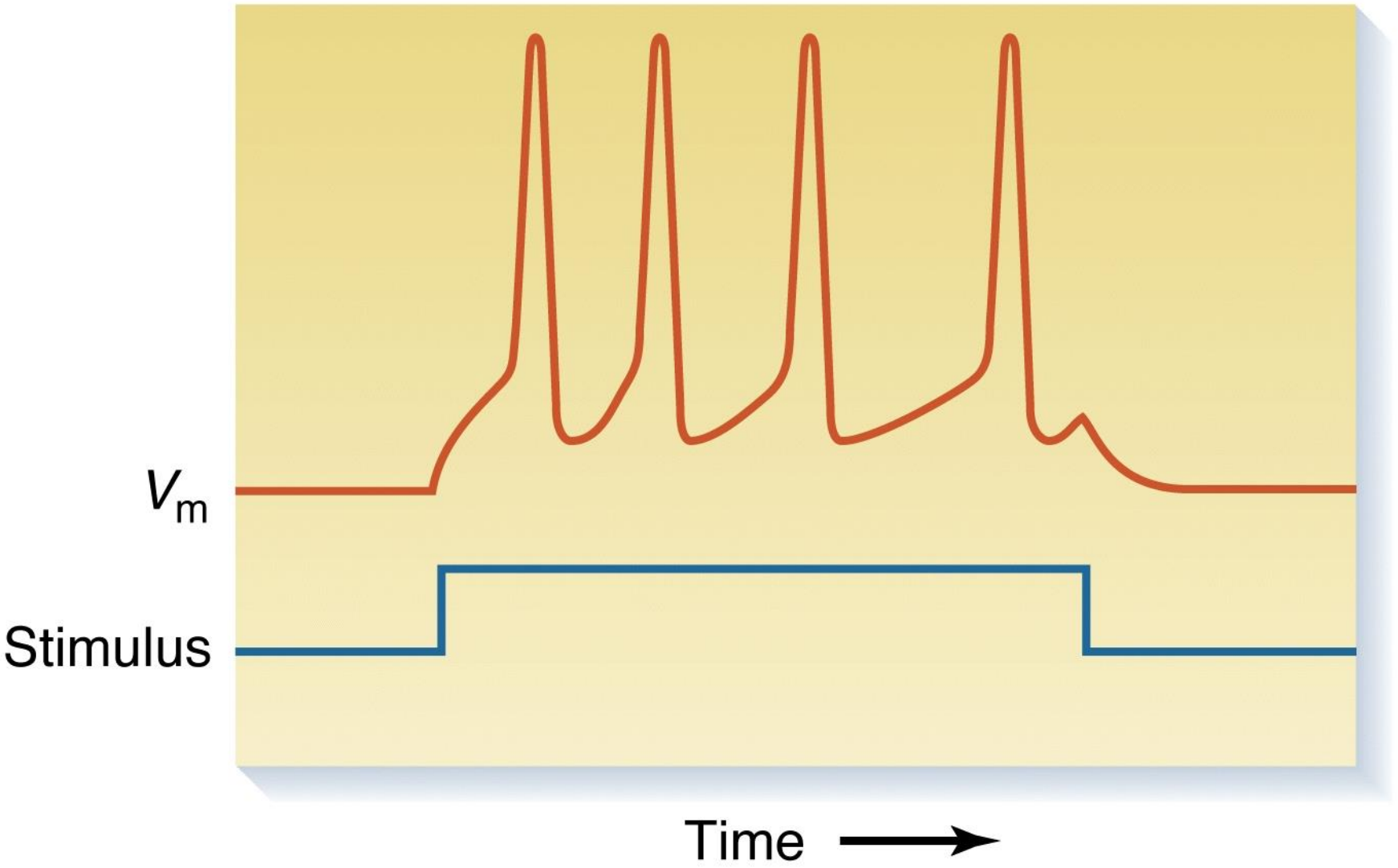

+60
0
−80
Membrane potential (mV)
Overshoot
3
2
1
Threshold potential
Local response
V_{rest}
After-hyperpolarization
Threshold current
Stimulus current
1
2
3
4
5
Time (ms)

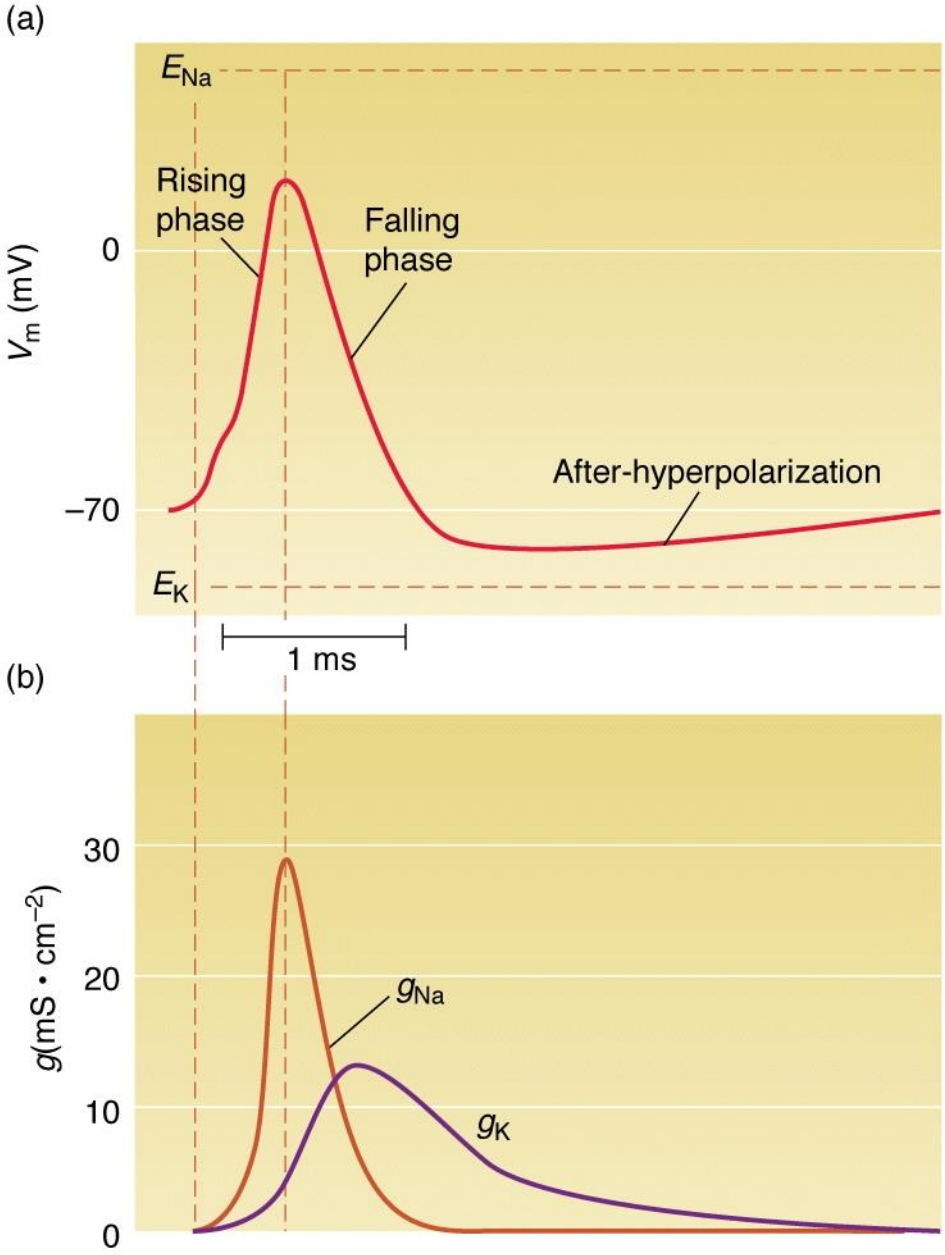

(a)
Absolute refractory period
Relative refractory period
1
Stimuli
2
3
V_m (mV)
(b)
Excitability
Time

(a) Phasic response

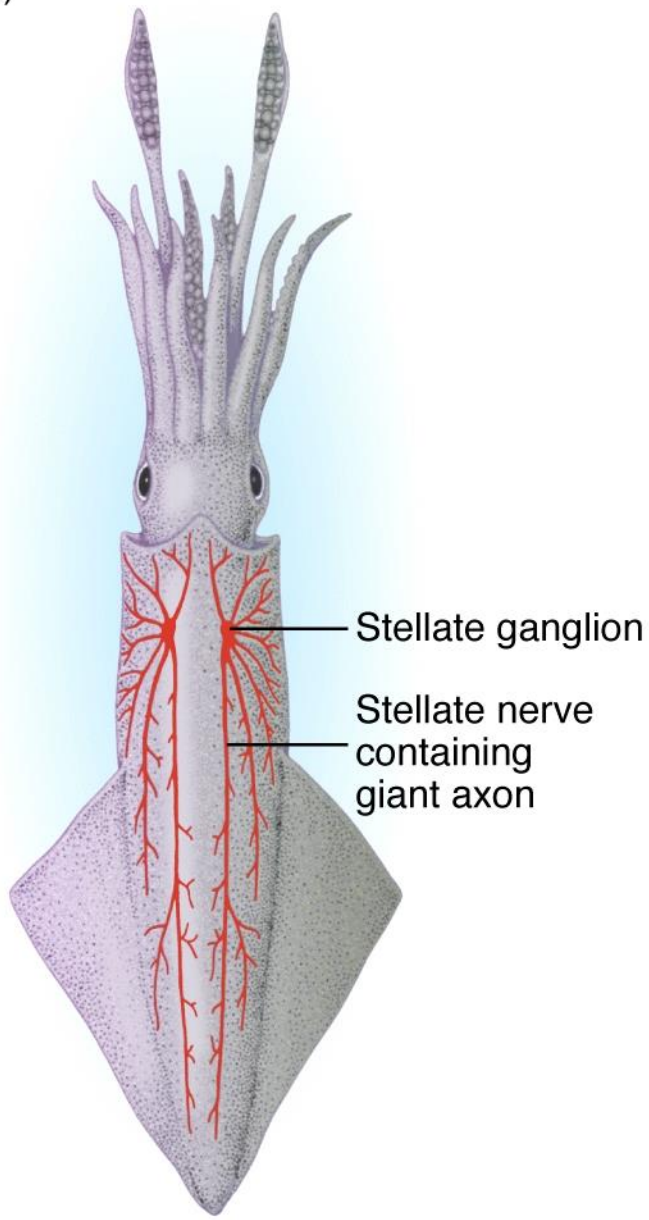


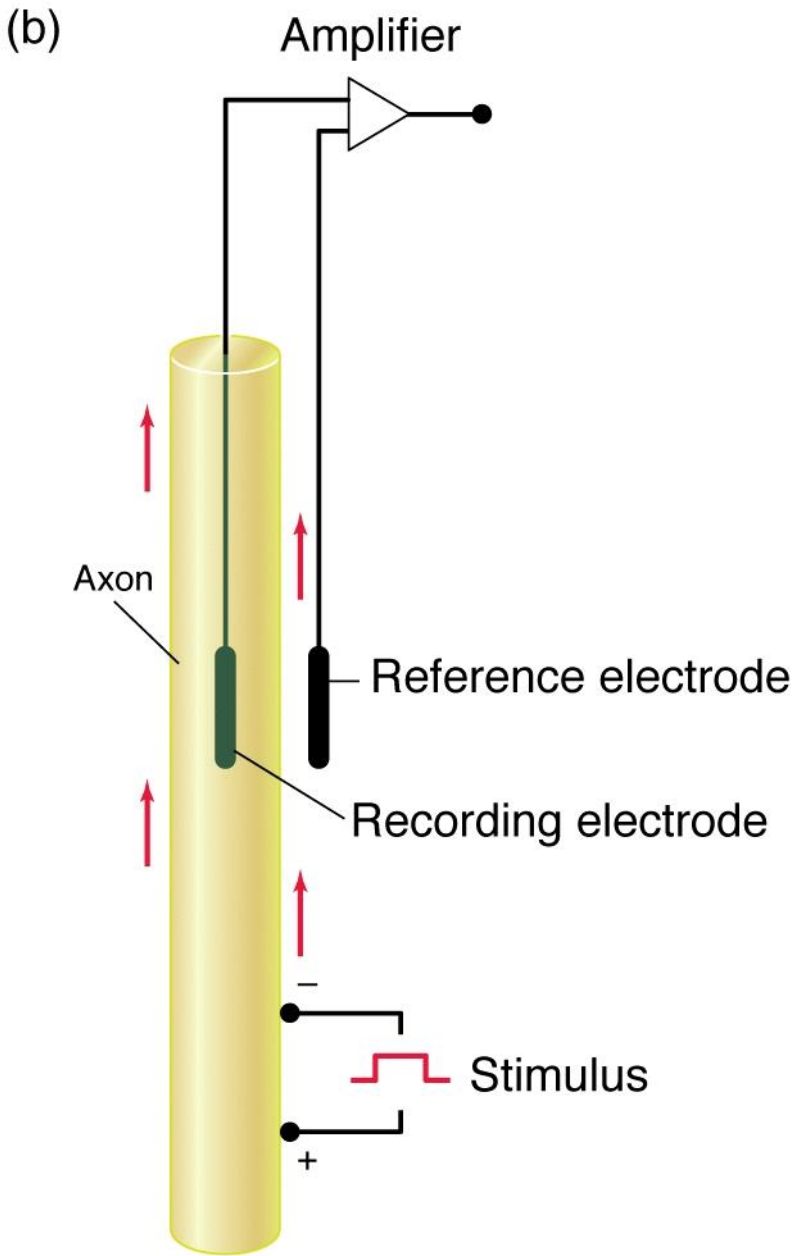
(b) Tonic response

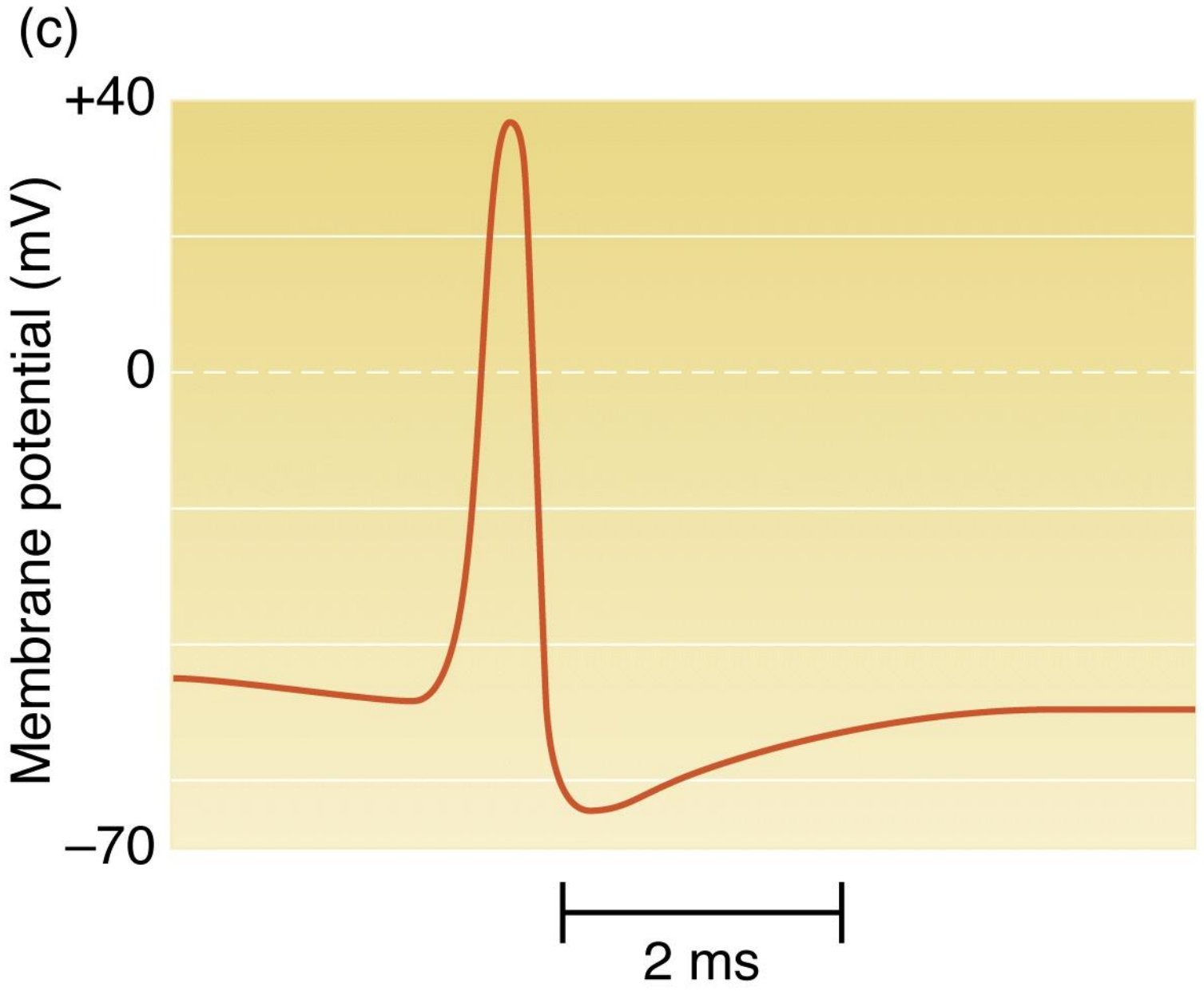


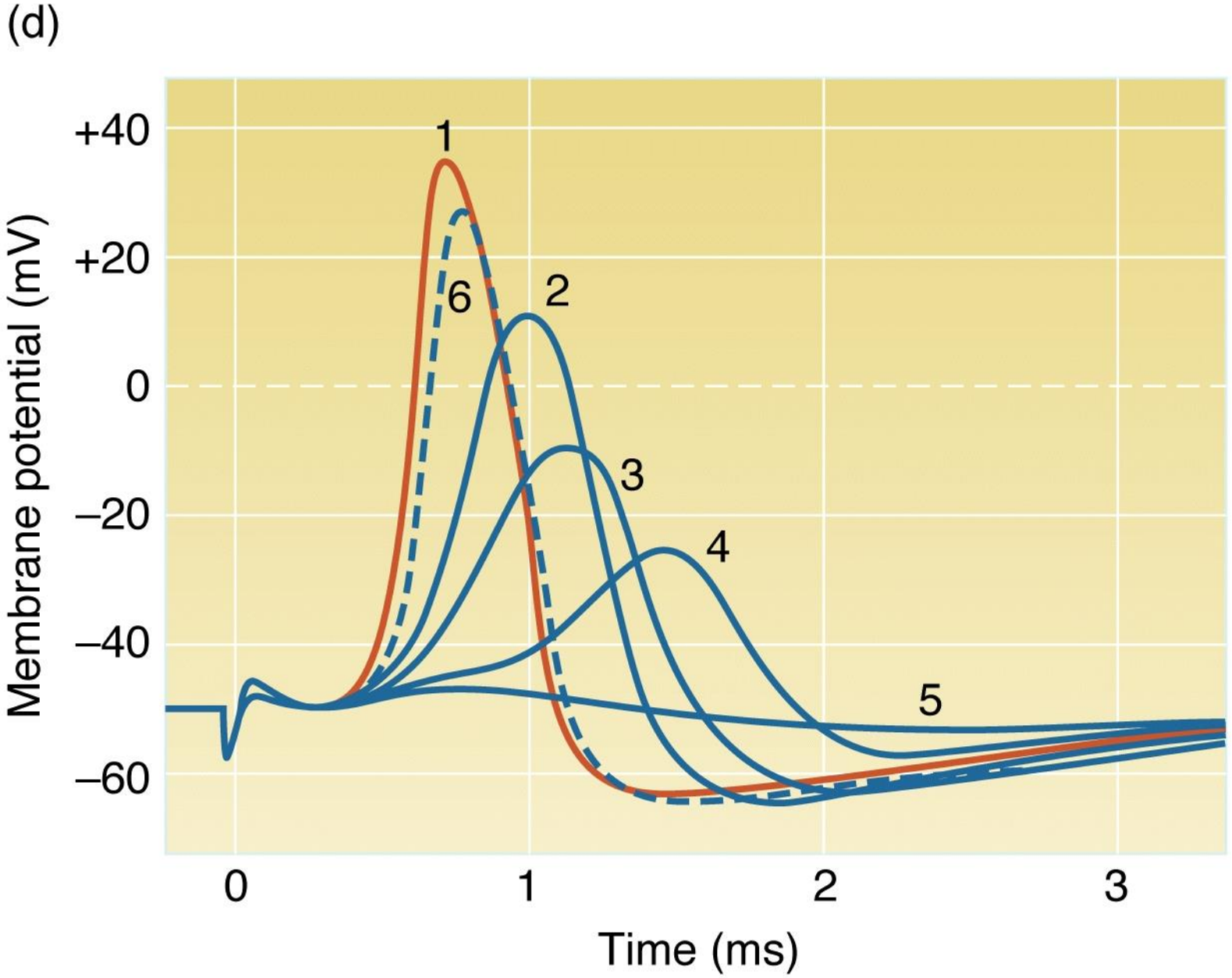

(a)
E_{Na}
Rising phase
Falling phase
0
V_m (mV)
After-hyperpolarization
–70
E_K
1 ms
(b)
30
20
10
0
g(mS • cm^{-2})
g_{Na}
g_K

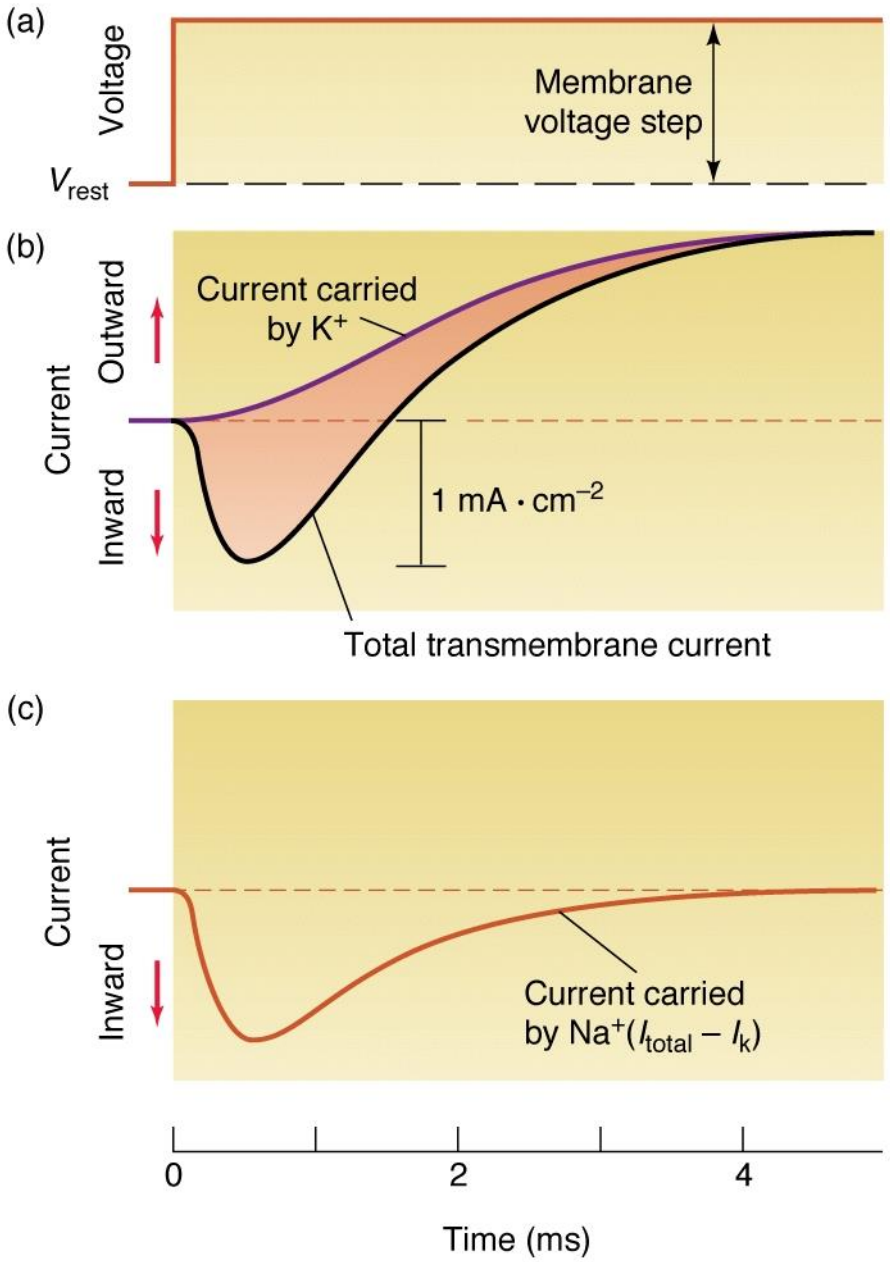
(a)



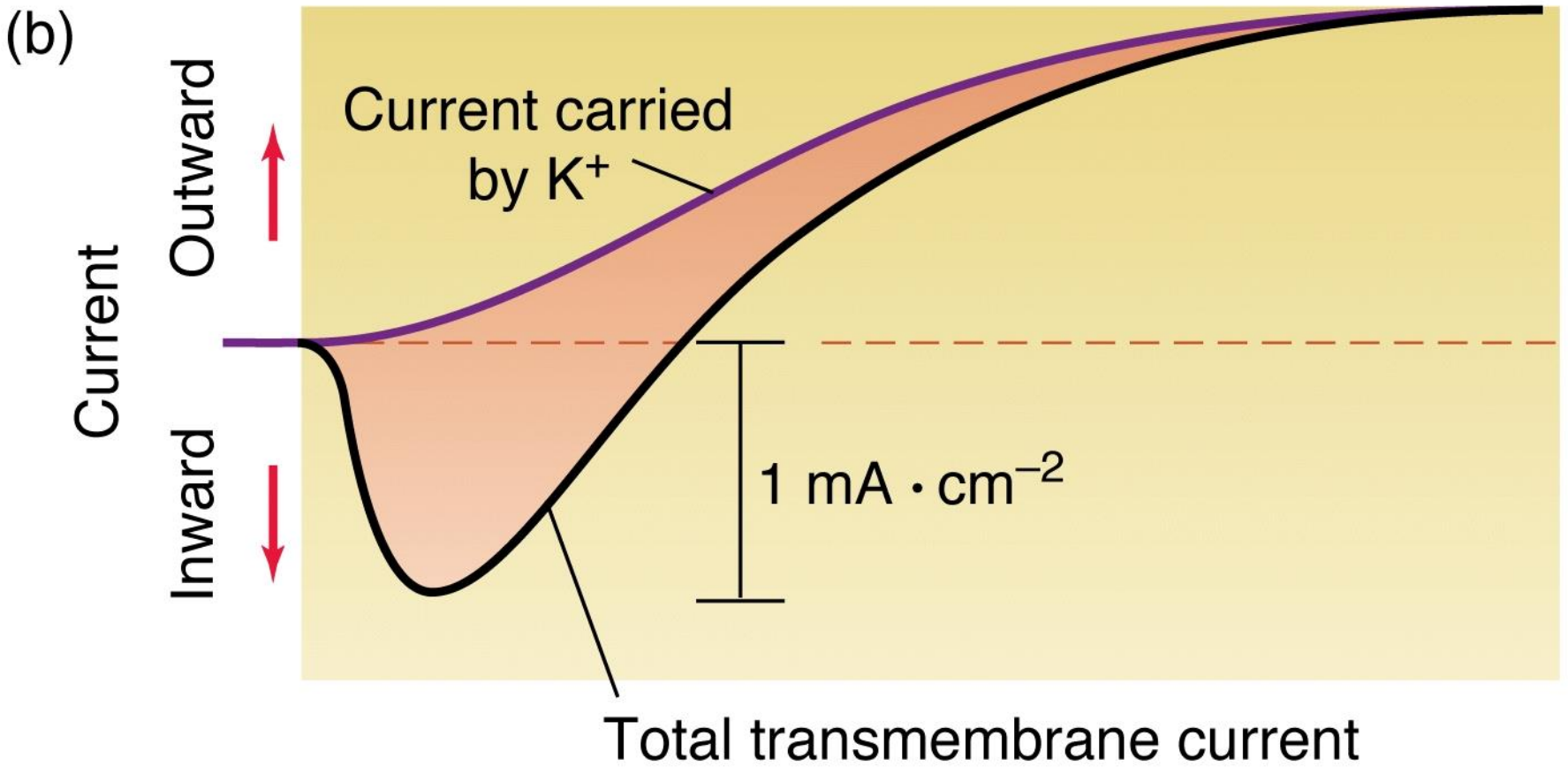

(b)
Amplifier
Axon
Reference electrode
Recording electrode
–
Stimulus
+

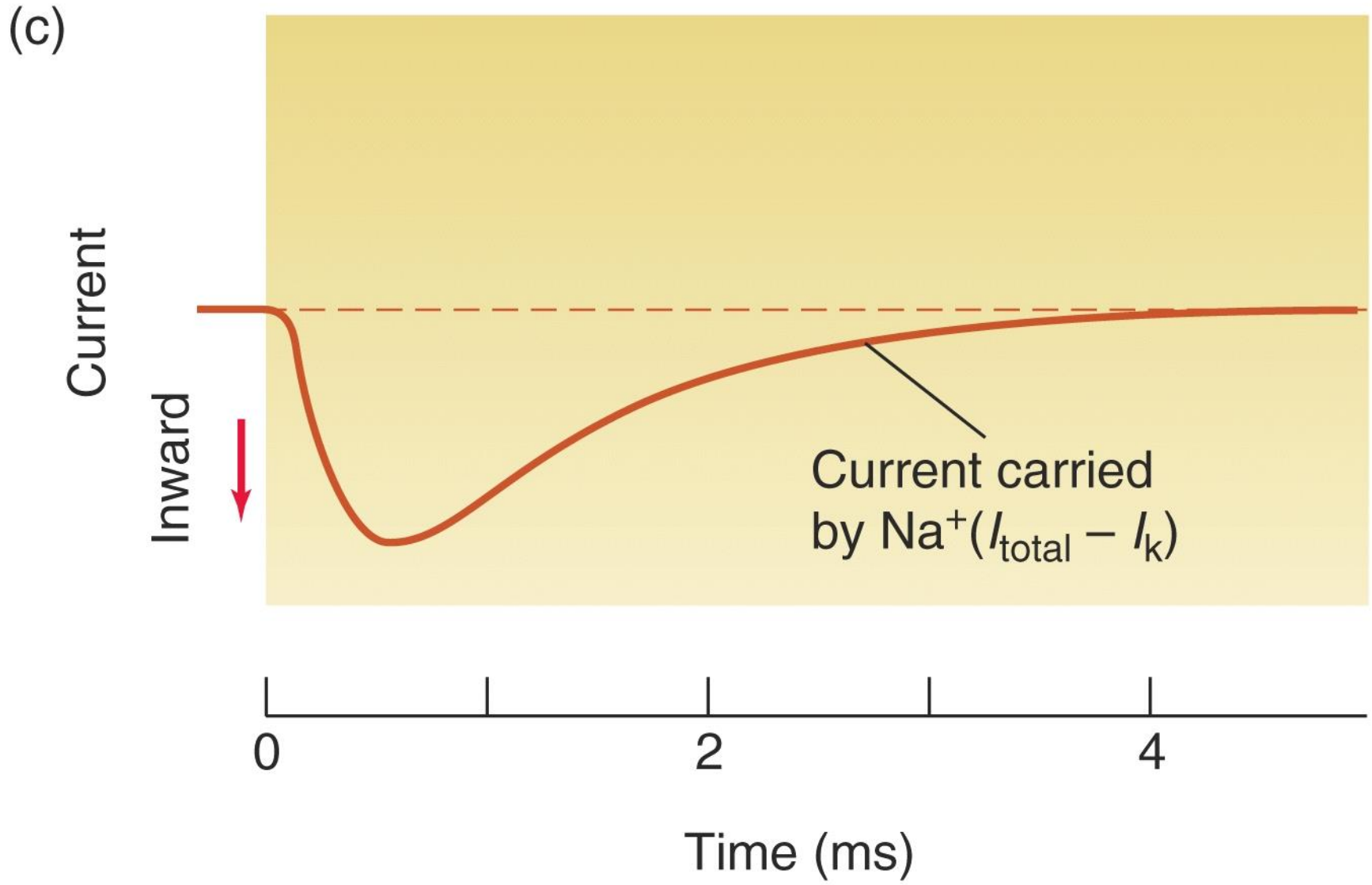

(c)
+40
0
–70
Membrane potential (mV)
2 ms

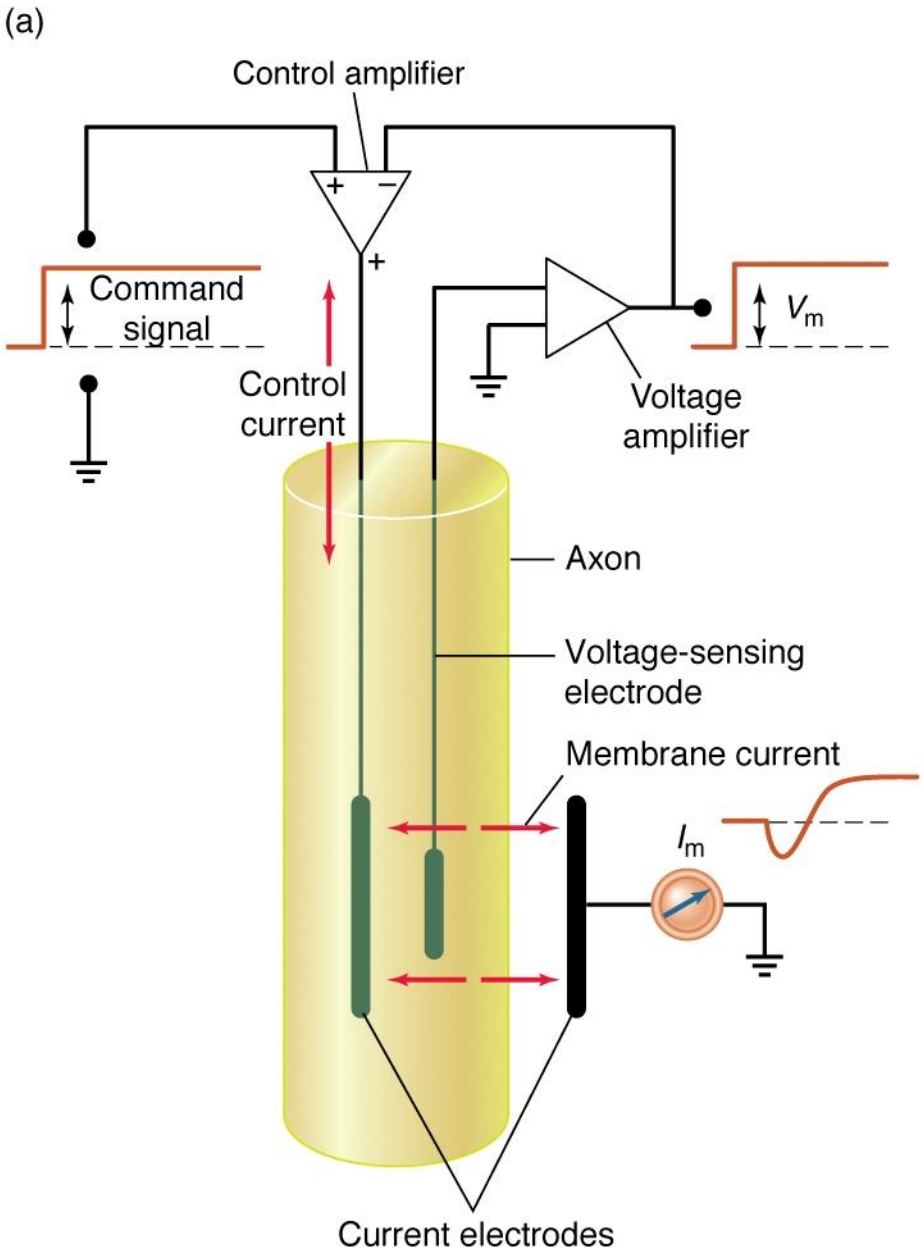

(d)
+40
+20
0
–20
–40
–60
Membrane potential (mV)
1
2
3
4
5
6
0
1
2
3
Time (ms)

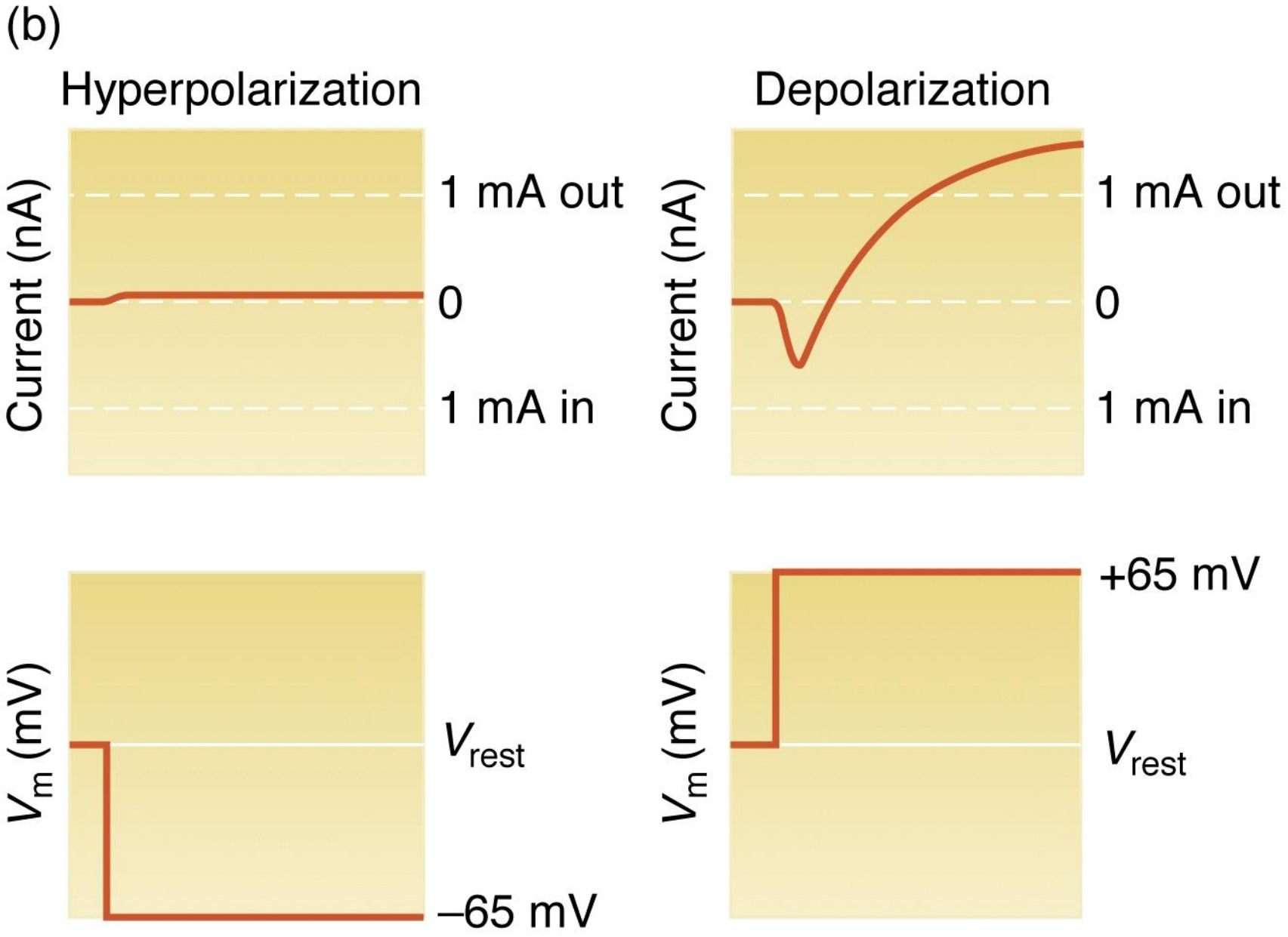

(a)
Voltage
Membrane
voltage step
V_{rest}
(b)
Current
Outward
Inward
Current carried
by K^+
1 mA · cm^{-2}
Total transmembrane current
(c)
Current
Inward
Current carried
by $Na^+(I_{total} - I_k)$
0
2
4
Time (ms)

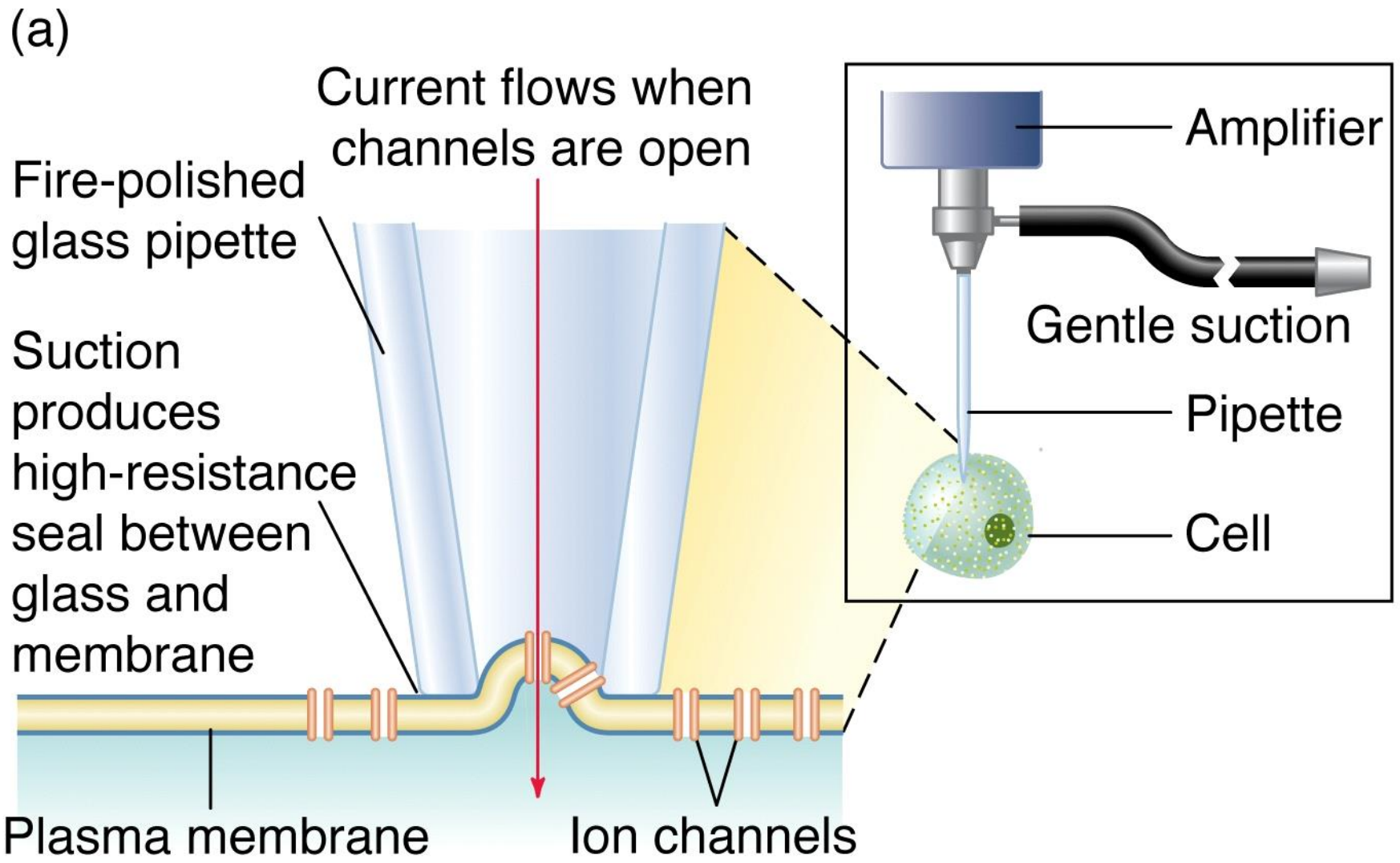

(a)
Voltage
V_{rest}
Membrane
voltage step


(b)
Current
Outward
Inward
Current carried
by K+
1 mA · cm−2
Total transmembrane current

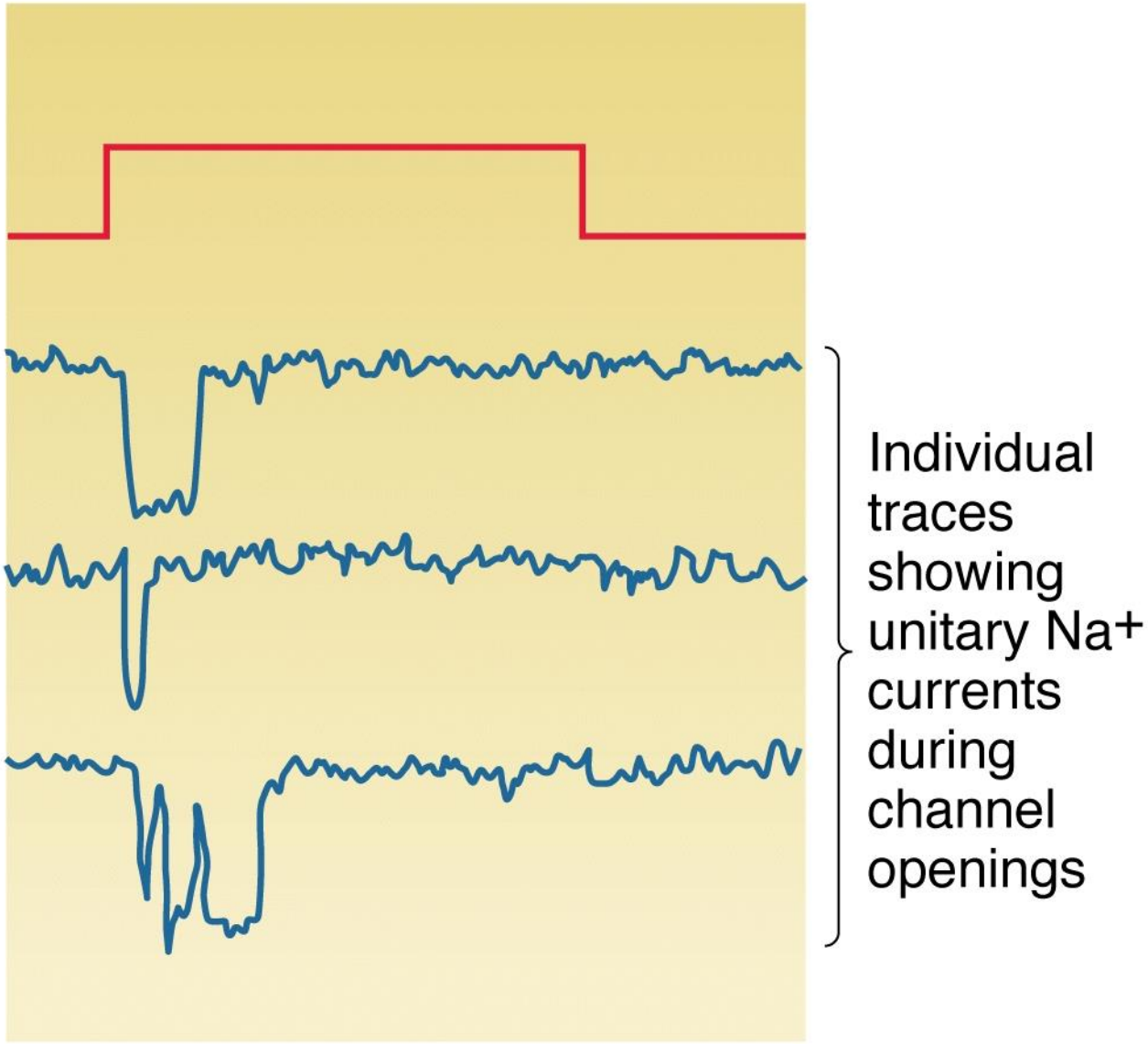

(c)
Current
Inward
Current carried
by $Na^+(I_{total} - I_k)$
0
2
4
Time (ms)


(a)
Control amplifier
+
−
+
Command
signal
Control
current
Voltage
amplifier
V_m
Axon
Voltage-sensing
electrode
Membrane current
I_m
Current electrodes

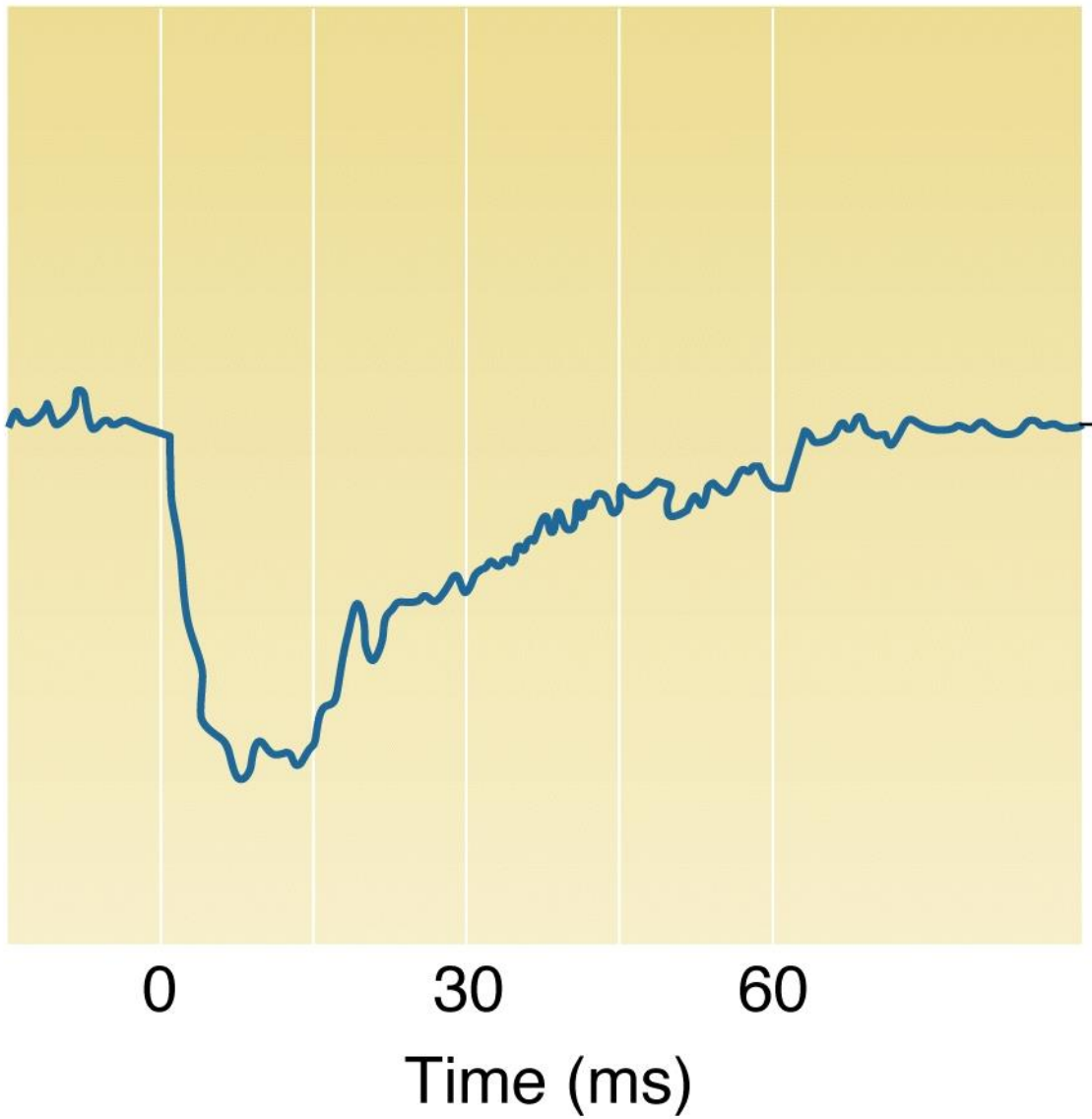

(b)
Hyperpolarization
Depolarization
Current (nA)
1 mA out
0
1 mA in
Current (nA)
1 mA out
0
1 mA in
V_m (mV)
V_{rest}
–65 mV
V_m (mV)
+65 mV
V_{rest}

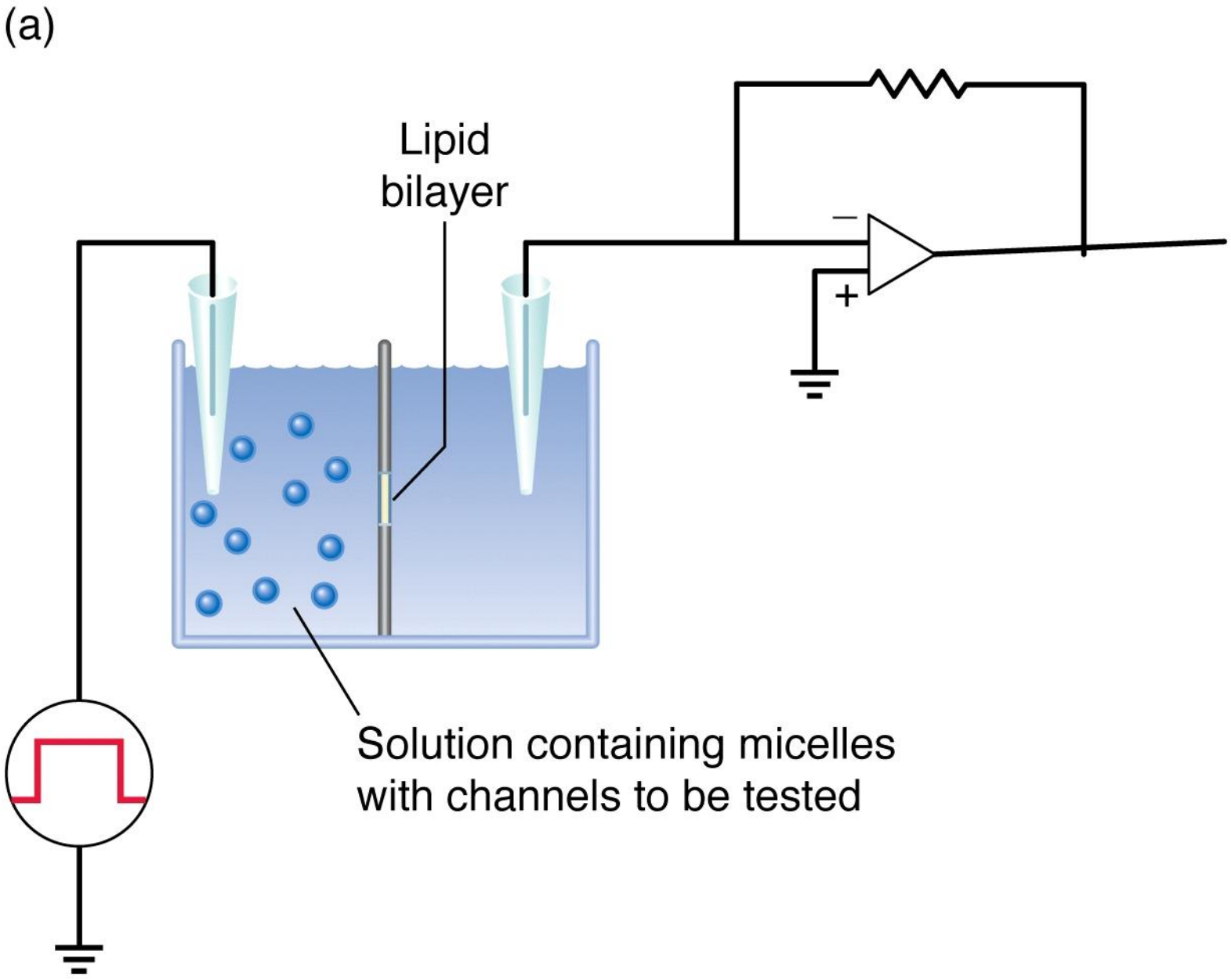

(a)
Current flows when channels are open
Fire-polished glass pipette
Suction produces high-resistance seal between glass and membrane
Amplifier
Gentle suction
Pipette
Cell
Plasma membrane
Ion channels

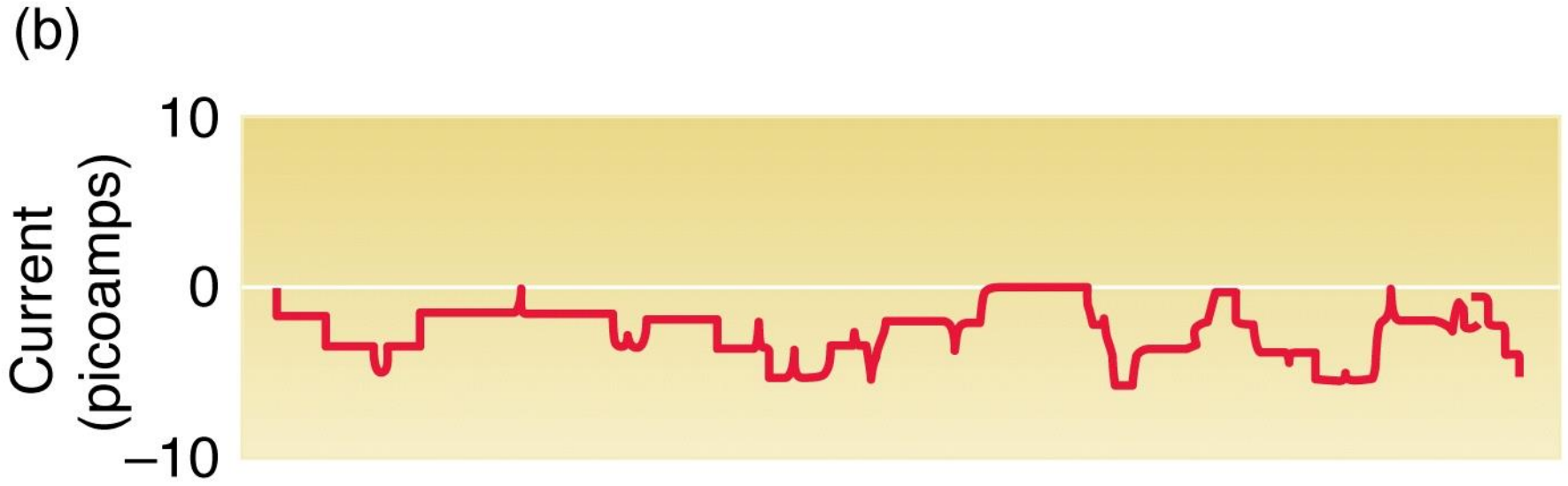
(b)

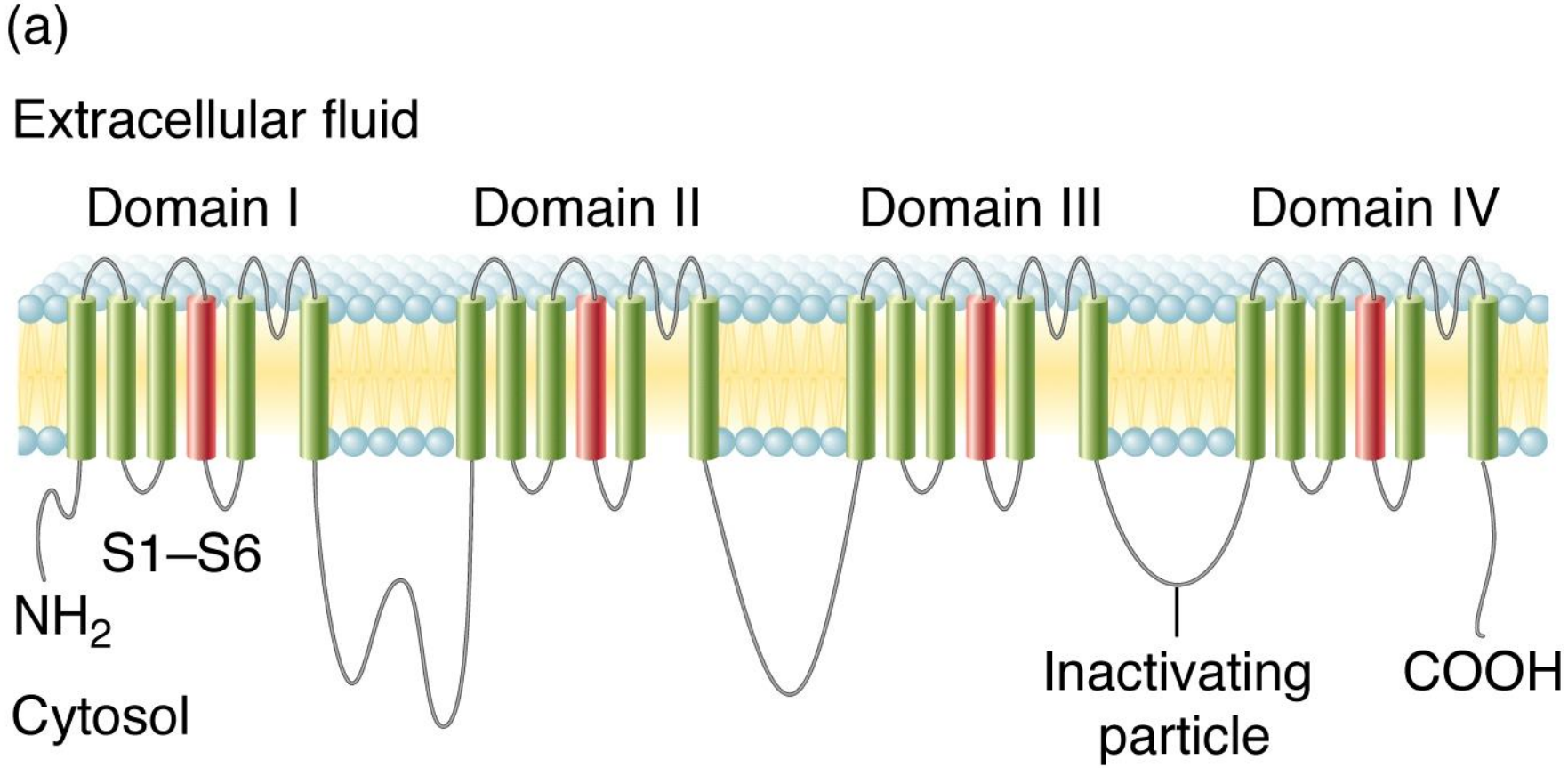

Individual traces showing unitary Na+ currents during channel openings

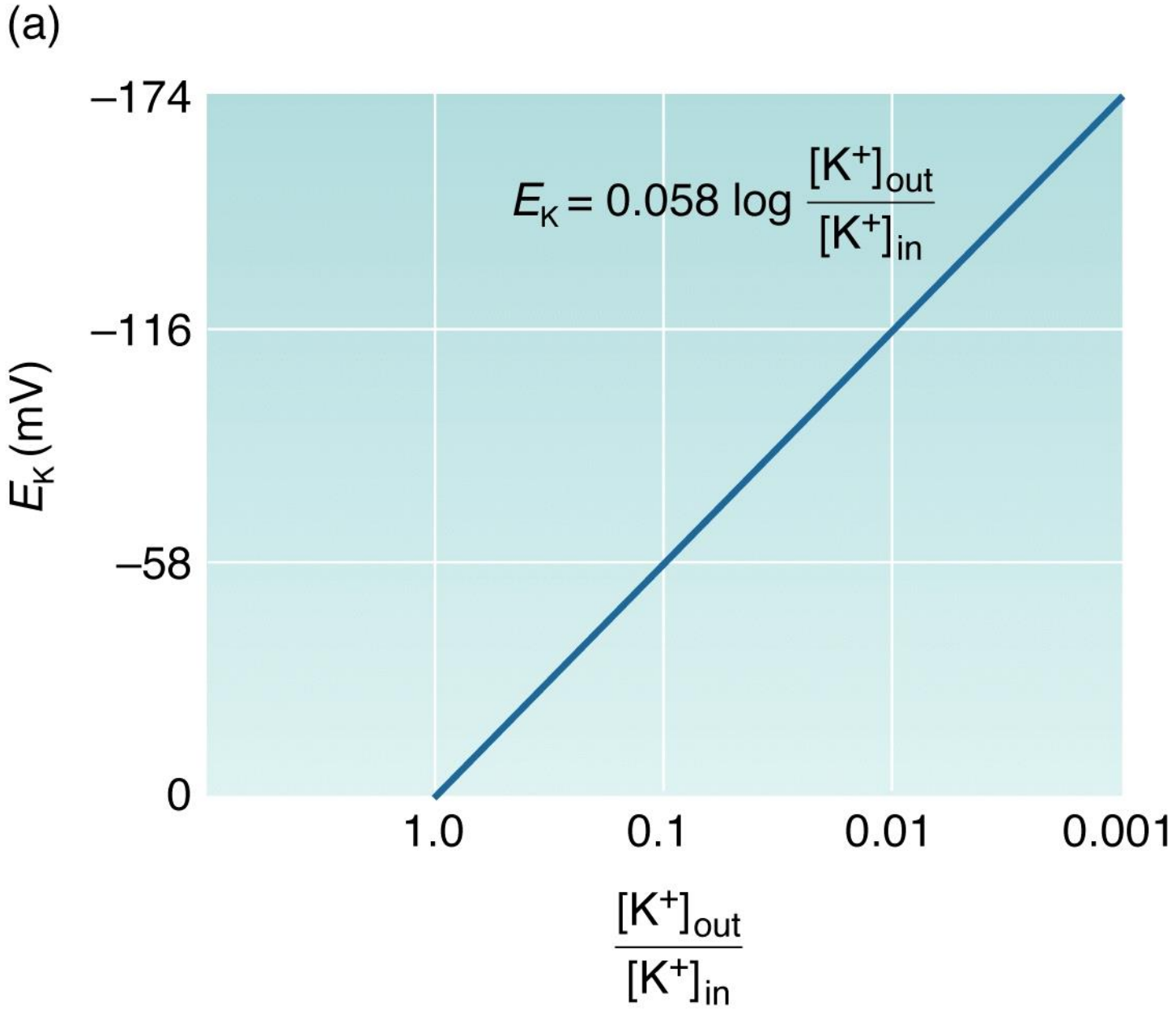
(c)

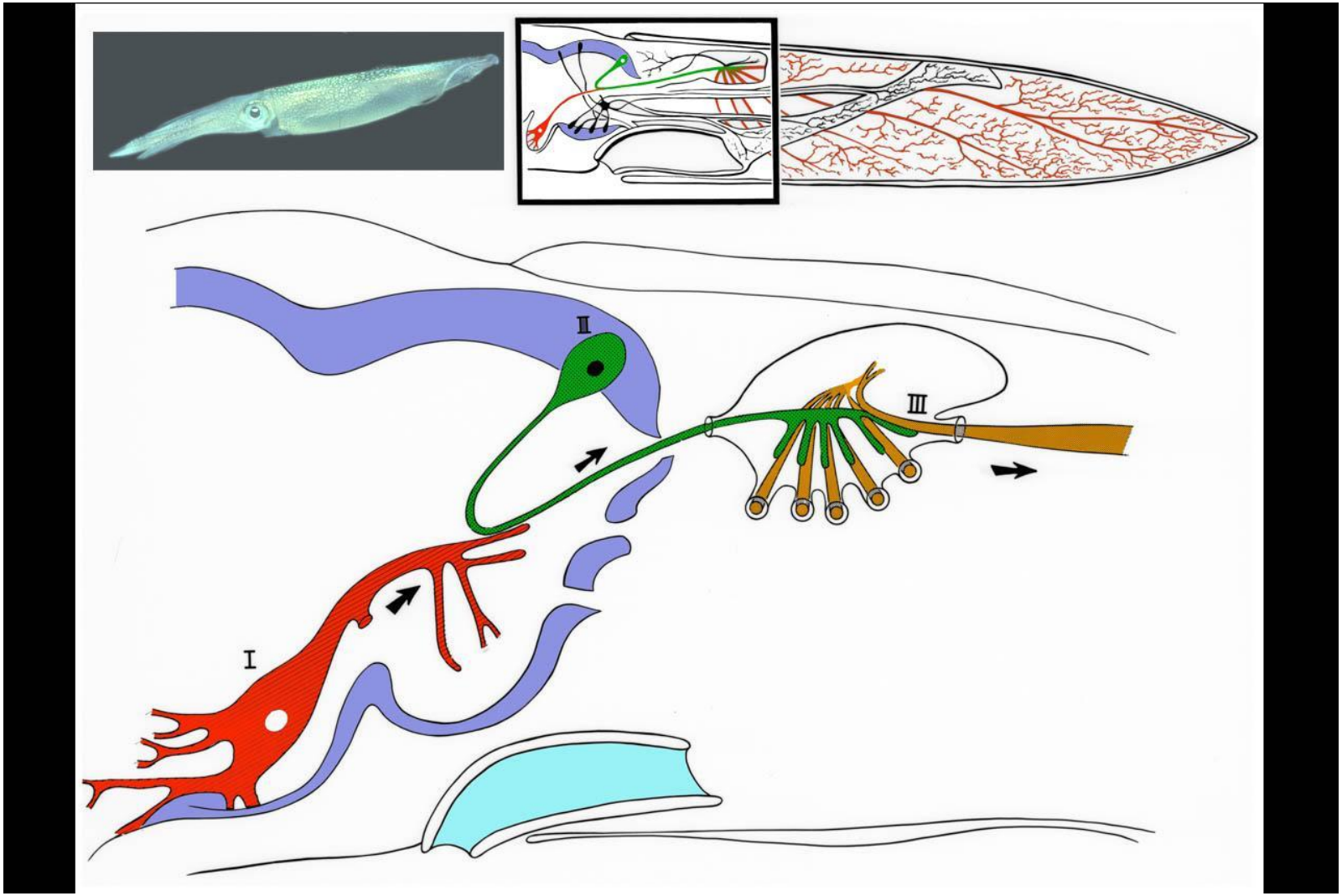

Ensemble current reconstructed by summing many traces like those in part b
0
30
60
Time (ms)


(a)
Lipid
bilayer
–
+
Solution containing micelles
with channels to be tested

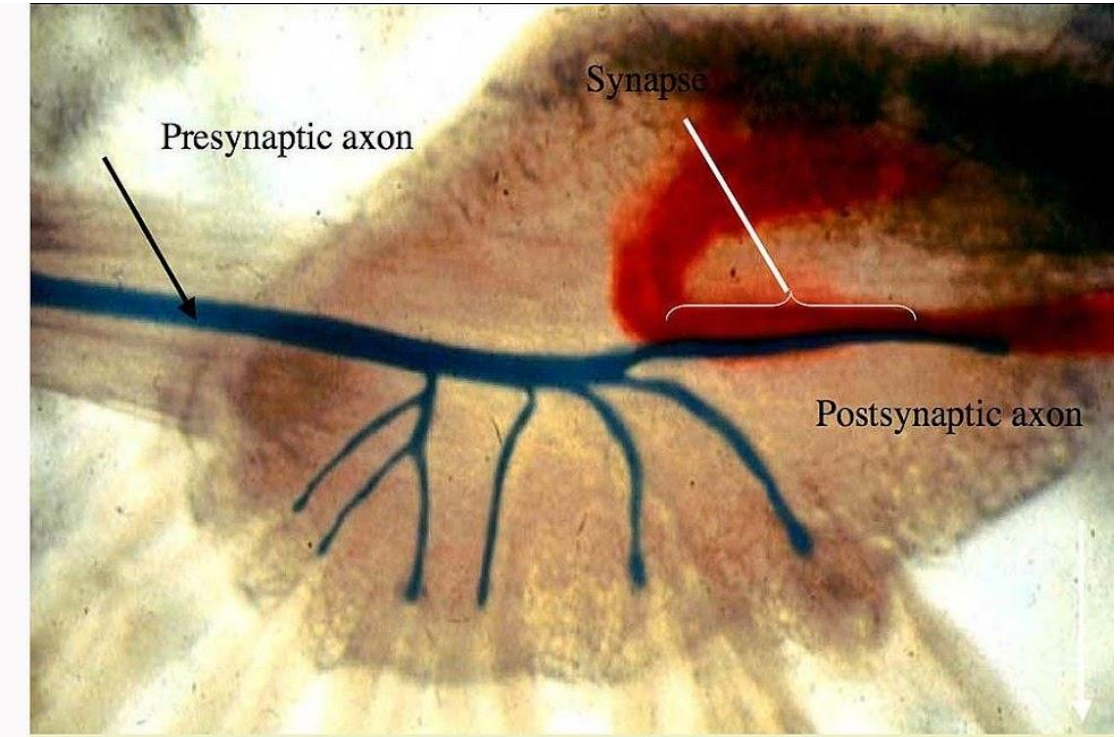

(b)
Current (picoamps)
10
0
–10

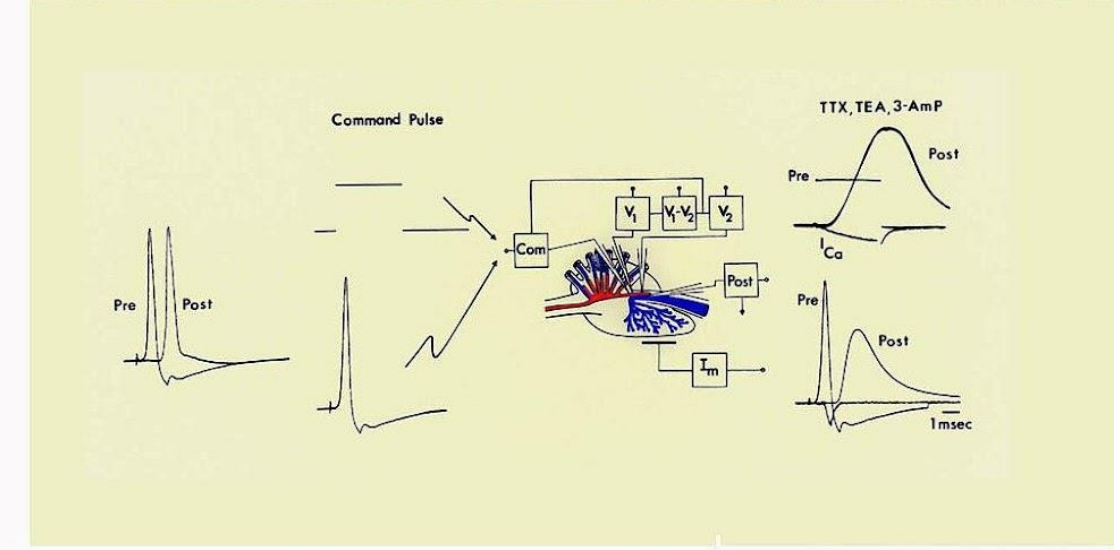

(a)
Extracellular fluid
Domain I
Domain II
Domain III
Domain IV
S1–S6
NH2
Cytosol
Inactivating particle
COOH


(a)
–174
–116
–58
0
E_K (mV)
$E_K = 0.058 \log \frac{[K^+]_{out}}{[K^+]_{in}}$
1.0
0.1
0.01
0.001
$\frac{[K^+]_{out}}{[K^+]_{in}}$



https://en.wikipedia.org/wiki/Squid_giant_synapse





The membrane potential

Nernst equation :

$$V = \frac{RT}{zF} \cdot ln \frac{[X]_{out}}{[X]_{in}}$$

X = ion of interest

V = equilibrium voltage for the X ion across the membrane

R = gas constant [8.314 J/(mol•K)]

T = absolute temperature [Kelvin]

Z = valence of the ion

F = Faraday's constant [9.649 × 104 C/mol]

For the K^+ ion at 20°C and transformation of ln to $\log_{10}$ along with filling in the constants, one arrives at:

$$Potential = 58\ log \frac{[K]_{out}}{[K]_{in}}$$

Goldman-Hodgkin-Katz (G-H-K) equation

Here is a generalized G-H-K equation for Na^+, K^+, and Cl^- ions:

$$Em_{K,Na,Cl} = \frac{RT}{F} ln \frac{P_{Na^+}[Na^+]_{out} + P_{K^+}[K^+]_{out} + PCl[Cl]in}{P_{Na^+}[Na^+]_{in} + P_{K^+}[K^+]_{in} + PCl[Cl]out}$$

E_{Na} or E_K

Given the $[K_{out}]$= for the saline used is 5.4 mM. Also, assume membrane potential is -70mV.

$$Potential = 58 \log \frac{5.4}{[K]_{in}}$$

-70/58=log 5.4/[K in]

-1.2069= log 5.4/[K in]

Antilog -1.2069= 5.4/[K in]

$10^{-1.2069}$= 5.4/[K in]

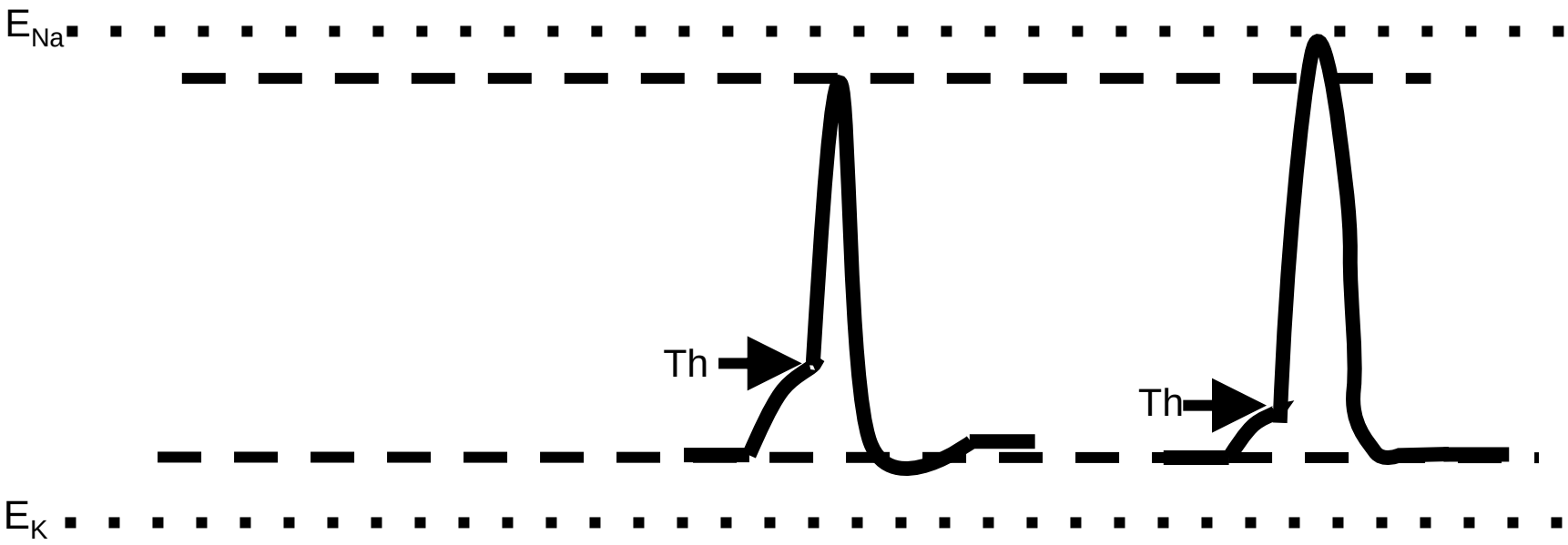
0.0621= 5.4/[K in]

[K in] =5.4/0.0621=86.95 mM

Double check

X= 58 Log (5.4/86.95)= -69.999 so close enough to -70 mV

E_{Na} & E_K are the equilibrium potentials
Th is threshold



There are values estimated for neurons of crayfish (Atwood 1982)

$[Na^+]_i$ = 17.4 mM (for neurons, Atwood 1982)

$[K^+]_i$ = 265 mM (for neurons, Atwood 1982)

$[Cl^-]_i$ = 12.7 (for neurons, Atwood 1982)

P_K = 1 (for neurons, Atwood 1982)

P_{Cl} = 0.1 (for neurons, Atwood 1982)

P_{Na} = 0.001 (for neurons, Atwood 1982)

$[K]_o$ = 5.3 mM (Saline)

$[Na]_o$ = 205 mM (Saline)

$[Cl]_o$ = 232.15 mM (assume from saline; 205 mM NaCl; 5.3 mM KCl; 13.5 mM $CaCl_2 2H_2O$; 2.45 mM $MgCl_2\ 6H_2O$)

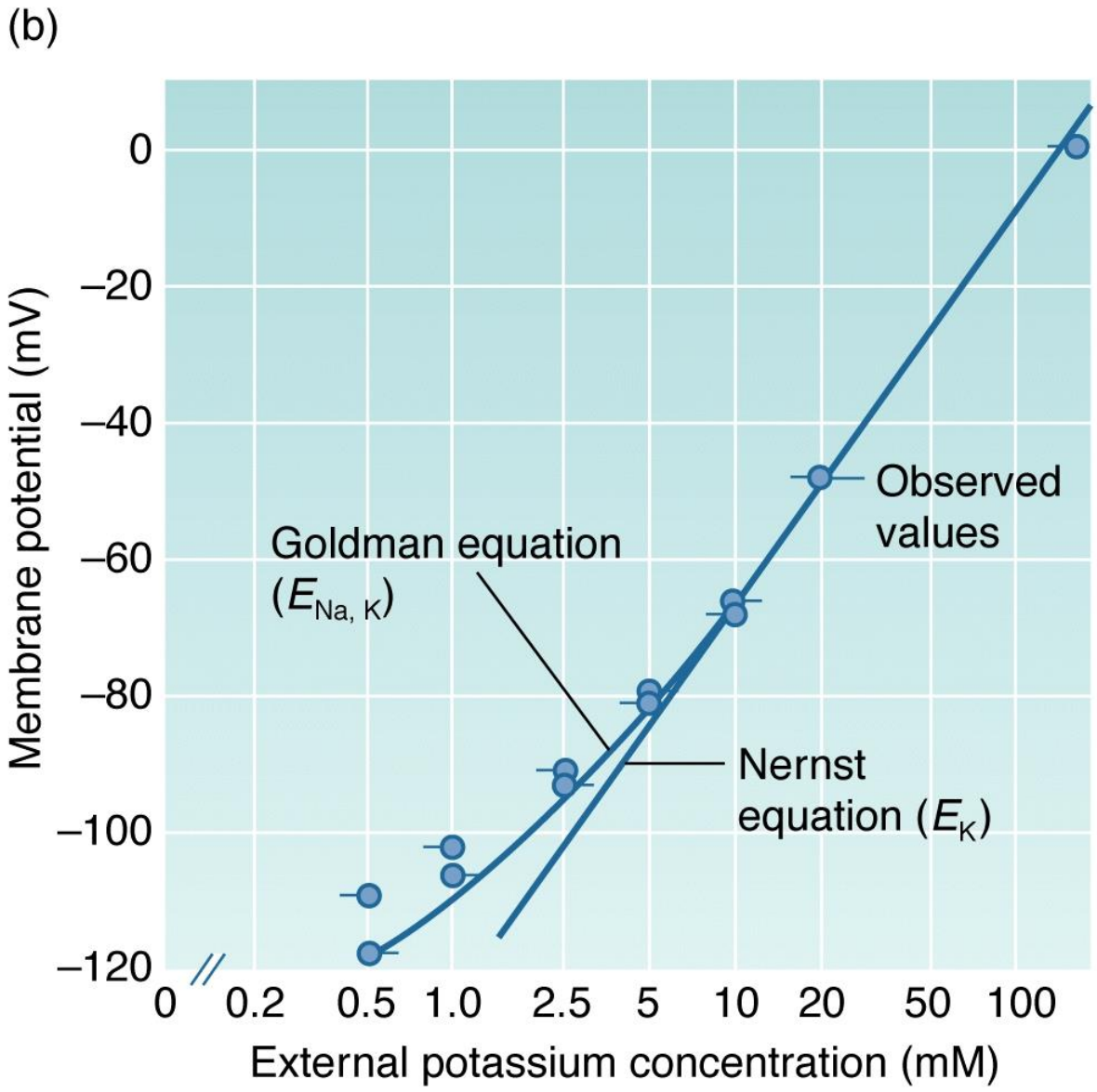
Use the on-line simulator from

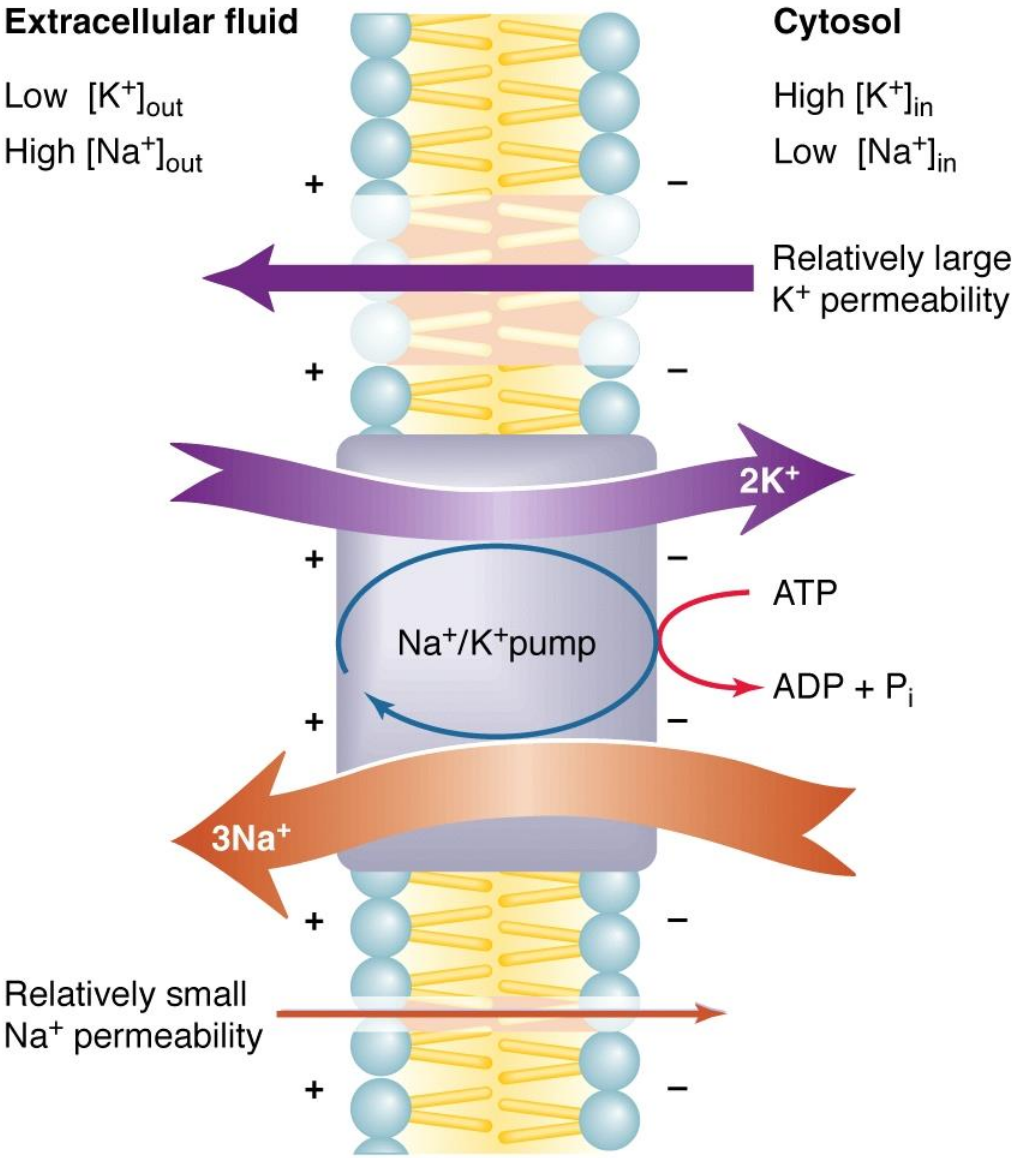
Online https://www.physiologyweb.com/calculators/ghk_equation_calculator.html

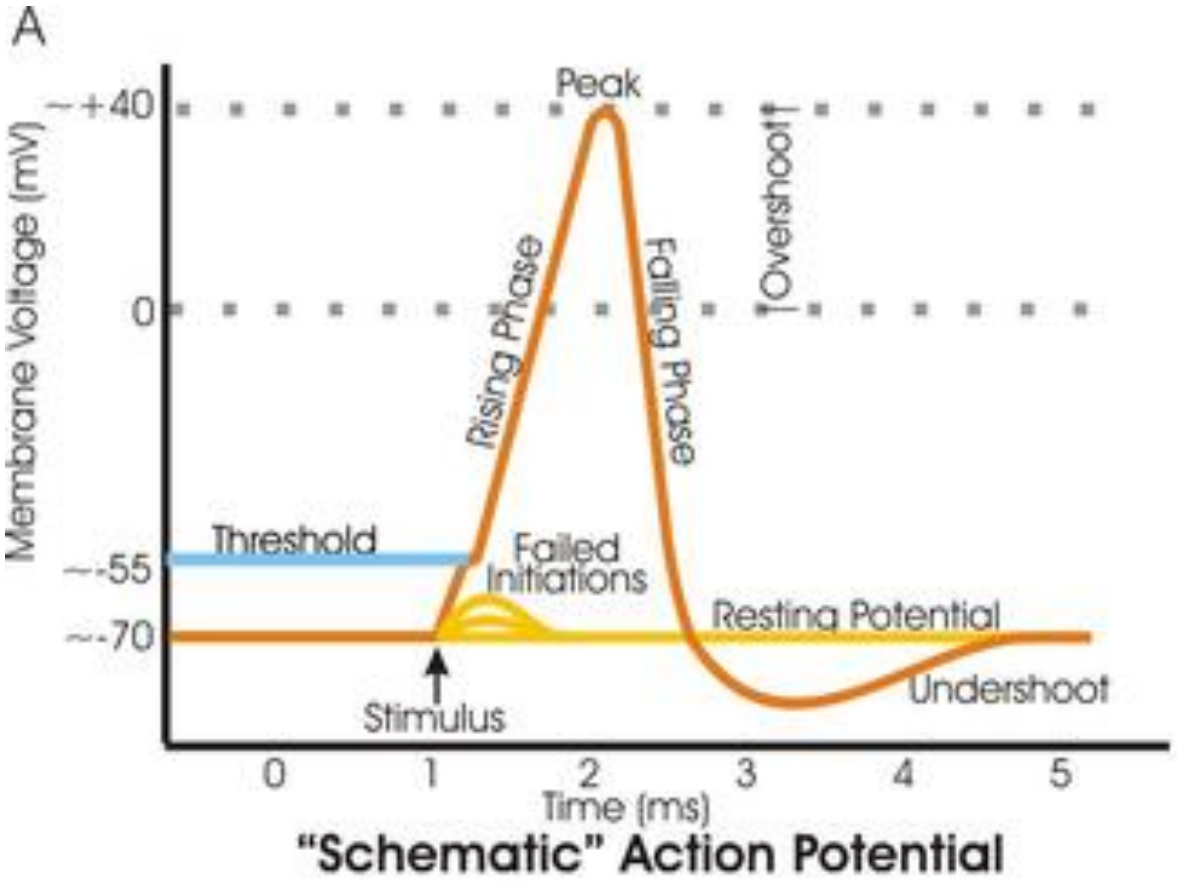
(note: values of temperature are in K which is 273.15 + the # in centigrade)

T		K						
p_K								
p_{Na}								
p_{Cl}								
$[K^+]_o$		mM	○ fM	○ pM	○ nM	○ µM	◉ mM	○ M
$[K^+]_i$		mM	○ fM	○ pM	○ nM	○ µM	◉ mM	○ M
$[Na^+]_o$		mM	○ fM	○ pM	○ nM	○ µM	◉ mM	○ M
$[Na^+]_i$		mM	○ fM	○ pM	○ nM	○ µM	◉ mM	○ M
$[Cl^-]_o$		mM	○ fM	○ pM	○ nM	○ µM	◉ mM	○ M
$[Cl^-]_i$		mM	○ fM	○ pM	○ nM	○ µM	◉ mM	○ M
V_m		mV	◉ mV	○ V				

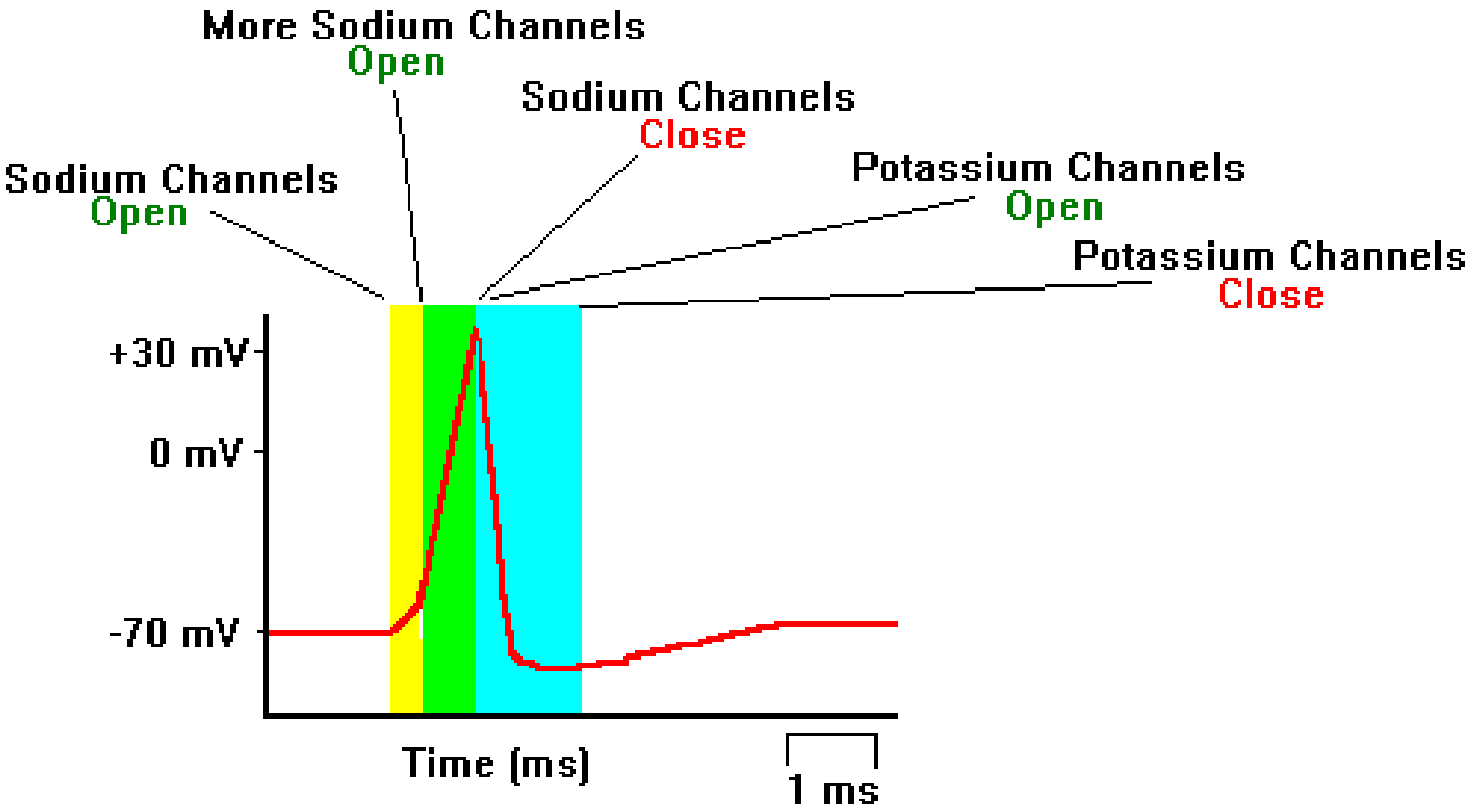
Calculate Clear All Fill Cells with Sample Data

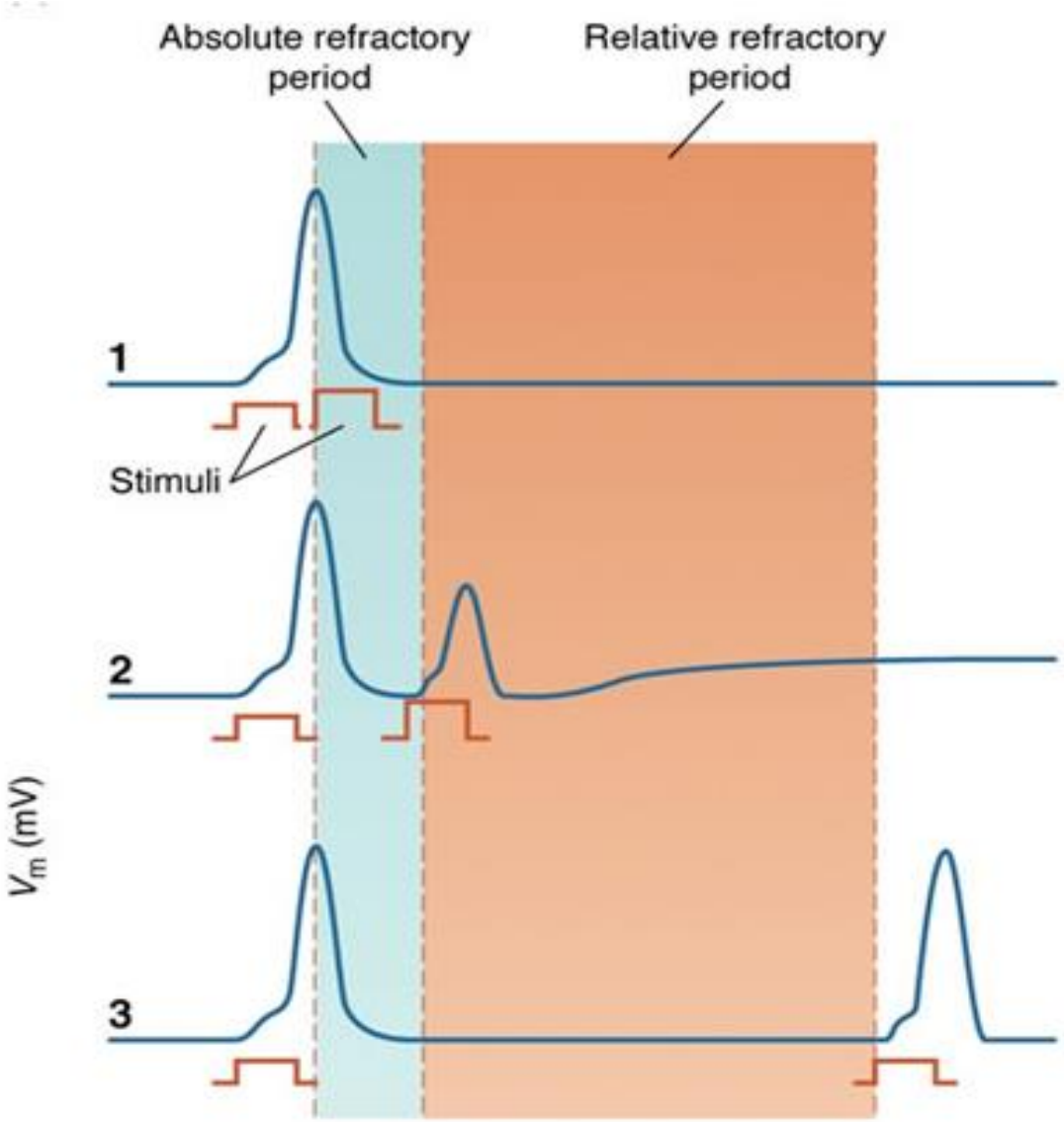

(b)
0
–20
–40
–60
–80
–100
–120
Membrane potential (mV)
0
0.2
0.5
1.0
2.5
5
10
20
50
100
External potassium concentration (mM)
Goldman equation
($E_{Na, K}$)
Observed
values
Nernst
equation (E_K)


Extracellular fluid
Low [K+]out
High [Na+]out
Cytosol
High [K+]in
Low [Na+]in
Relatively large
K+ permeability
2K+
ATP
Na+/K+pump
ADP + Pi
3Na+
Relatively small
Na+ permeability

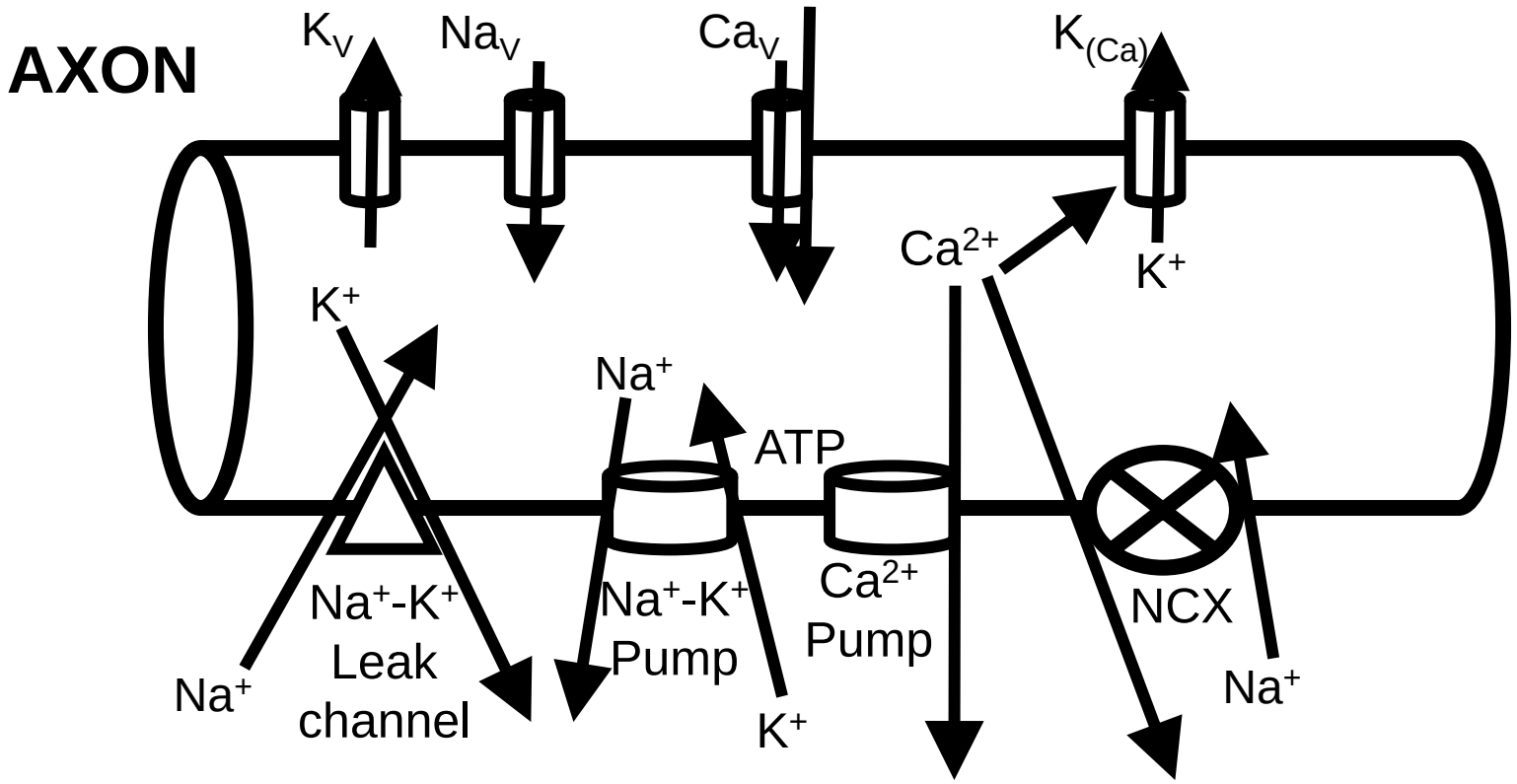


"Schematic" Action Potential


More Sodium Channels
Open
Sodium Channels
Close
Sodium Channels
Open
Potassium Channels
Open
Potassium Channels
Close
+30 mV
0 mV
-70 mV
Time (ms)
1 ms



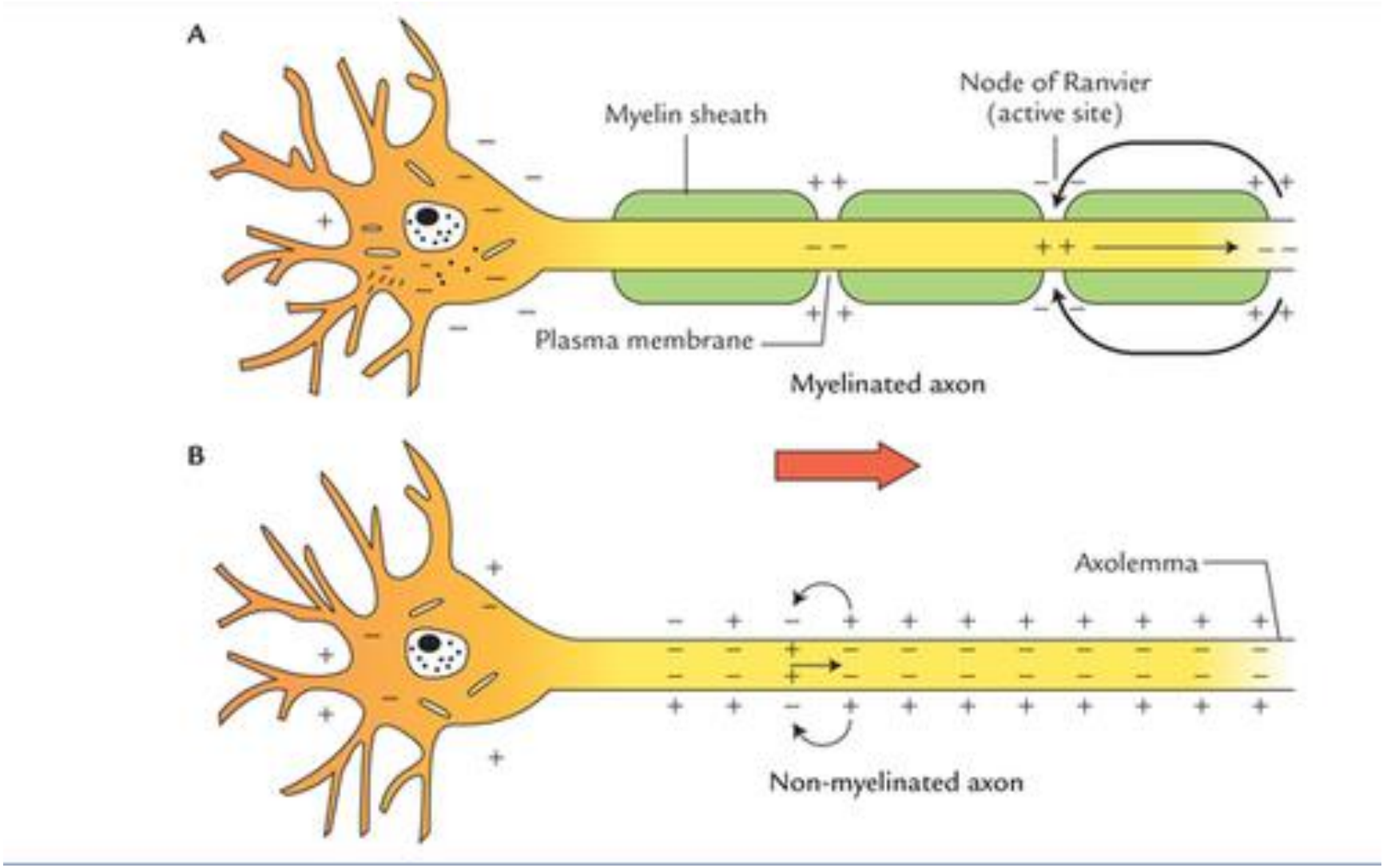
Na_V channel inactivation
& removal of inactivation



K_V, Na_V, Ca_V are voltage gated ion channels

NCX is the Na^+-Ca^{2+} exchanger

$K_{(Ca)}$ is the Ca^{2+} activated K^+ channel



https://vivadifferences.com/myelinated-vs-unmyelinated-neurons/

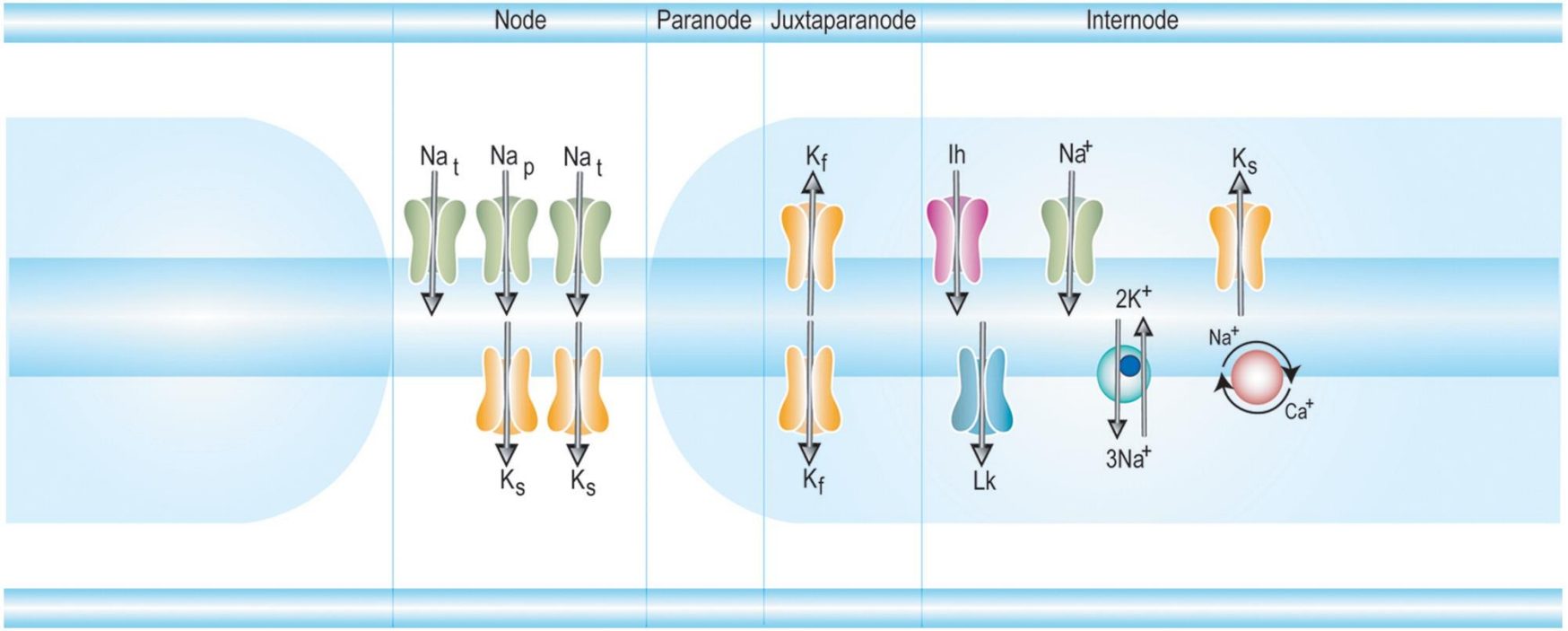
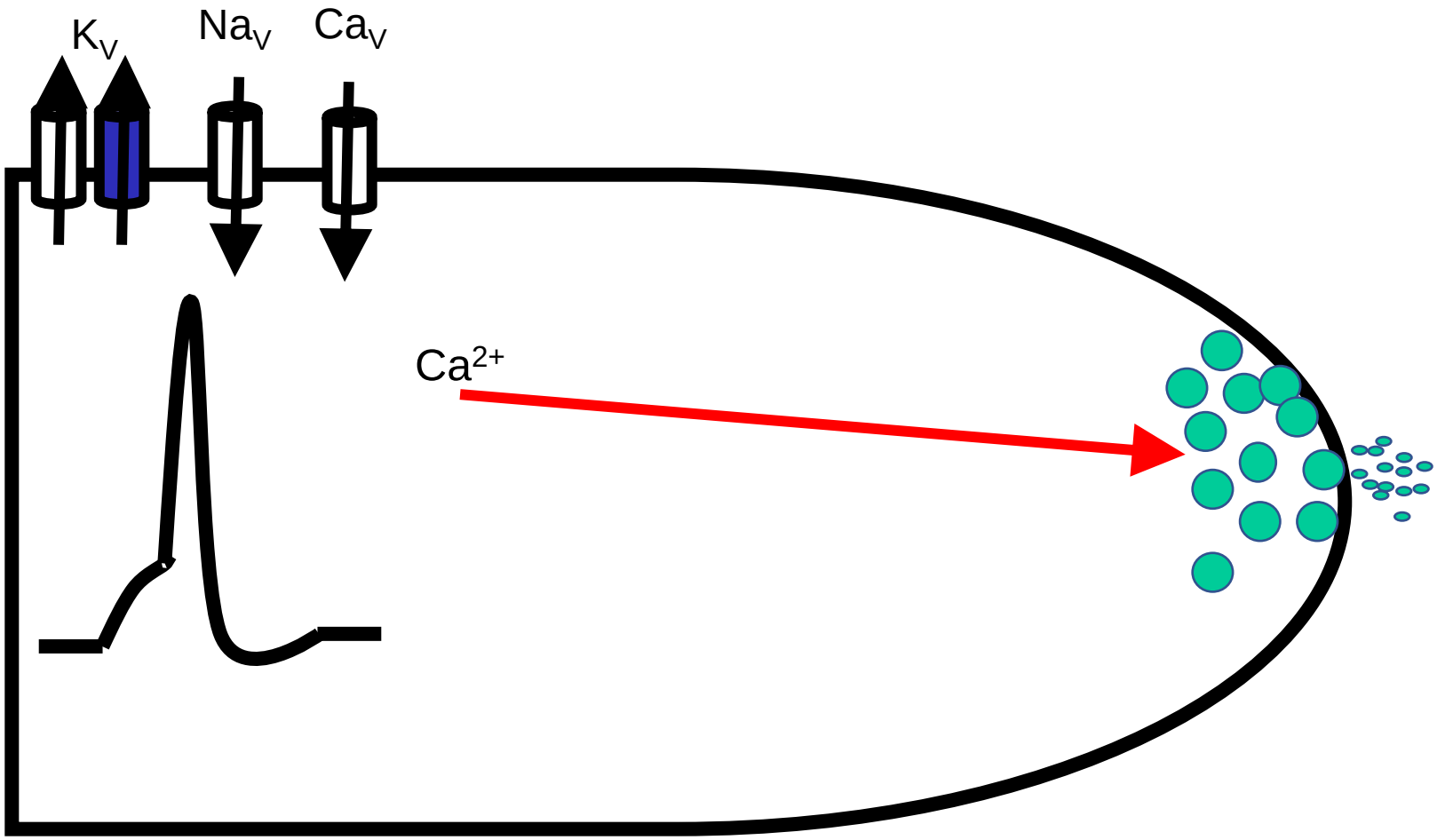


Figure 1. An overview of the various ion channels, pumps and exchangers that are important in axonal impulse conduction. Na+ channels are present in highest density at the Node of Ranvier as are slow K+ channels (Ks). Fast K+ channels, also known as Kv 1.1 channels are present in the highest concentration in the juxtaparanodal region and are blocked by 4-aminopyridine (fampridine). Inwardly rectifying channels (Ih) are permeable to Na+ and K+ ions and limit axonal hyperpolarisation. Transient Na+ channels (Nat) are responsible for action potential propagation while persistent Na+ conductances (Nap) modulate resting membrane potential. The sodium-calcium exchanger (Na+/Ca2+) plays an important role in the processes of axonal degeneration. Lk refers to leak conductances.

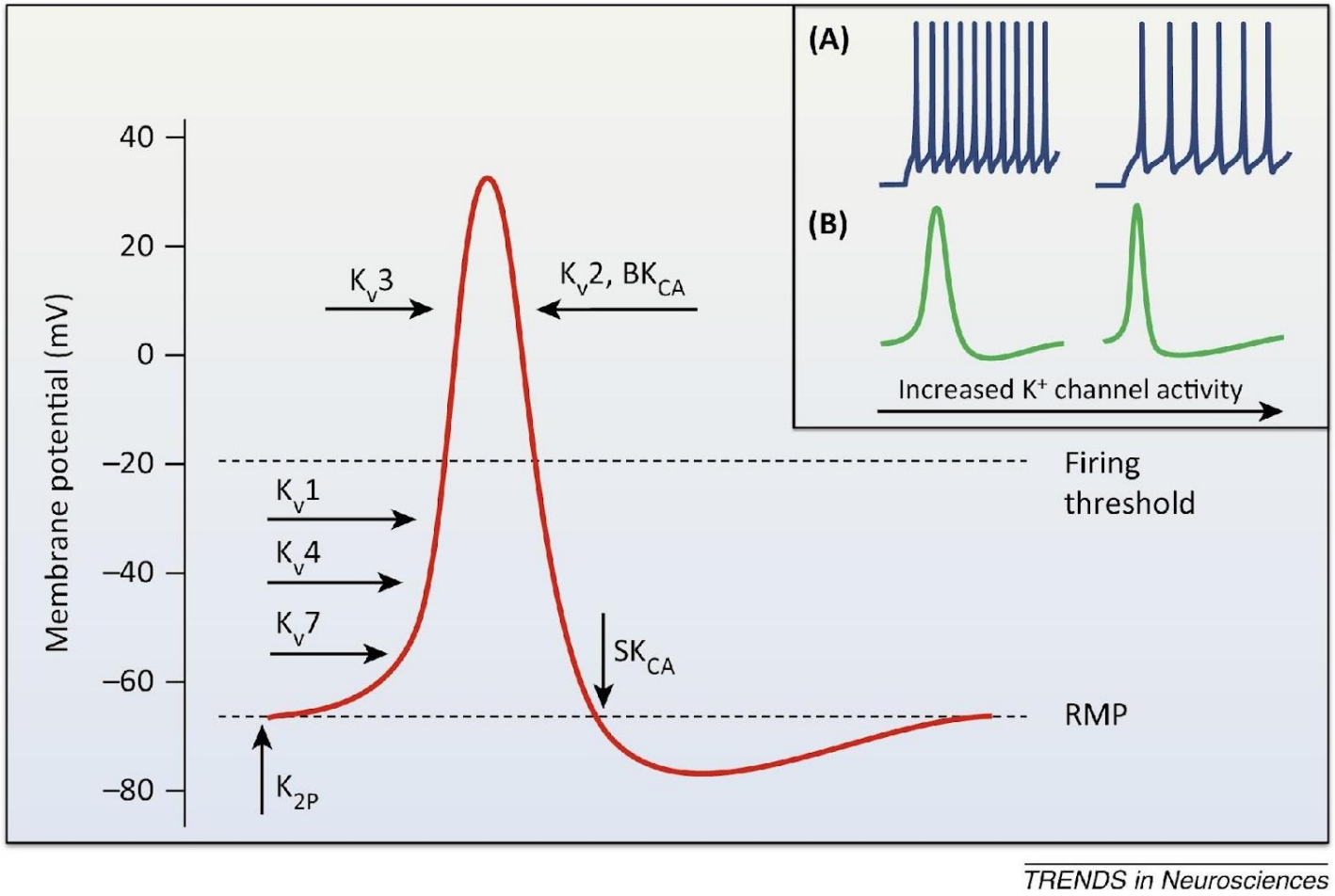
4-AP sensitive one



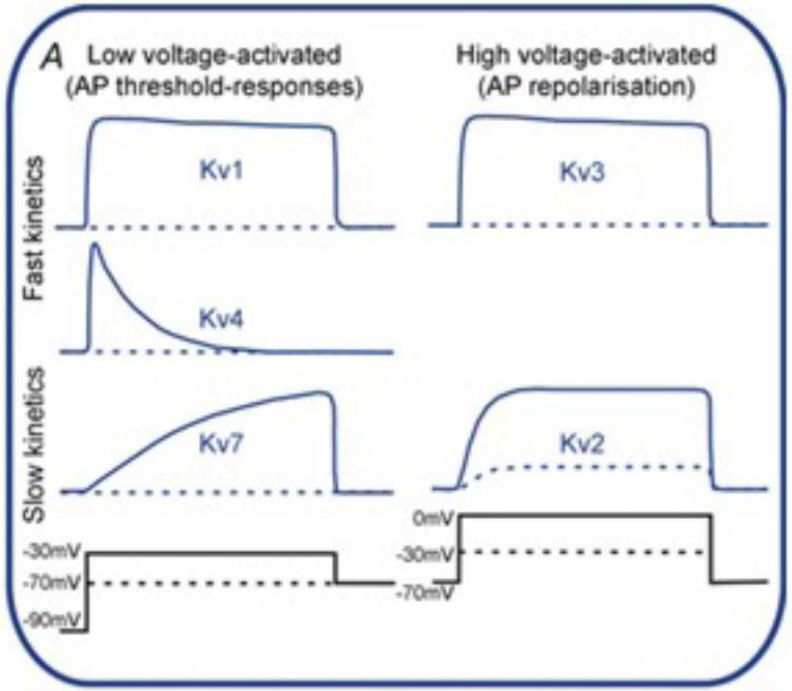
Goldman-Hodgkin-Katz (G-H-K) equation

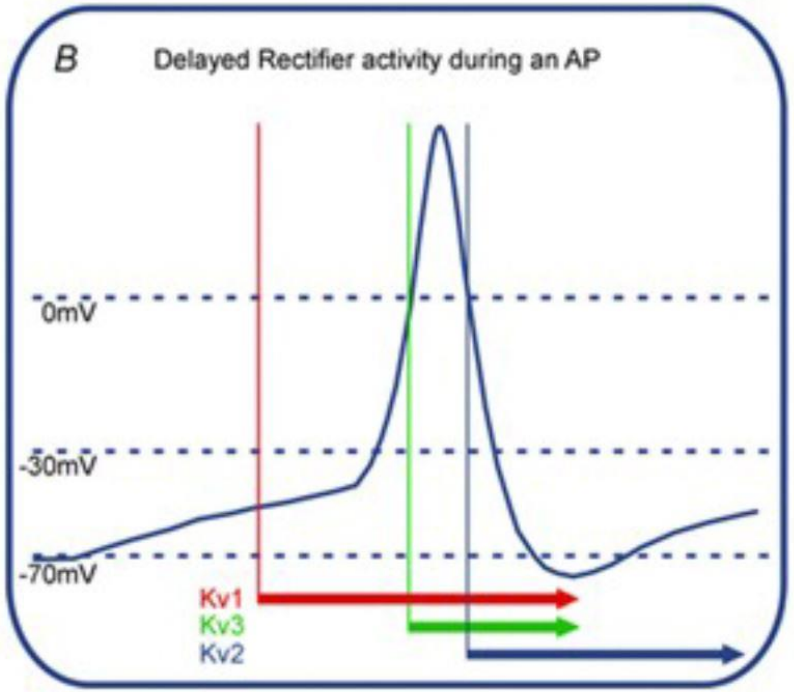
Here is a generalized G-H-K equation for Na^+, K^+, and Cl^- ions:

$$Em_{K,Na,Cl} = \frac{RT}{F} lnln \frac{P_{Na^+}[Na^+]_{out} + P_{K^+}[K^+]_{out} + PCl[Cl]in}{P_{Na^+}[Na^+]_{in} + P_{K^+}[K^+]_{in} + PCl[Cl]out}$$

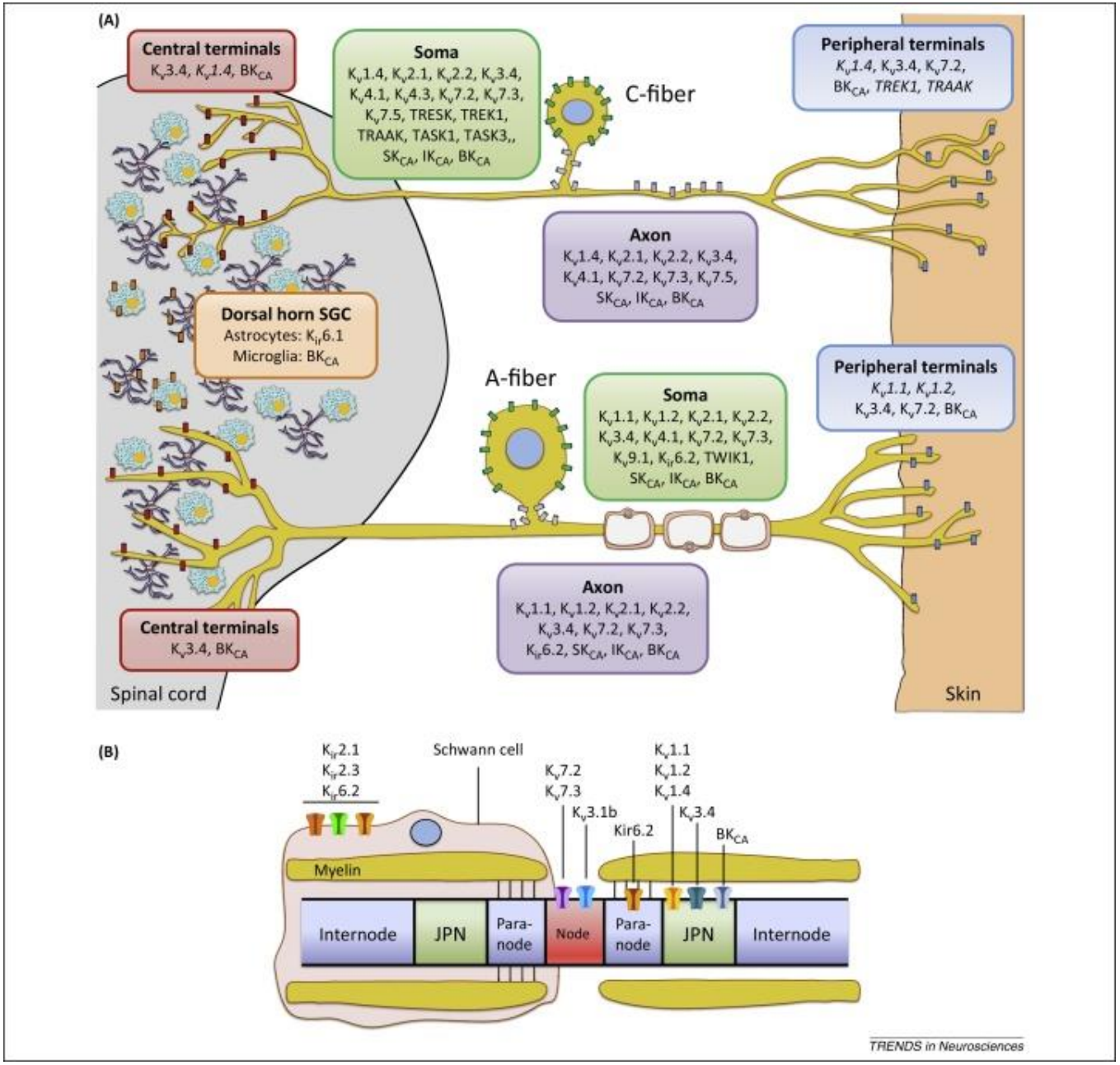


Tsantoulas C, McMahon SB. Opening paths to novel analgesics: the role of potassium channels in chronic pain. Trends Neurosci. 2014 Mar;37(3):146-58. doi: 10.1016/j.tins.2013.12.002. Epub 2014 Jan 21. PMID: 24461875; PMCID: PMC3945816.

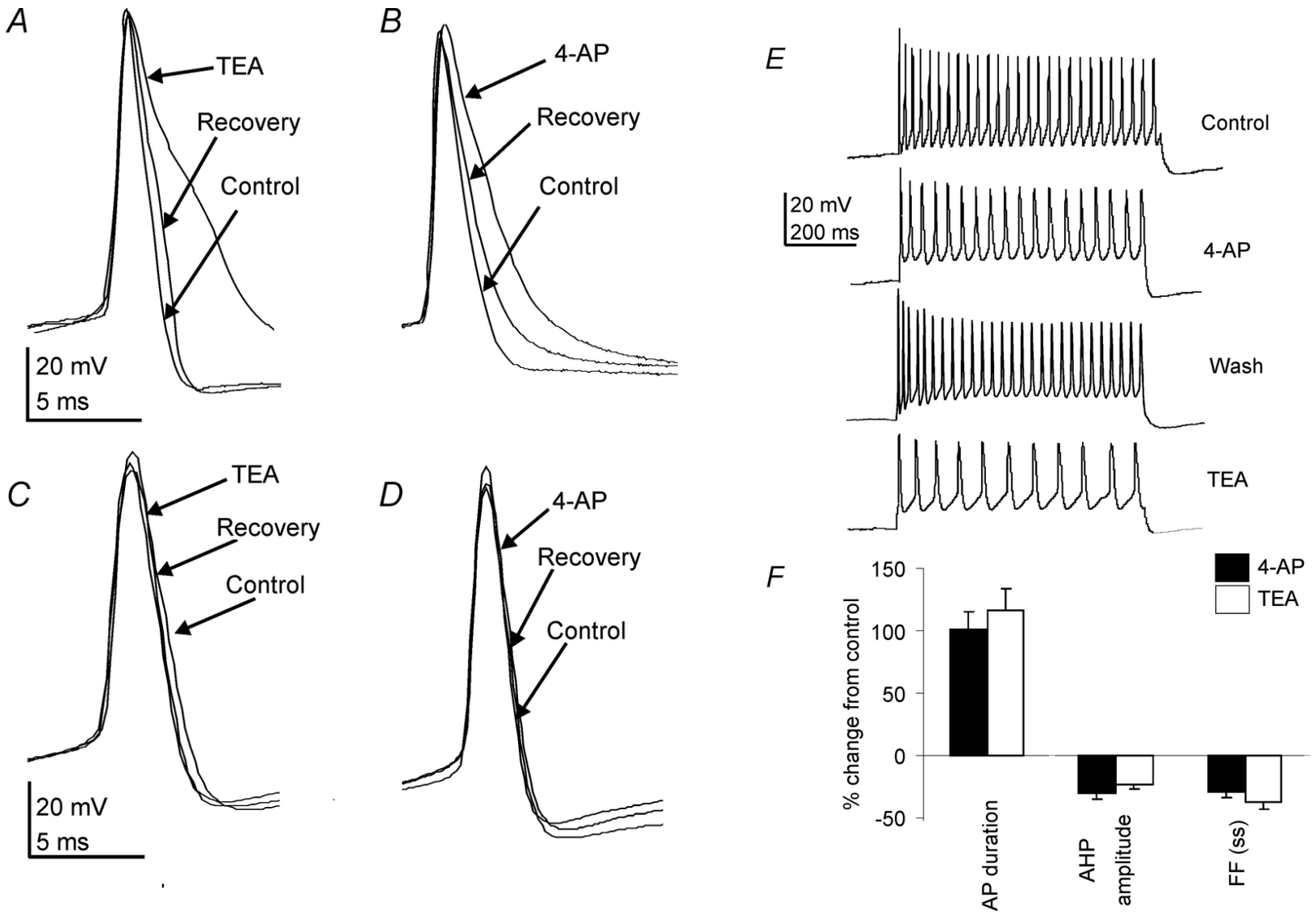




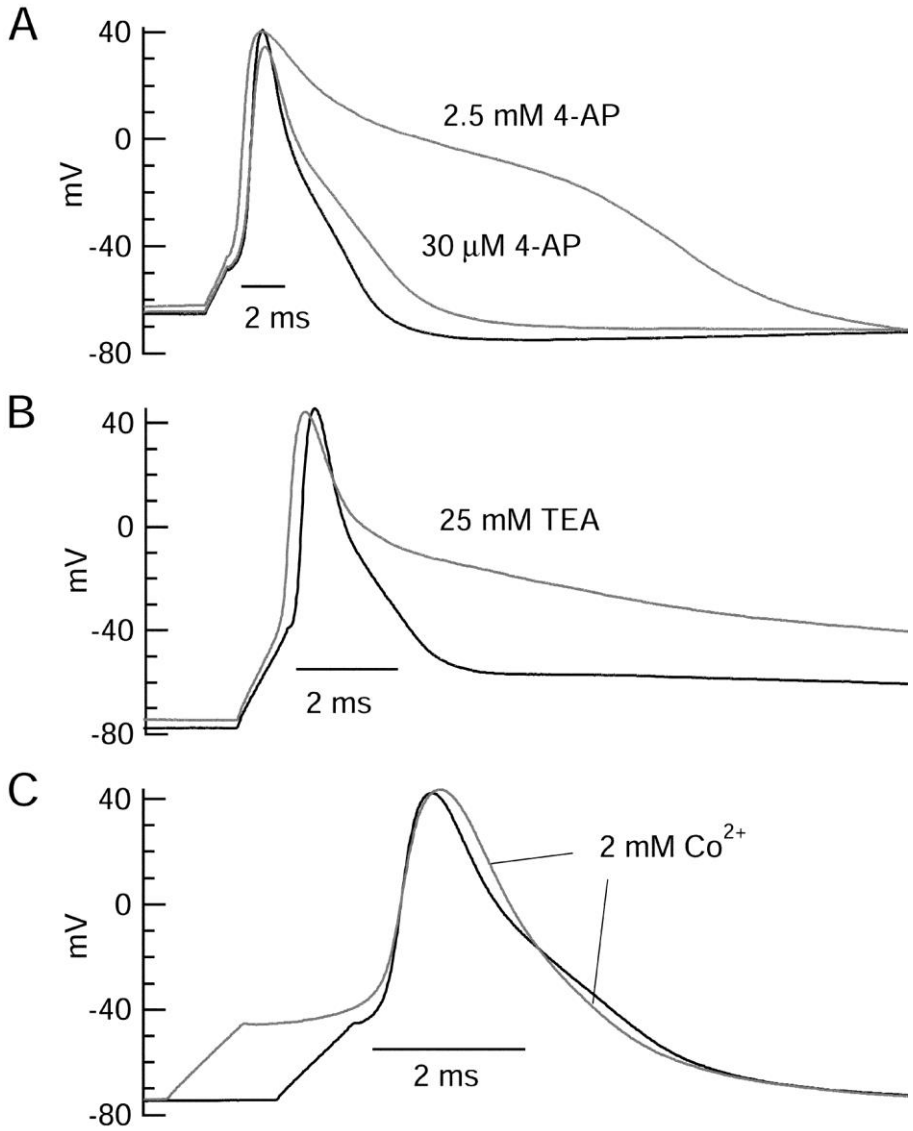
Johnston, J., I.D. Forsythe, and C. Kopp-Scheinpflug, Going native: voltage-gated potassium channels controlling neuronal excitability. J Physiol, 2010. 588(Pt 17): p. 3187-200



Tsantoulas C, McMahon SB. Opening paths to novel analgesics: the role of potassium channels in chronic pain. Trends Neurosci. 2014 Mar;37(3):146-58. doi: 10.1016/j.tins.2013.12.002. Epub 2014 Jan 21. PMID: 24461875; PMCID: PMC3945816.



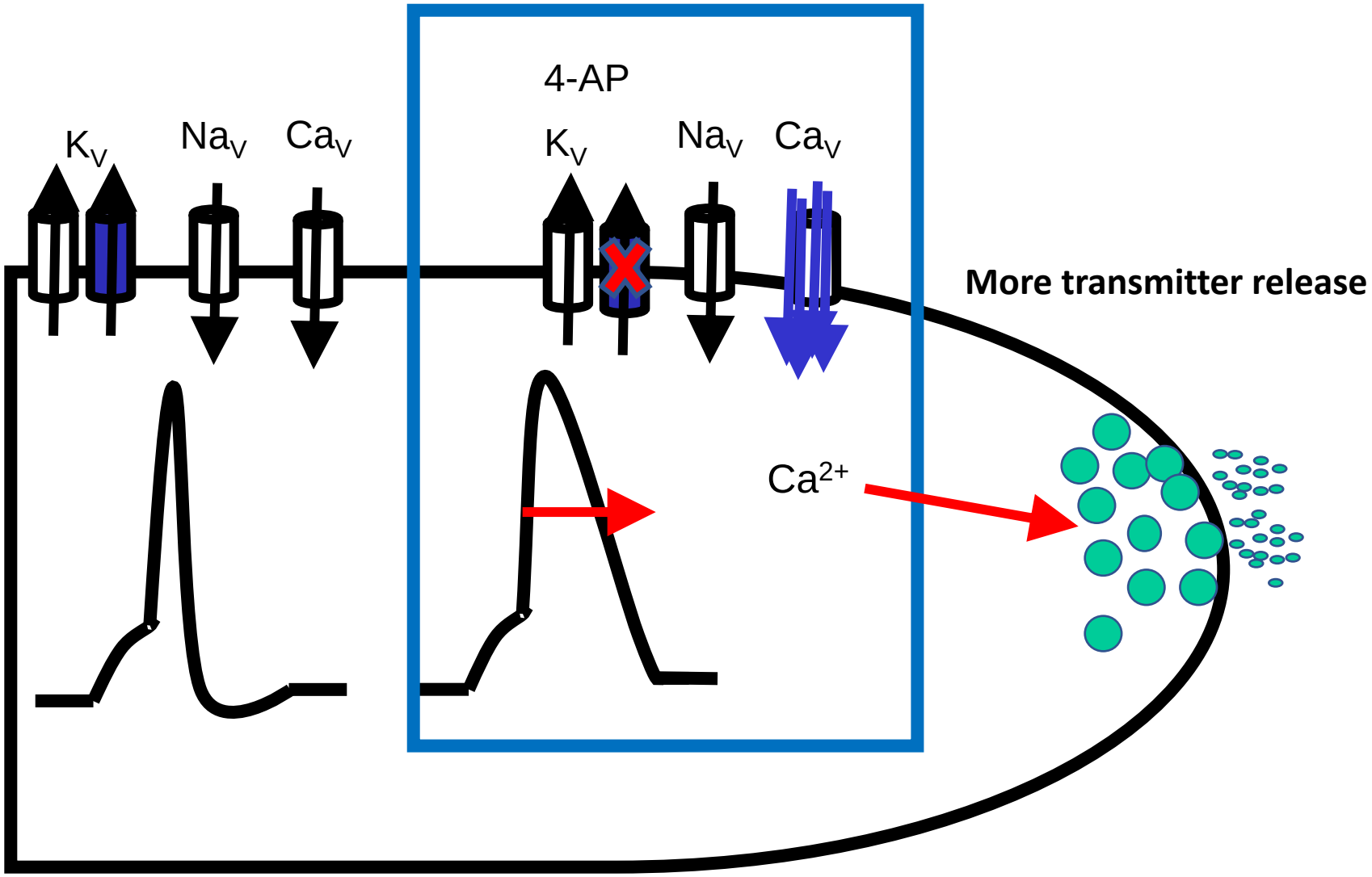
Dallas ML, Atkinson L, Milligan CJ, Morris NP, Lewis DI, Deuchars SA, Deuchars J. Localization and function of the Kv3.1b subunit in the rat medulla oblongata: focus on the nucleus tractus solitarii. J Physiol. 2005 Feb 1;562(Pt 3):655-72. doi: 10.1113/jphysiol.2004.073338. Epub 2004 Nov 4. PMID: 15528247; PMCID: PMC1665536.



The overall voltage-dependent potassium current in the neurons could be split into three major components based on pharmacology and kinetics during step voltage pulses: I_D (fast activating, slowly inactivating, and sensitive to 4-aminopyridine at 30 µm),I_A (fast activating, fast inactivating, and sensitive to 4-aminopyridine at 3 mm), andI_K (slowly activating, noninactivating, and sensitive to external TEA at 3–25 mm). The potassium current during the action potential was composed of approximately equal contributions of I_D andI_A, with a negligible contribution ofI_K.

https://www.jneurosci.org/content/22/23/10106

Mitterdorfer J, Bean BP. Potassium currents during the action potential of hippocampal CA3 neurons. J Neurosci. 2002 Dec 1;22(23):10106-15. doi: 10.1523/JNEUROSCI.22-23-10106.2002. PMID: 12451111; PMCID: PMC6758734.


4-AP
K_V
Na_V
Ca_V
K_V
Na_V
Ca_V
More transmitter release
Ca^{2+}

MS ……..**Multiple sclerosis**

The general idea: **Multiple sclerosis**

Multiple sclerosis (MS) is a potentially disabling disease of the brain and spinal cord (central nervous system).

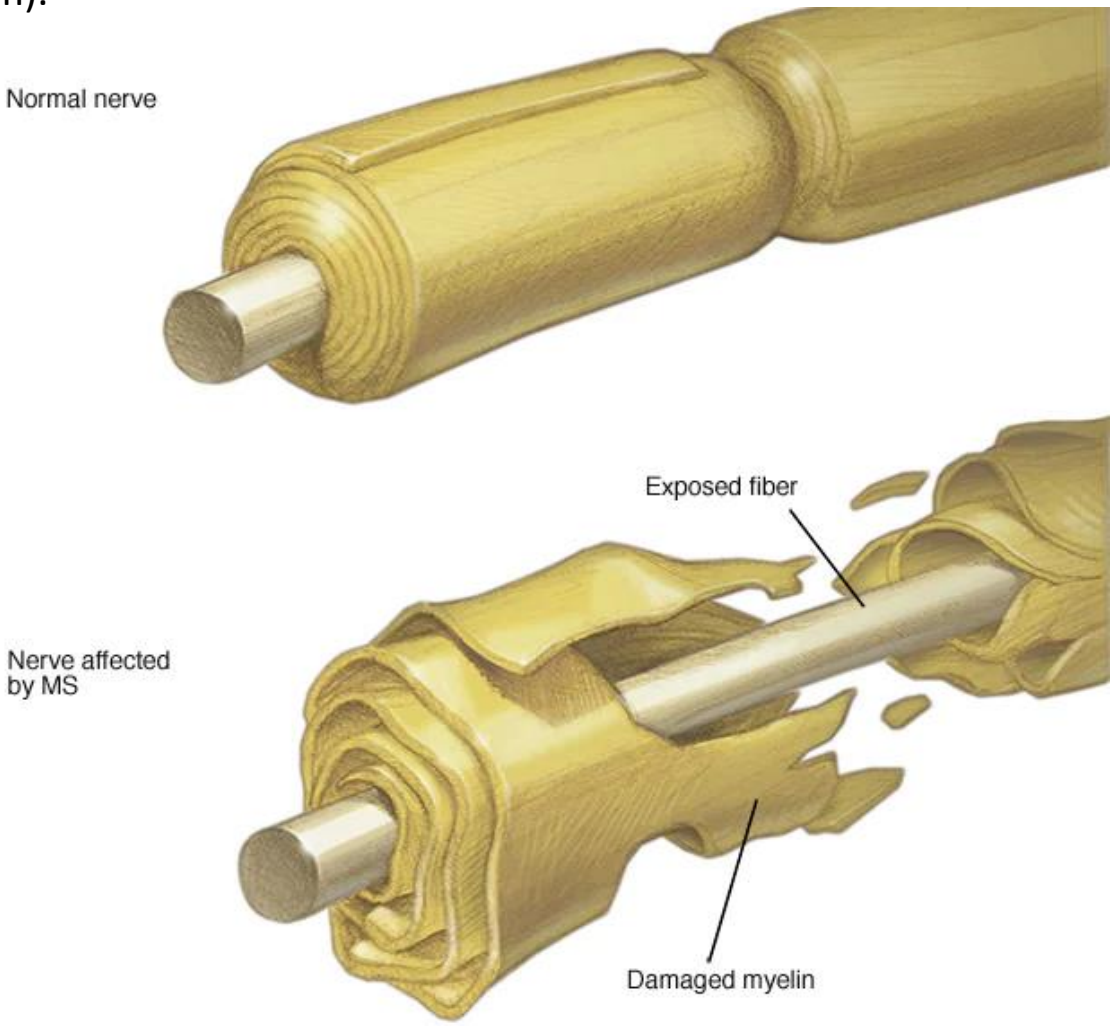
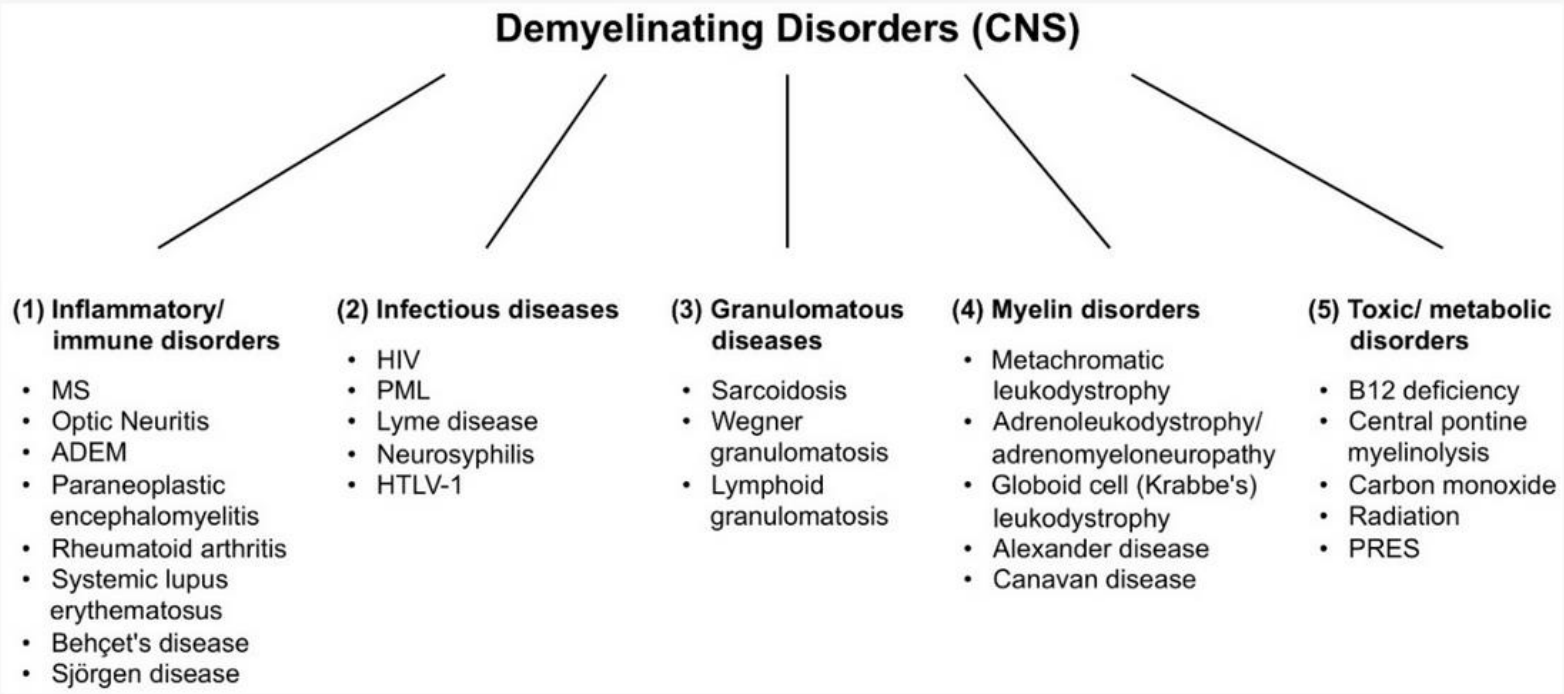
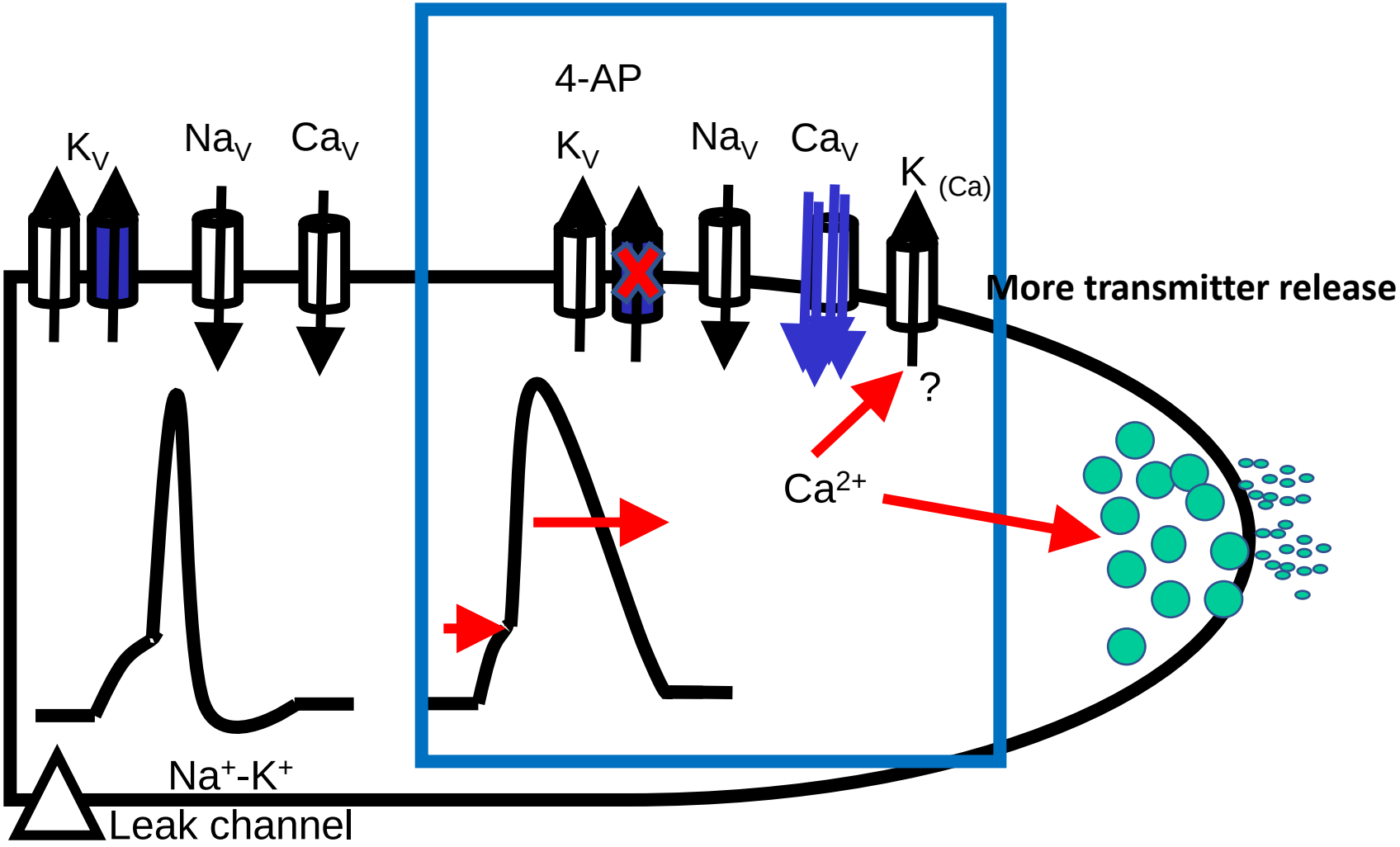


Figure 2. Demyelinating disorders of the central nervous system (CNS). Abbreviations: MS: multiple sclerosis; ADEM: acute disseminated encephalomyelitis; HIV: human immunodeficiency virus; PML: progressive multifocal leukoencephalopathy; HTLV-1: human T-lymphotropic virus 1; PRES: posterior reversible encephalopathy syndrome.



Lassmann, H., van Horssen, J. & Mahad, D. Progressive multiple sclerosis: pathology and pathogenesis. *Nat Rev Neurol* **8,** 647–656 (2012). https://doi.org/10.1038/nrneurol.2012.168



1. Block Kv so stays depolarized longer. This leads to more CaV action and more transmitter release.
2. There is some evidence that the RP is changed ….block some leak channels so excitability of neuron is increased.

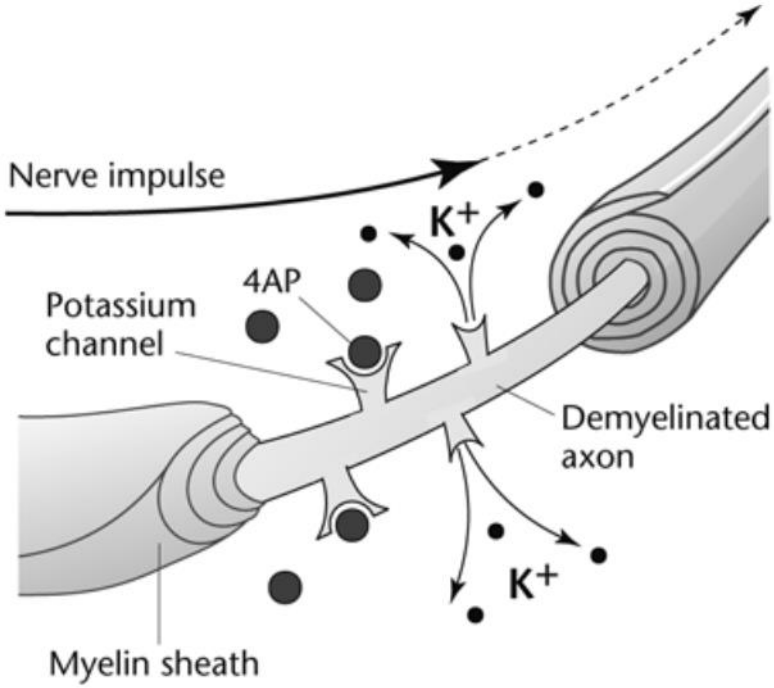


Figure 7. Fampridine-SR (4-AP) blocks open potassium channels and helps to maintain a resting potential.

Anderberg L, Aldskogius H, Holtz A. Spinal cord injury--scientific challenges for the unknown future. Ups J Med Sci. 2007;112(3):259-88. doi: 10.3109/2000-1967-200. PMID: 18484069.

Multiple Sclerosis and Related Disorders (2013) 2, 270–280

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journal homepage: www.elsevier.com/locate/msard

REVIEW

Potential therapeutic mechanism of K^+ channel block for MS

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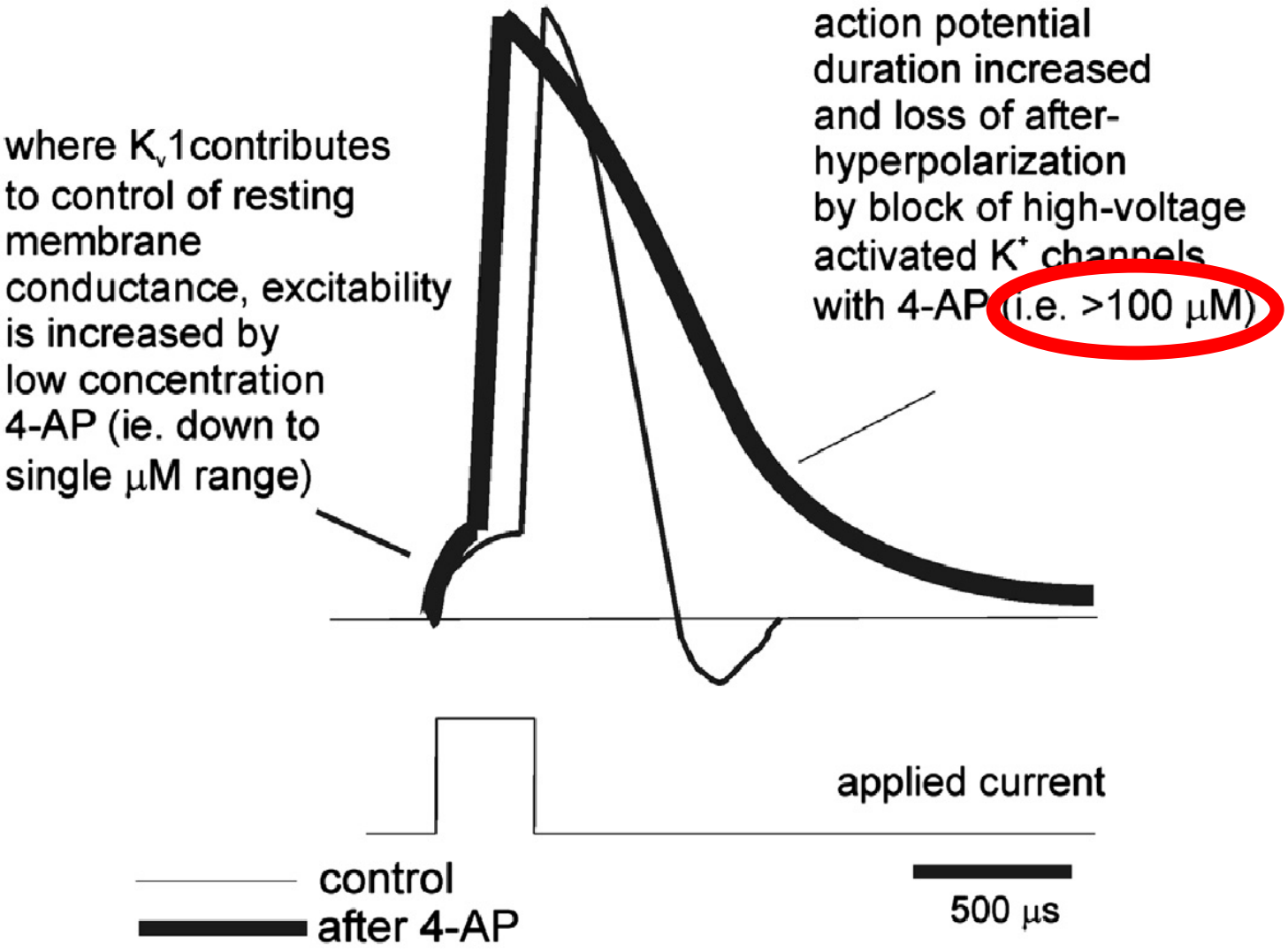
Abstract

While the potential use of K^+ channel blockers in MS has been explored over many years, the approval in the US, and more recently in the UK, of fampyra (fampridine, 4-aminopyridine, 4-AP) as a symptomatic treatment for walking disability, has reawakened interest. Recent years have seen a real improvement in the treatment options for relapsing remitting MS, but the disease remains inadequately treated, with the progressive phase (characterised by irreversible functional loss) lacking any effective therapy. Whether the symptomatic relief afforded by 4-AP translates into neuroprotection, remains poorly investigated, although there is no clear reason why this would be expected. Importantly, future clinical studies may shed light on this question. This review includes an overview of axonal K^+ channel expression and pharmacology, and the logic of the use of K^+ channel blockers derived from observations in experimental studies of demyelination and synaptic transmission. It provides an insight into the probable biophysical actions of 4-AP, and how its action may aid in the symptomatic treatment of MS. The key message of this review is that 4-AP is a blocker of neuronal K^+ channels, and its administration is known to be of value in the symptomatic treatment of some patients. The details of the mechanism underlying the beneficial effects remain somewhat vague, and the molecular target has not been properly defined. The useful mechanism is likely to include an action on synaptic function, but whether it is the presynaptic terminal or the presynaptic axon that is the primary target is unknown. It is argued that because of the apparent inability of 4-AP to increase safety factor in experimental demyelination when clinically relevant concentrations are used, it cannot be the ideal pharmacological agent for treating demyelination by the widening of axonal action potentials. That said, it remains a possibility that the useful therapeutic effect of 4-AP may involve subtle changes in axonal excitability mediated by a selective K^+ channel block, exploiting a naturally occurring redundancy of synaptic function.


where K_v1contributes to control of resting membrane conductance, excitability is increased by low concentration 4-AP (ie. down to single μM range)
action potential duration increased and loss of after-hyperpolarization by block of high-voltage activated K^+ channels with 4-AP (i.e. >100 μM)
applied current
control
after 4-AP
500 μs

We demonstrate using autoradiography that 4-AP has higher binding in non-myelinated and demyelinated *versus* well-myelinated CNS regions, and describe a fluorine-containing derivative, 3-F-4-AP, that has similar pharmacological properties and can be labeled with ^{18}F for PET imaging.

Upon demyelination, axonal potassium (K^+) channels, which normally reside at the juxtaparanodal region beneath the myelin sheath (*e.g.*, $K_v1.1$ and $K_v1.2$), become exposed, disperse throughout the internodes, and increase in expression[23–26]. This aberrant distribution of K^+ channels causes leakage of intracellular K^+ ions and renders neurons unable to fully depolarize and propagate action potentials. The clinically approved drug for MS, 4-aminopyridine (4-AP), binds to and blocks these channels, reducing the aberrant efflux of K^+ ions and restoring conduction of demyelinated axons[27–31].

Brugarolas P, Sánchez-Rodríguez JE, Tsai HM, Basuli F, Cheng SH, Zhang X, Caprariello AV, Lacroix JJ, Freifelder R, Murali D, DeJesus O, Miller RH, Swenson RE, Chen CT, Herscovitch P, Reich DS, Bezanilla F, Popko B. Development of a PET radioligand for potassium channels to image CNS demyelination. Sci Rep. 2018 Jan 12;8(1):607. doi: 10.1038/s41598-017-18747-3. PMID: 29330383; PMCID: PMC5766510.

MS

Address from what you can gather from the latest literature how 4-AP is mechanistically working to improve the symptoms of MS.

4-AP may involve subtle changes in axonal excitability mediated by a selective K+ channel block, exploiting a naturally occurring redundancy of synaptic function.

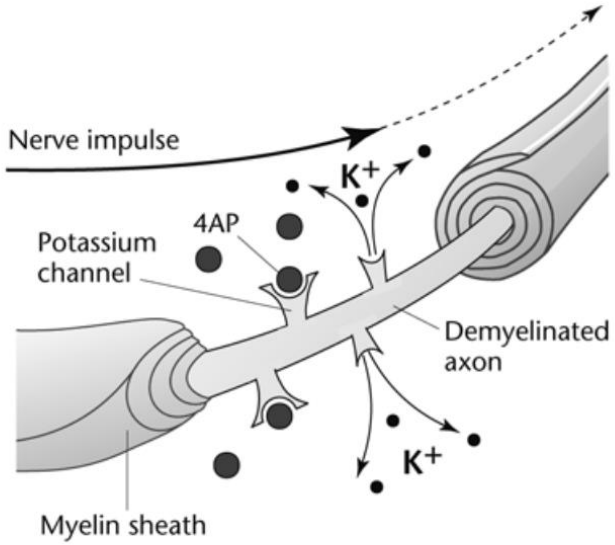


Figure 7. Fampridine-SR (4-AP) blocks open potassium channels and helps to maintain a resting potential.

Anderberg L, Aldskogius H, Holtz A. Spinal cord injury--scientific challenges for the unknown future. Ups J Med Sci. 2007;112(3):259-88. doi: 10.3109/2000-1967-200. PMID: 18484069.

Multiple sclerosis (MS) is an immune-mediated disorder in which inflammatory cells from the peripheral blood (PB) migrate to the CNS and cause demyelination and subsequent axonal degeneration (1–4). Several lines of evidence support an early role of autoreactive CD4 CNS myelin-specific T cells (1, 2). In addition, there is epitope spreading such that T cell responses are directed against multiple different myelin antigens.

Activated T cells require high levels of intracellular calcium, which enters cells through calcium-release-activated calcium channels (CRAC) after intracellular stores are depleted of calcium. Membrane hyperpolarization brought about by the opening of the two lymphocyte potassium (K) channels, the voltage-gated K channel (Kv1.3), and the calcium-dependent K channel (KCa3.1, also known as IKCa1), promotes calcium entry through CRAC channels

Rus H, Pardo CA, Hu L, Darrah E, Cudrici C, Niculescu T, Niculescu F, Mullen KM, Allie R, Guo L, Wulff H, Beeton C, Judge SI, Kerr DA, Knaus HG, Chandy KG, Calabresi PA. The voltage-gated potassium channel Kv1.3 is highly expressed on inflammatory infiltrates in multiple sclerosis brain. Proc Natl Acad Sci U S A. 2005 Aug 2;102(31):11094-9. doi: 10.1073/pnas.0501770102. Epub 2005 Jul 25. PMID: 16043714; PMCID: PMC1182417.

In summary, these pathological findings, in conjunction with our previous *in vitro* report, suggest that Kv1.3 is a functional marker of activated TEM cells, and that these are the predominant lymphocyte cell type in MS inflammatory brain infiltrates. The therapeutic appeal of Kv1.3 is that it does not require knowledge of antigen specificity, which may be critical in diseases where epitope spreading occurs. Further, the presence of elevated Kv1.3 levels on both CD4 and CD8 activated TEM cells suggests that Kv1.3 antagonists could target both CD4 and CD8 TEM functions such as the release of the destructive protease granzyme B, which has been implicated in mediating direct cytolytic damage in progressive MS (44, 45). The availability of Kv1.3-specific antagonists with demonstrated efficacy *in vitro* and in Lewis rat adoptive EAE makes Kv1.3 an attractive therapeutic target in MS, and possibly other autoimmune diseases (10, 11, 14).

Rus H, Pardo CA, Hu L, Darrah E, Cudrici C, Niculescu T, Niculescu F, Mullen KM, Allie R, Guo L, Wulff H, Beeton C, Judge SI, Kerr DA, Knaus HG, Chandy KG, Calabresi PA. The voltage-gated potassium channel Kv1.3 is highly expressed on inflammatory infiltrates in multiple sclerosis brain. Proc Natl Acad Sci U S A. 2005 Aug 2;102(31):11094-9. doi: 10.1073/pnas.0501770102. Epub 2005 Jul 25. PMID: 16043714; PMCID: PMC1182417.

Kv1.3 and Kv1.5 are inhibited by 4-aminopyridine (4-AP) and tetraethylammonium (TEA), which are general K^+ channel blockers (Grissmer et al., 1994).

Grissmer S., Nguyen A. N., Aiyar J., Hanson D. C., Mather R. J., Gutman G. A., et al. (1994). Pharmacological characterization of five cloned voltage-gated K+ channels, types Kv1.1, 1.2, 1.3, 1.5, and 3.1, stably expressed in mammalian cell lines. Mol. Pharmacol. 45, 1227–1234

Comes, N., Bielanska, J., Vallejo-Gracia, A., Serrano-Albarrás, A., Marruecos, L., Gómez, D., Soler, C., Condom, E., Ramón Y Cajal, S., Hernández-Losa, J., Ferreres, J. C., & Felipe, A. (2013). The voltage-dependent K(+) channels Kv1.3 and Kv1.5 in human cancer. *Frontiers in physiology*, *4*, 283. https://doi.org/10.3389/fphys.2013.00283

MS

From the readings and your knowledge, address why you think only a subset of people with MS benefit from treatments of 4-AP.

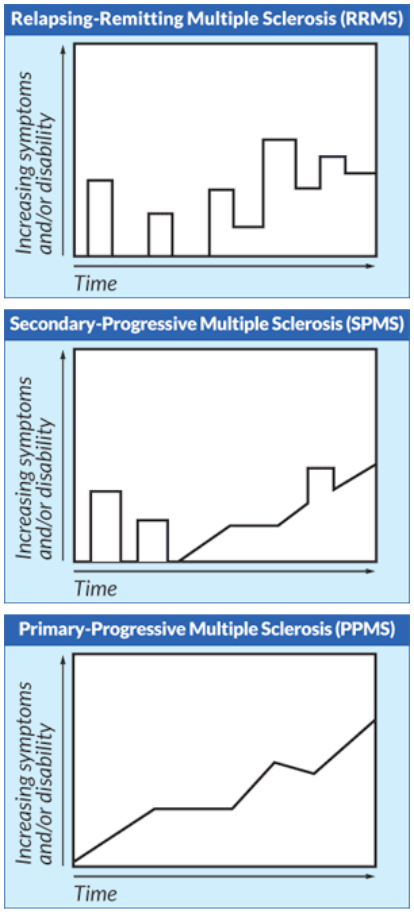
CLASS DISCUSSION

MS

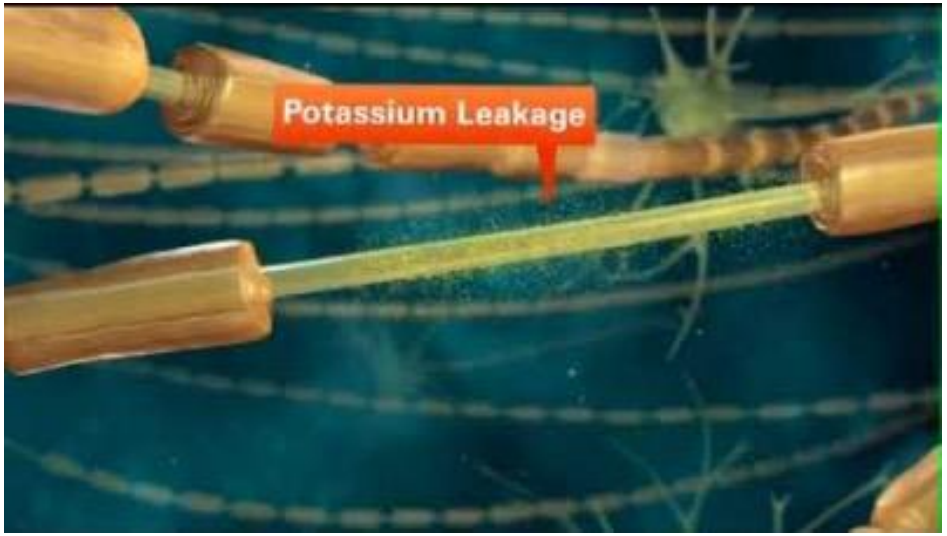
What do you see as the next research steps required to address how 4-AP maybe working to improve MS.

CLASS DISCUSSION

Therapies



https://ampyra.com/real-patient-videos



Therapies

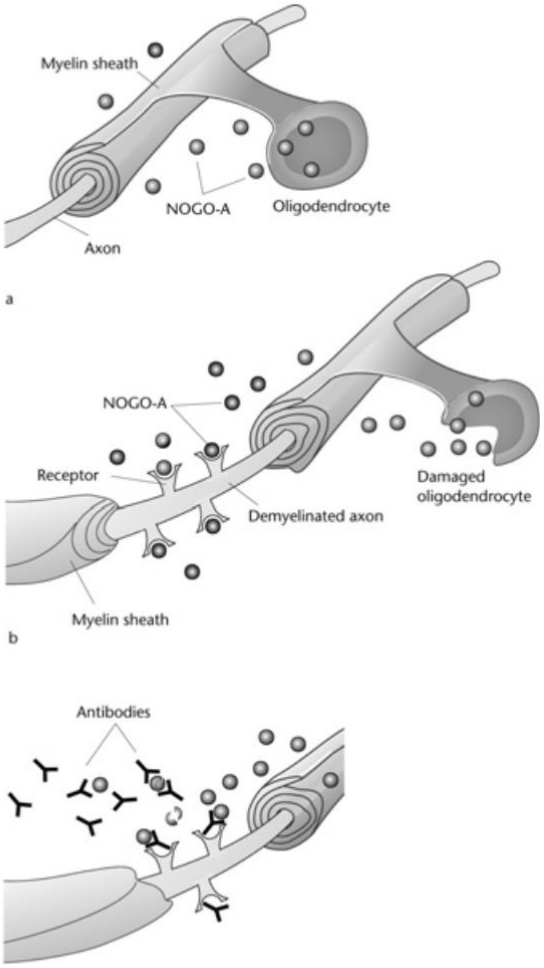


Figure 4. Blocking the growth inhibitory influence of NOGO-A by administration of NOGO-A antibodies.

a) NOGO-A is produced and released by oligodendrocytes.
b) Binding of NOGO-A to specific receptors on injured neurons inhibits axon elongation.
c) NOGO-A antibodies bind NOGO-A as well as its receptor, thereby allowing the injured axon to grow.

Anderberg L, Aldskogius H, Holtz A. Spinal cord injury--scientific challenges for the unknown future. Ups J Med Sci. 2007;112(3):259-88. doi: 10.3109/2000-1967-200. PMID: 18484069.