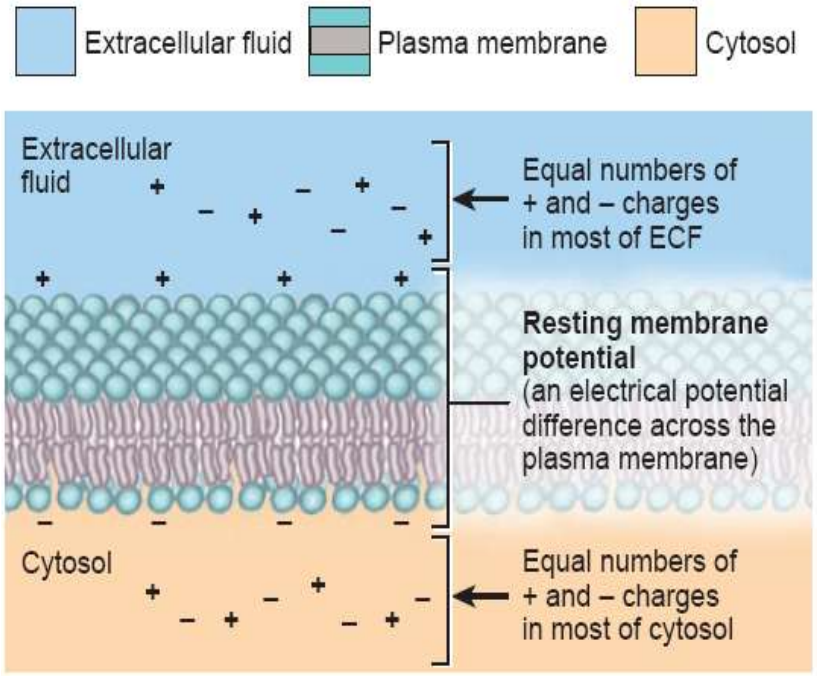
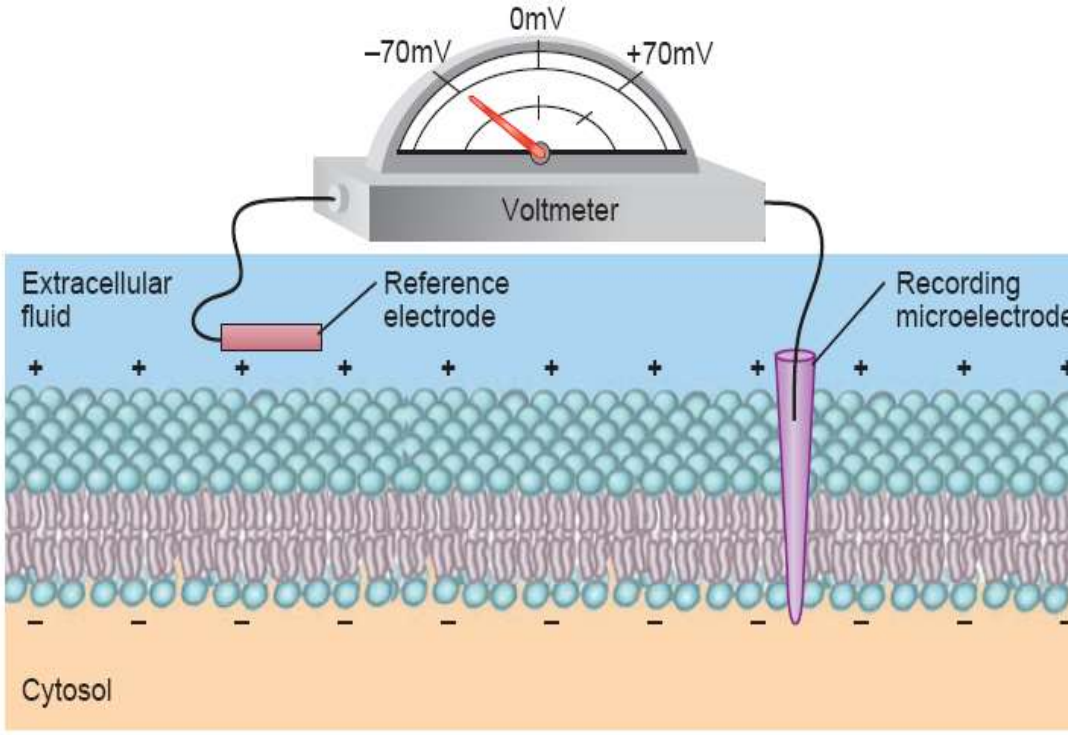
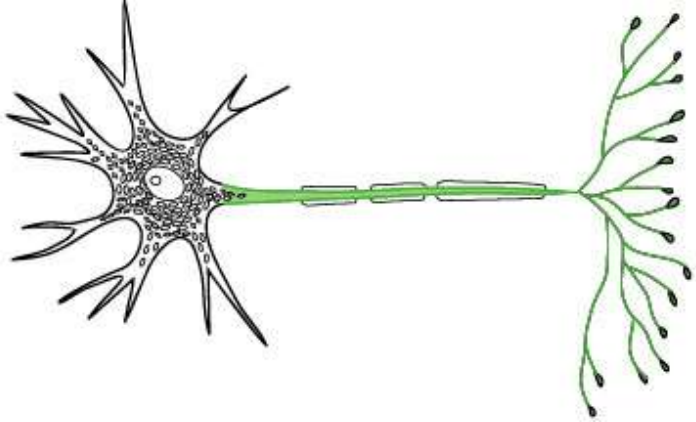
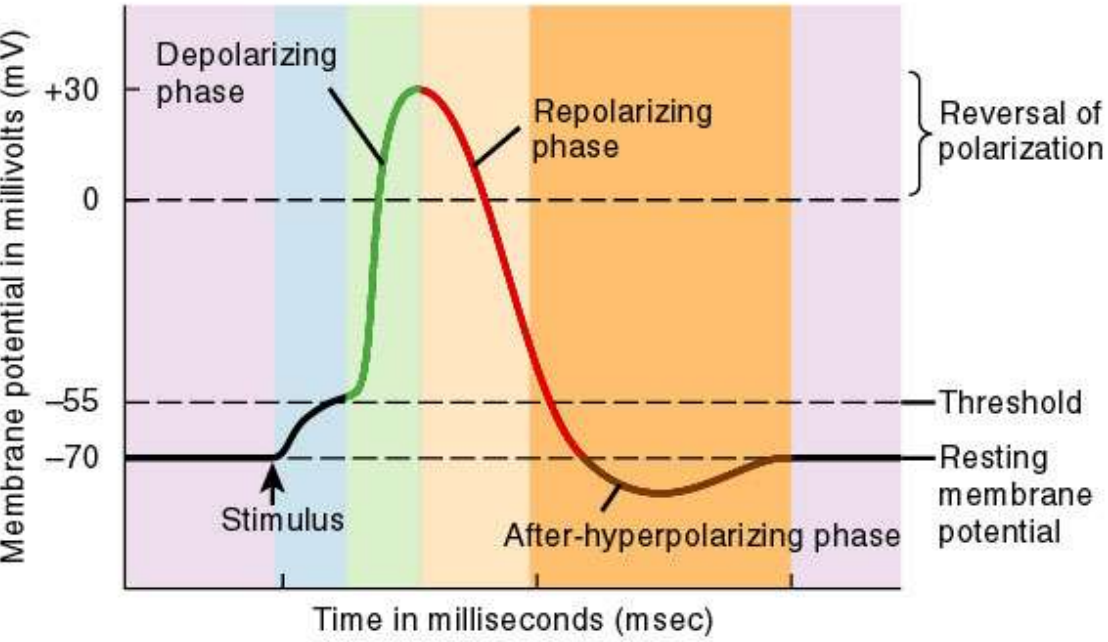

Extracellular fluid
Plasma membrane
Cytosol
Extracellular fluid
Equal numbers of + and – charges in most of ECF
Resting membrane potential
(an electrical potential difference across the plasma membrane)
Cytosol
Equal numbers of + and – charges in most of cytosol


0mV
–70mV
+70mV
Voltmeter
Extracellular fluid
Reference electrode
Recording microelectrode
Cytosol





Key:

- Resting membrane potential: Voltage-gated Na^+ channels are in the resting state and voltage-gated K^+ channels are closed
- Stimulus causes depolarization to threshold
- Voltage-gated Na^+ channel activation gates are open
- Voltage-gated K^+ channels are open; Na^+ channels are inactivating

  } Absolute refractory period

- Voltage-gated K^+ channels are still open; Na^+ channels are in the resting state

  } Relative refractory period

12.11

Resting Membrane Potential & Goldman Equation

$$V_m = \frac{RT}{F} \log \frac{P_K[K^+]_o + P_{Na}[Na^+]_o + P_{cl}[Cl^-]_o}{P_K[K^+]_i + P_{Na}[Na^+]_i + P_{cl}[Cl^-]_i}$$

- P = permeability
- at rest: P_K: P_{Na}: P_{Cl} = 1.0 : 0.04 : 0.45 –
- Net potential movement for all ions
- known V_m:Can predict direction of movement of any ion ~

Effect of K Ions on the RMP

Effect of K Ions on the RMP

- hyperkalemia :
- weakness, ascending paralysis,
- If untreated cardiac arrhythmias
- Hypokalemia : serum K+ <3.5 mEq/L

Myopathies (**Myotonia**)

weakness, fatigue, paralysis

Effect of K Ions on the RMP

- hyperkalemia : serum K+ >5 mEq/L, moderate (6 to 7 mEq/L) and severe (>7 mEq/L)

- Hypokalemia :

Weakness , fatigue, motor paralysis

Myopathies (**Myotonia**)

Effect of Na Ions on the RMP

Effect of Na Ions on the RMP

- **Hyponatremia**

Effect of Na Ions on the RMP

- **Hyponatremia**
- lethergy, confusion, weakness and muscle cramps, nausea and vomiting >>>> coma >>>>seizures
- Tt
- only 1 mlmol/L/hour
- Osmotic demyelination syndrome (central pontine myelinolysis)

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Effect of Na Ions on the RMP

Effect of Na Ions on the RMP

- **Hypernatremia**

Effect of Na Ions on the RMP

- **Hypernatremia**
- nausea, and vomiting, altered mental status, confusion, neuromuscular excitability and hyperreflexia, irritability, seizures, and even coma or death.
- Tt
- 0.45% sodium chloride
- brain edema or hemorrhage, potentially seizures, permanent brain damage, or death

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- nausea, and vomiting, altered mental status, confusion, neuromuscular excitability and hyperreflexia, irritability, seizures, and even coma or death.
- Tt
- 0.45% sodium chloride
- brain edema or hemorrhage, potentially seizures, permanent brain damage, or death

Effect of Ca Ions on the RMP

Effect of Ca Ions on the RMP

- **Hypercalcemia**

Effect of Ca Ions on the RMP

- **Hypercalcemia**

Headache, and lethargy. anxiety, depression, and cognitive dysfunction, insomnia, coma

Effect of Ca Ions on the RMP

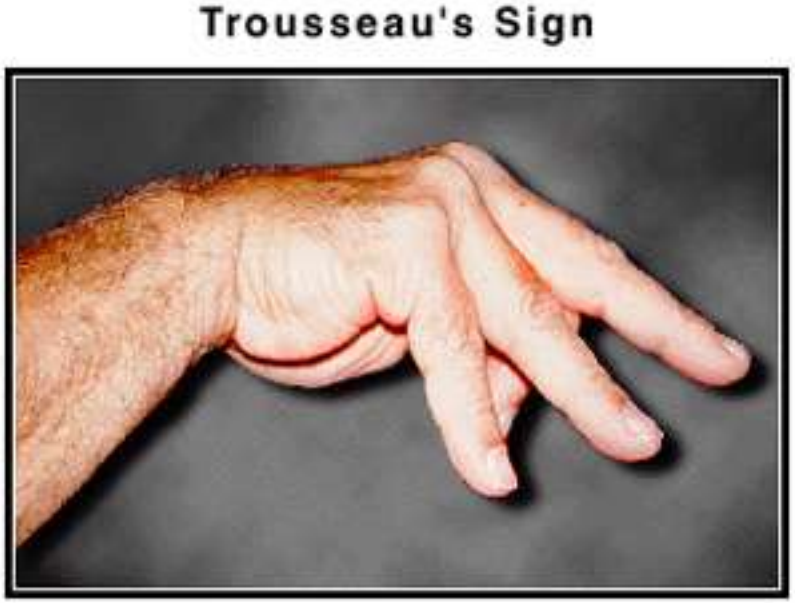
- **Hypocalcemia**

Effect of Ca Ions on the RMP

- **Hypocalcemia**

- The hallmark is neuromuscular irritability and tetany

(Trousseau's sign & Chvostek's sign)



- Irritability , hyperreflexia, Seizures, psychosis and hallucination

Effect of Ca Ions on the RMP

- **Hypocalcemia**

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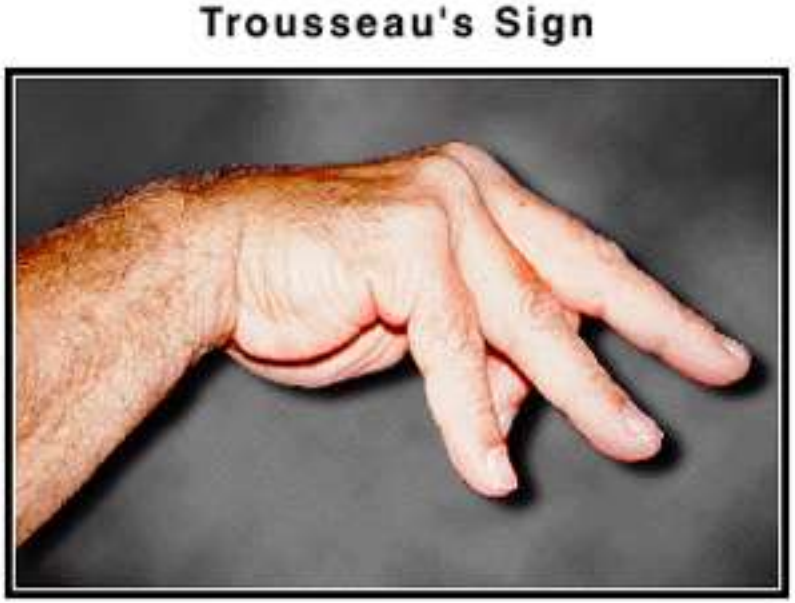
(Trousseau's sign & Chvostek's sign)



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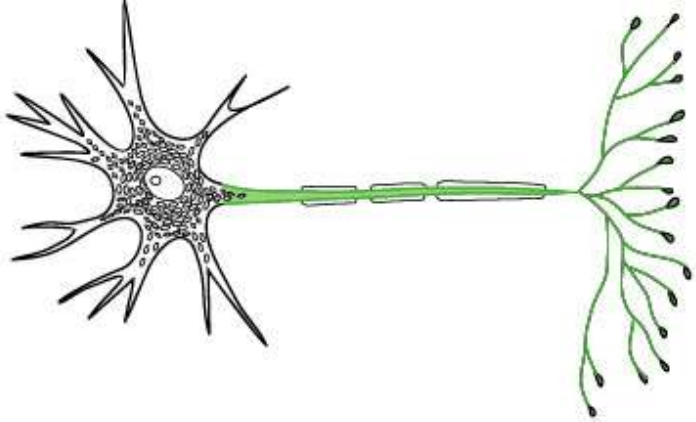

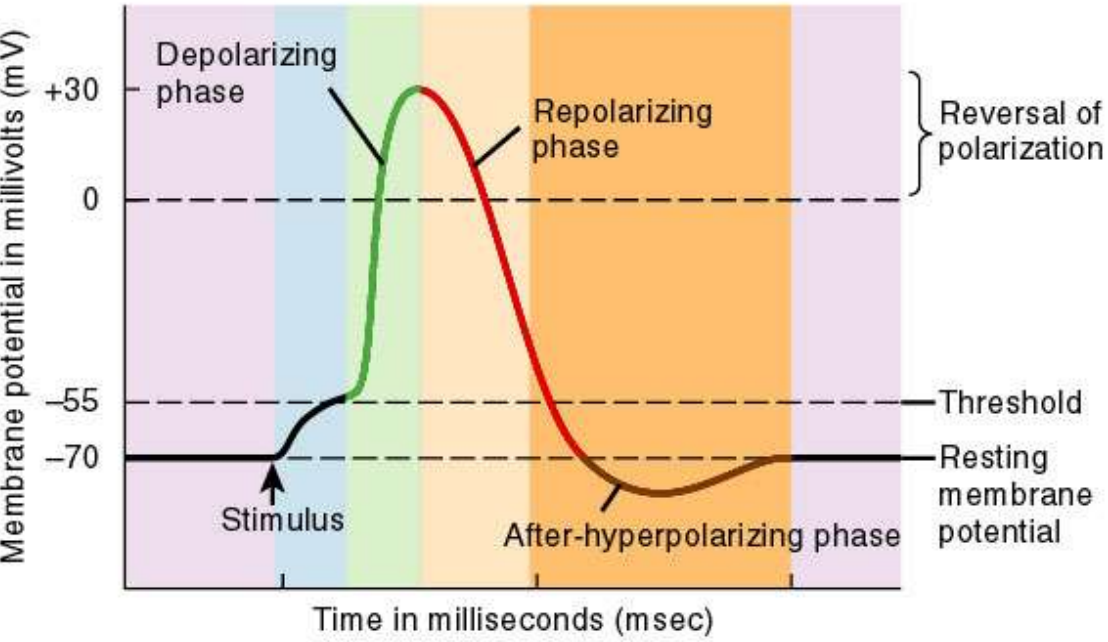

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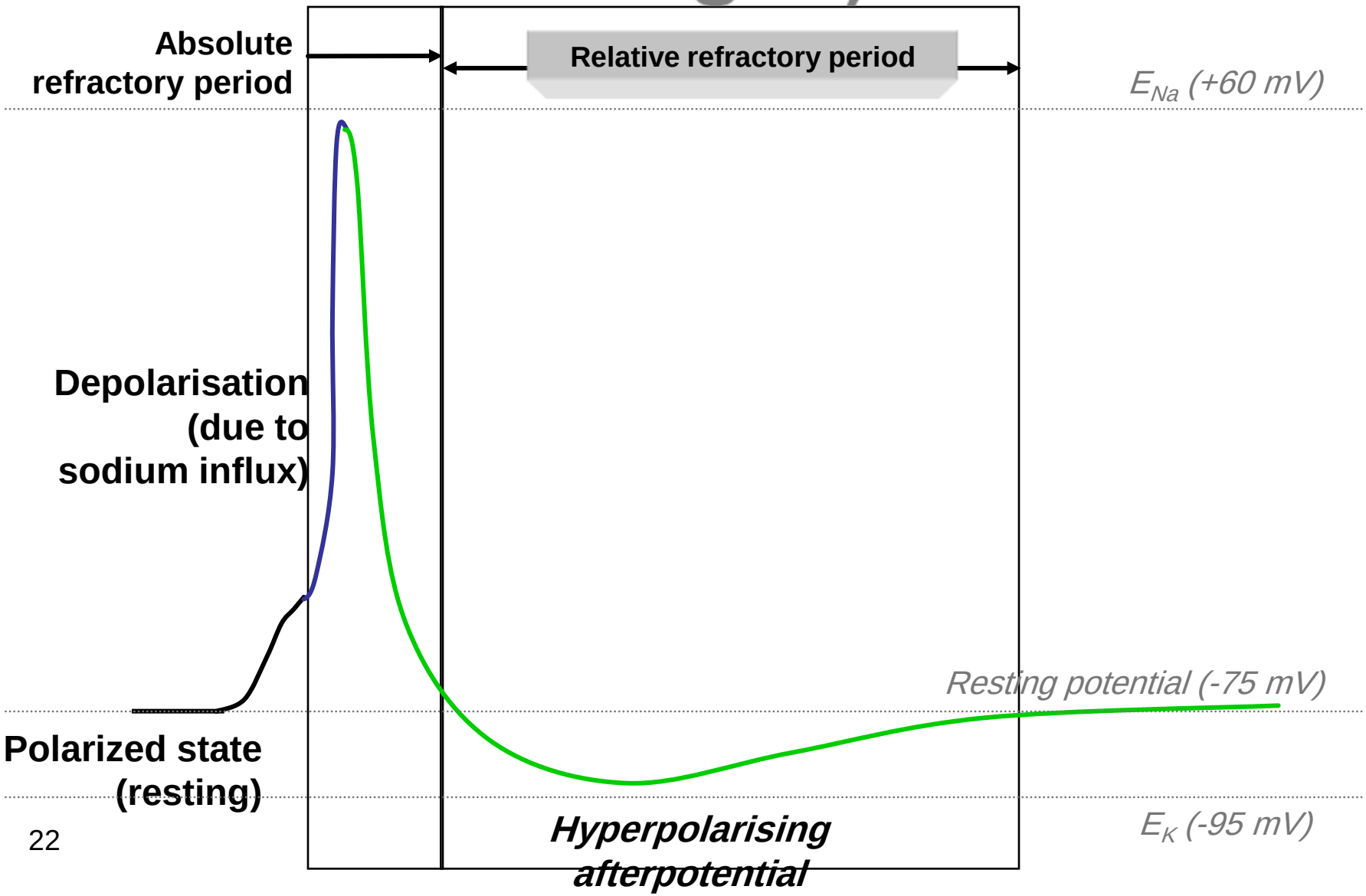
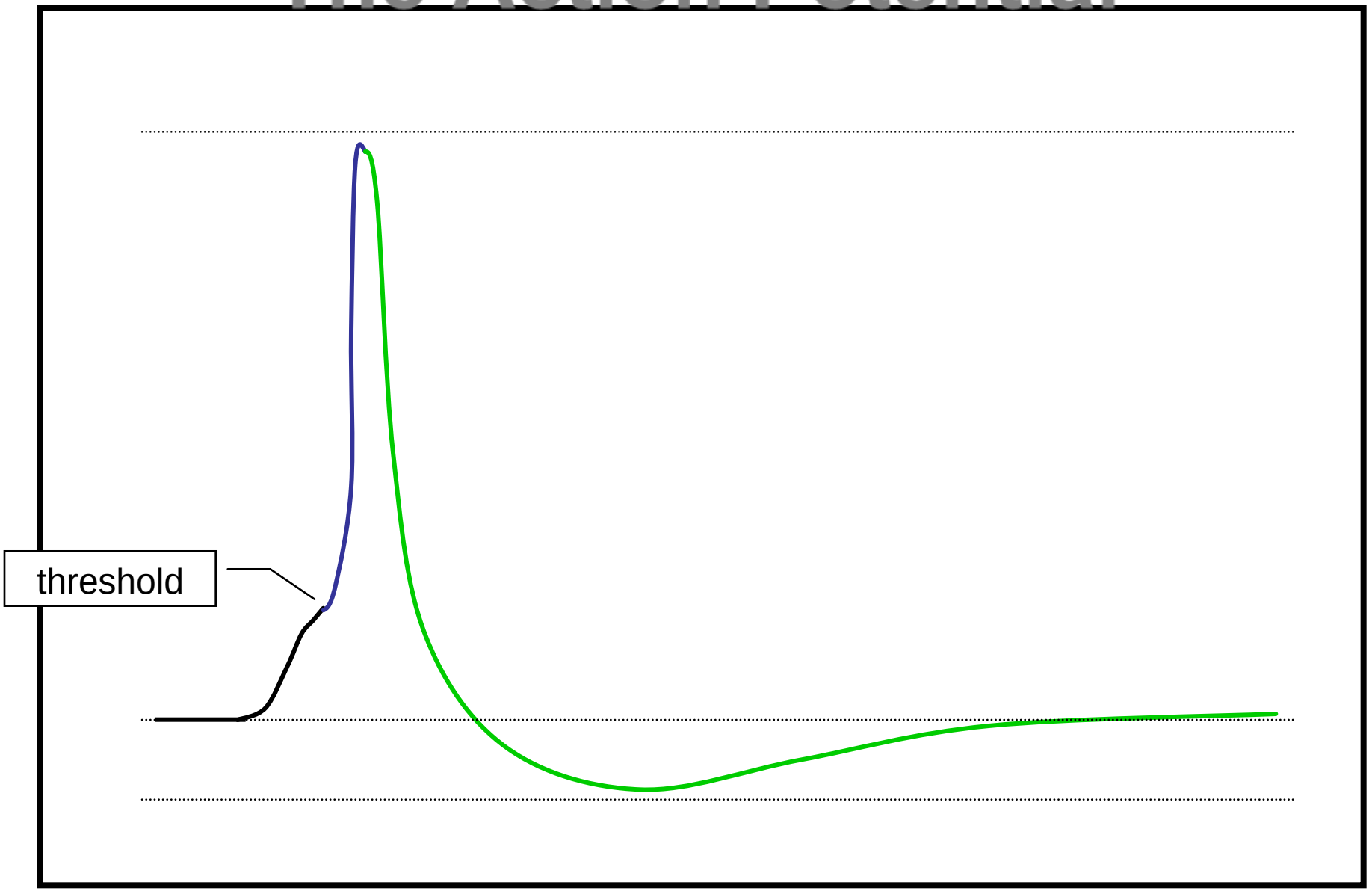
  } Relative refractory period

12.11

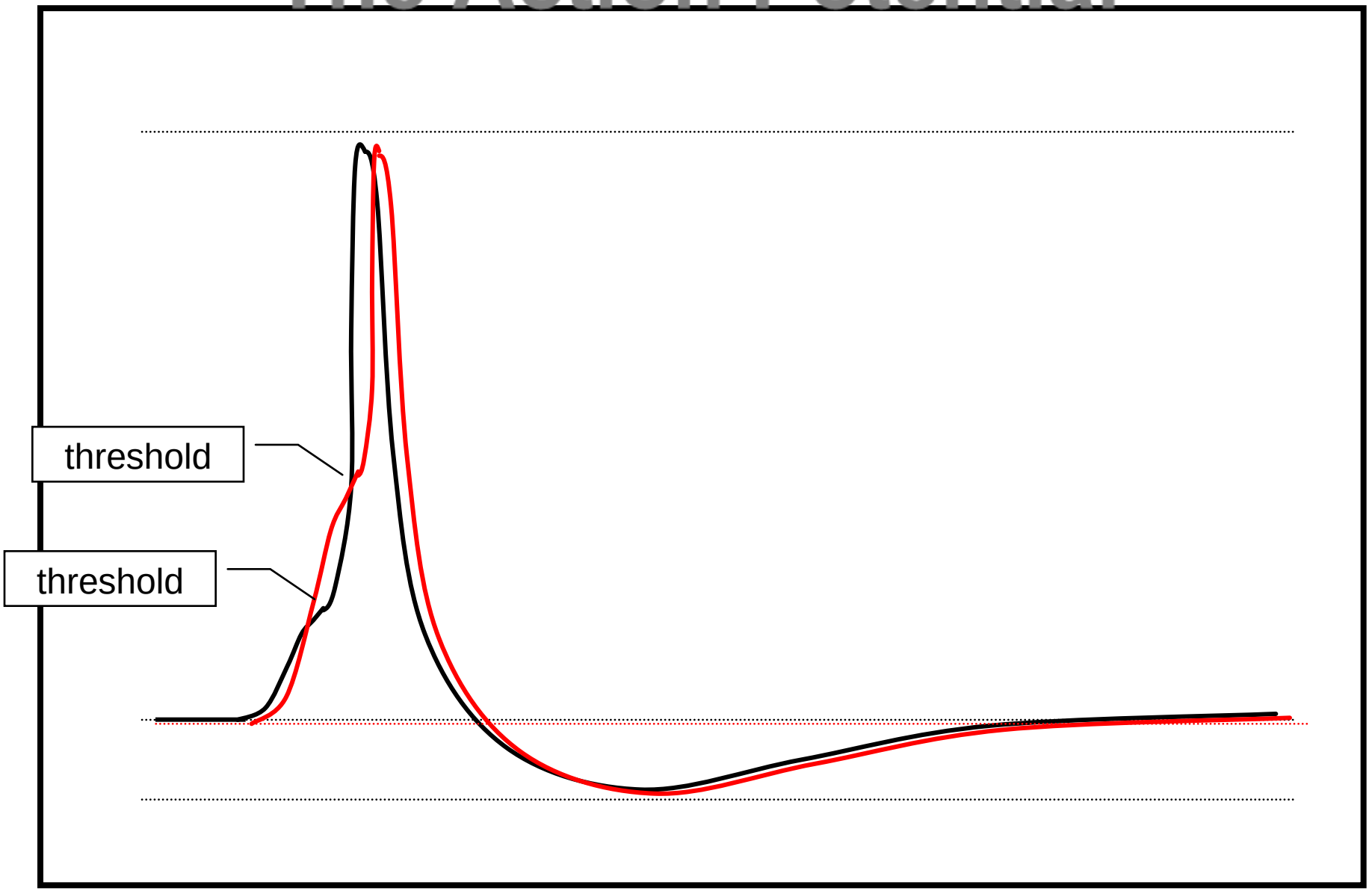
The Action Potential (excitability changes)



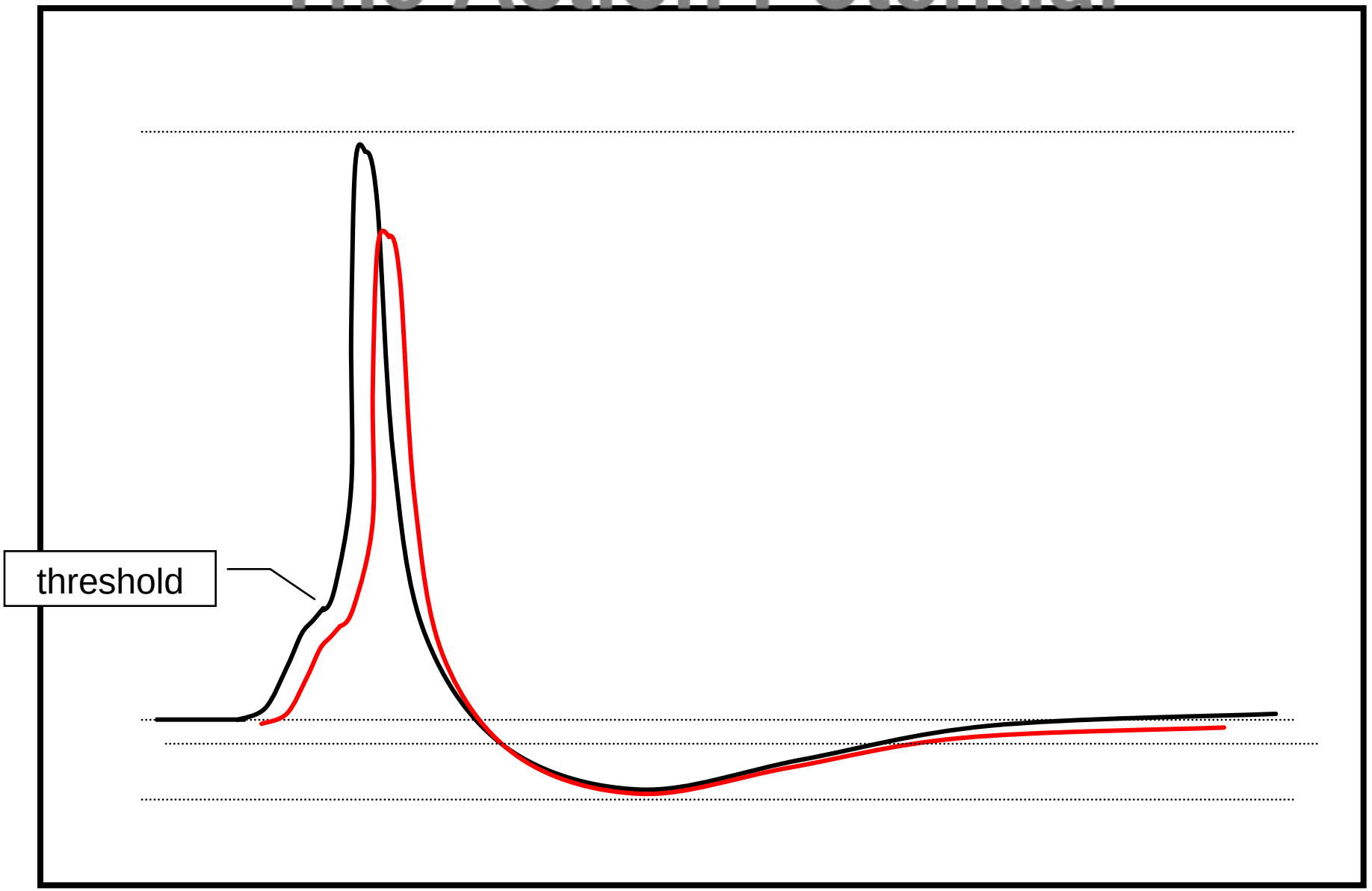
The Action Potential

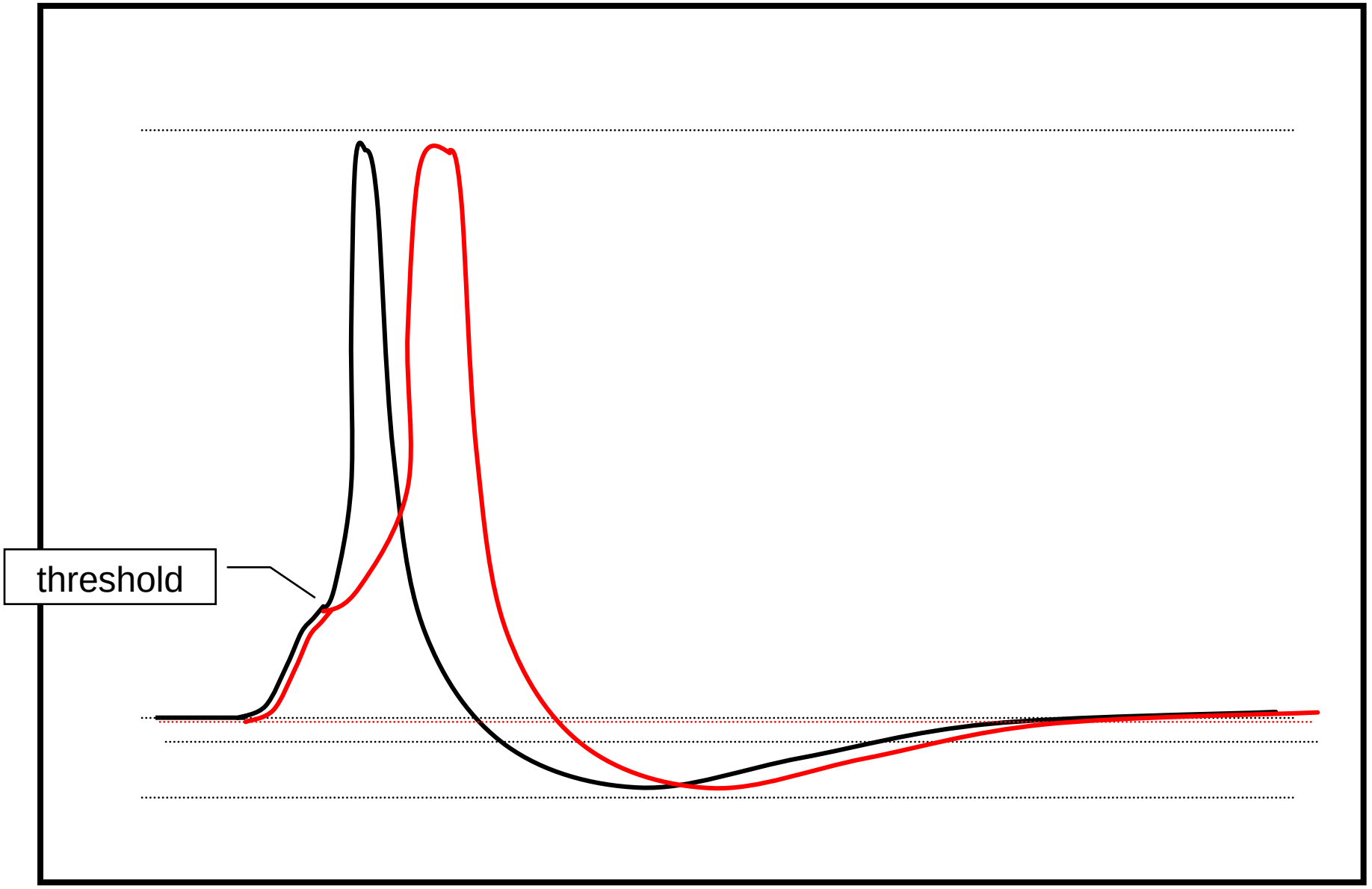


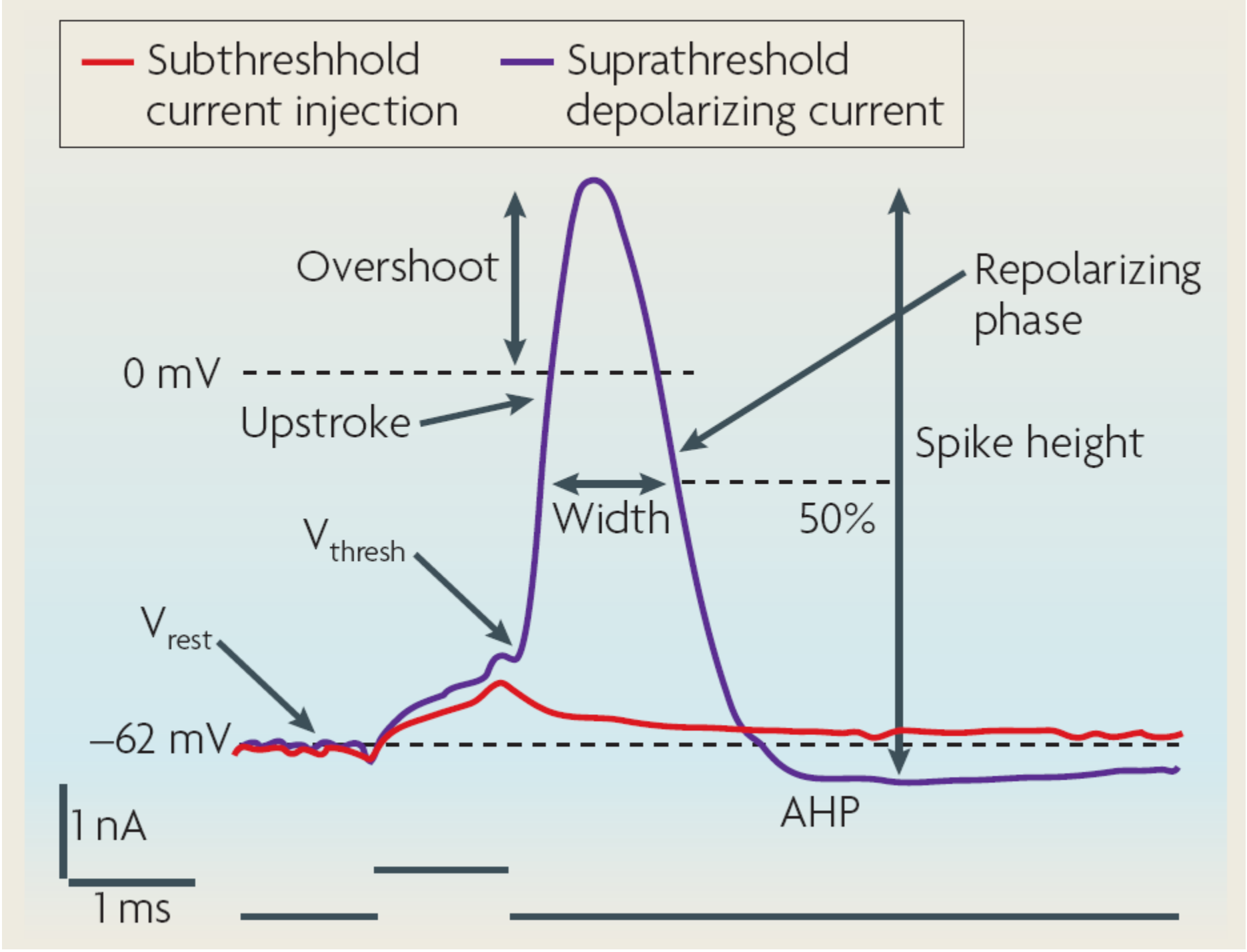
The Action Potential

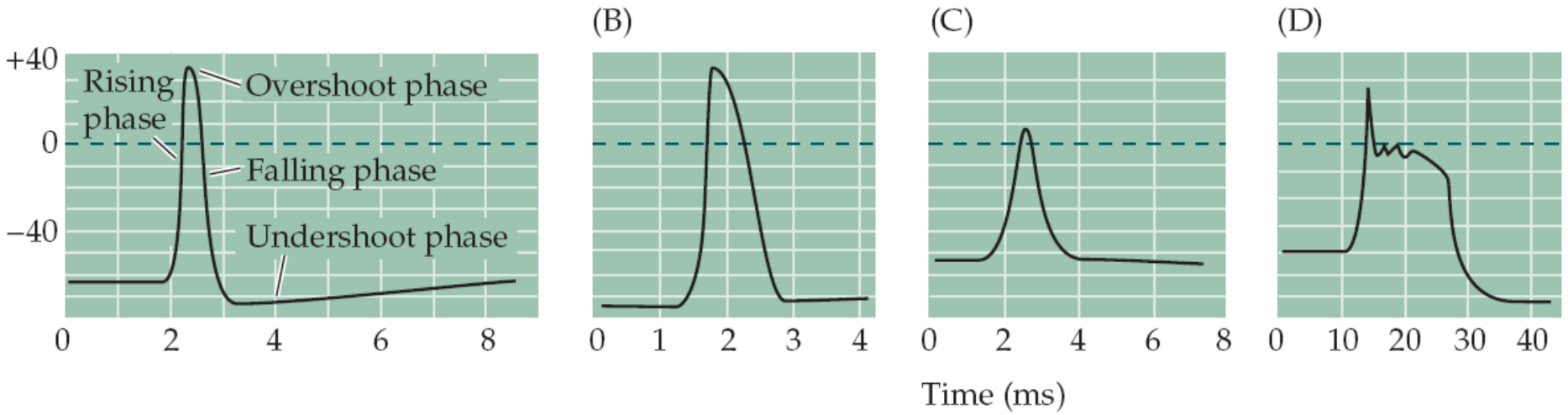


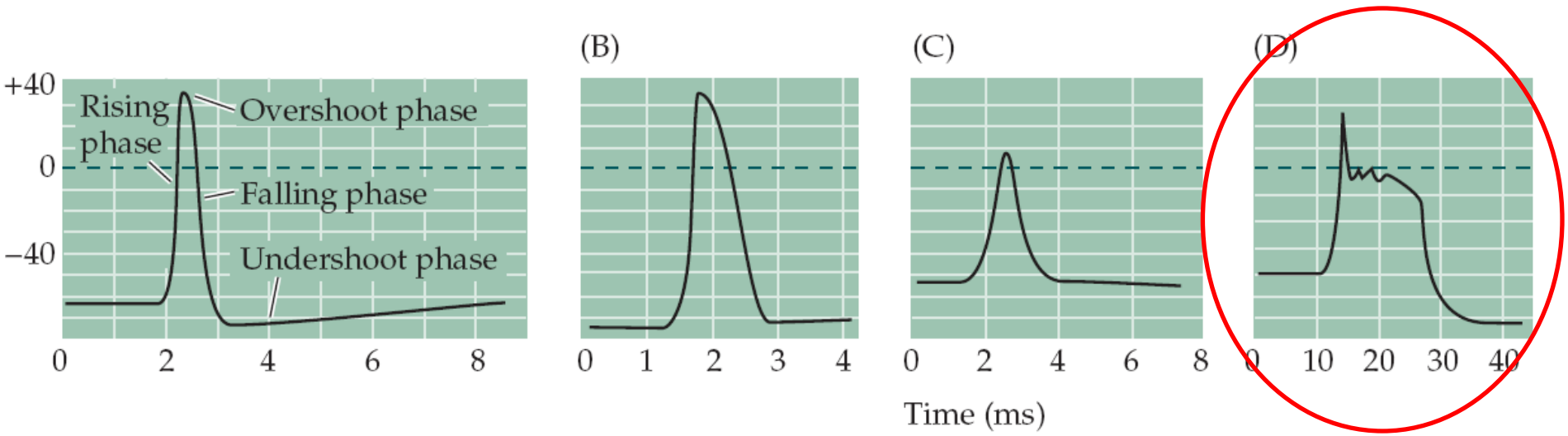
The Action Potential

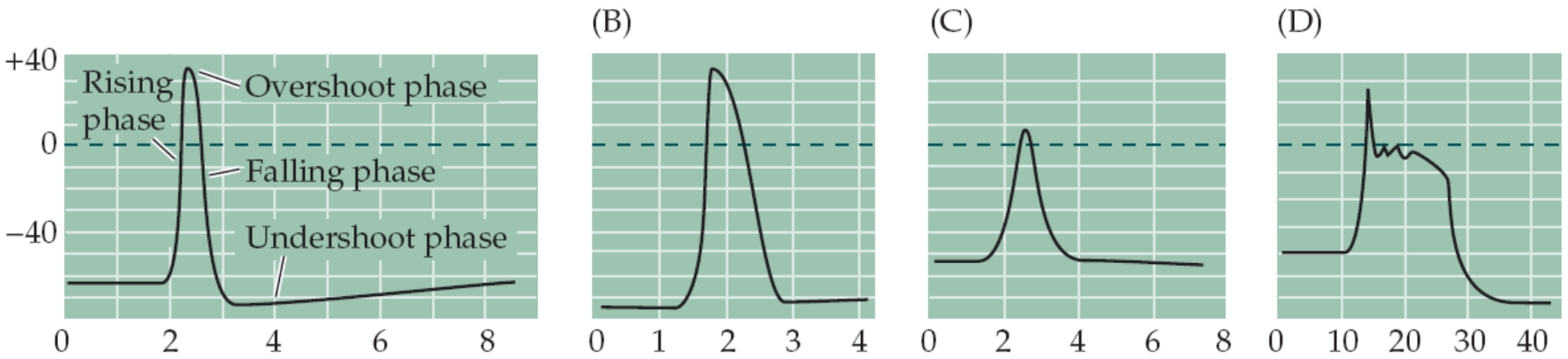



threshold


Subthreshhold current injection
Suprathreshold depolarizing current
Overshoot
Repolarizing phase
0 mV
Upstroke
Spike height
Width
50%
V_{thresh}
V_{rest}
–62 mV
AHP
1 nA
1 ms

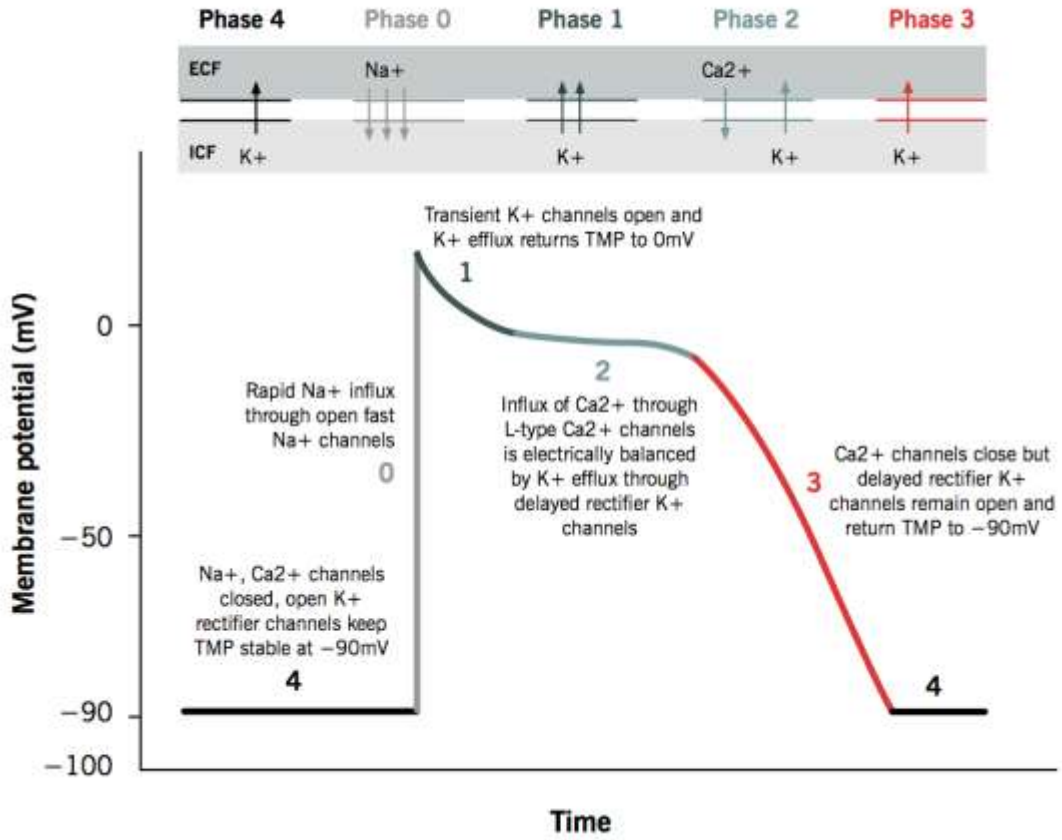

+40
0
−40
Rising phase
Overshoot phase
Falling phase
Undershoot phase
0
2
4
6
8
(B)
0
1
2
3
4
(C)
0
2
4
6
8
(D)
0
10
20
30
40
Time (ms)

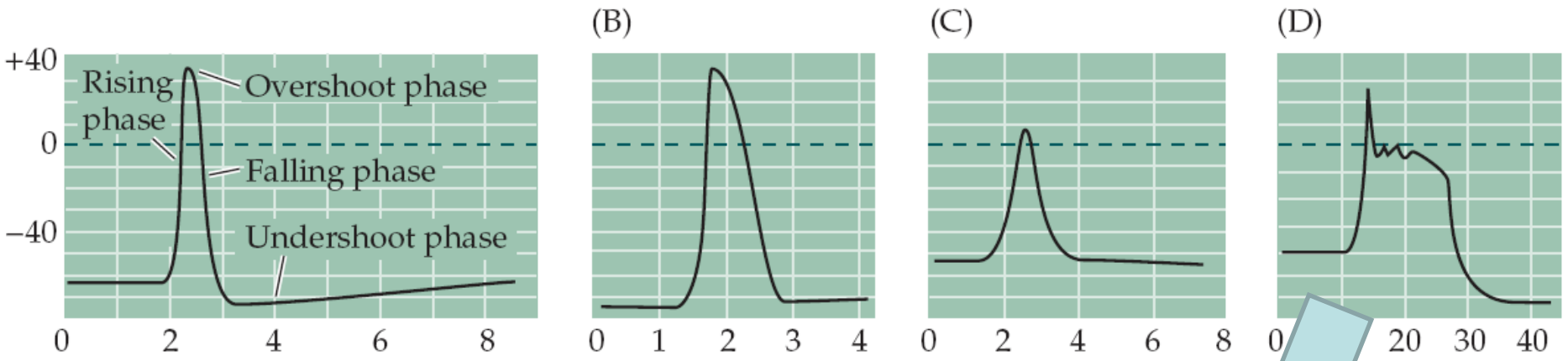

+40
0
−40
Rising phase
Overshoot phase
Falling phase
Undershoot phase
0 2 4 6 8
(B)
0 1 2 3 4
(C)
0 2 4 6 8
(D)
0 10 20 30 40
Time (ms)



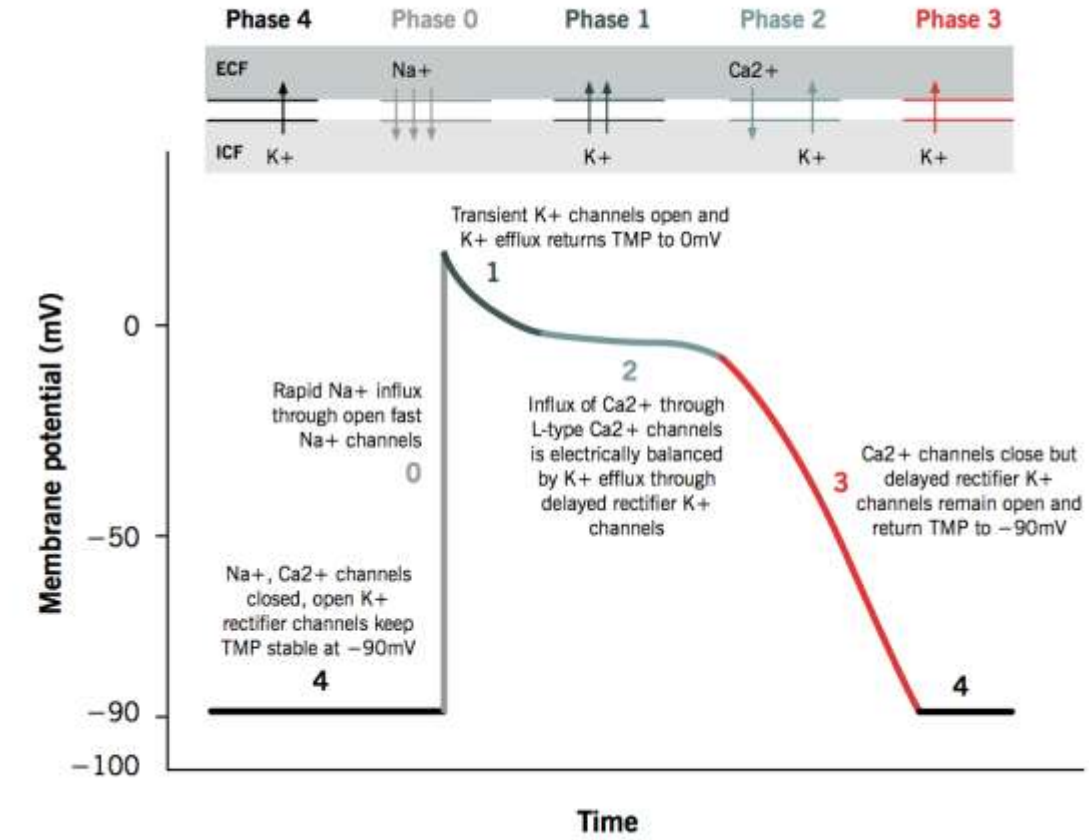
Action potential of cardiac muscles

Grigoriy Ikonnikov and Eric Wong





neuron from the inferior olive



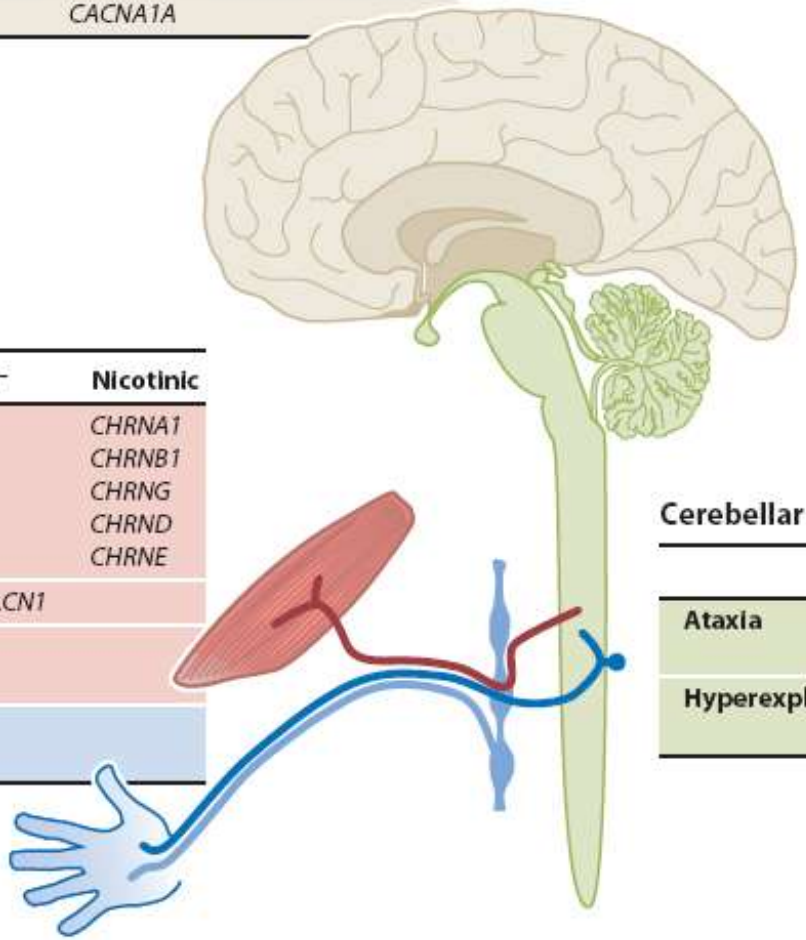
Channelopathies

Epilepsy and migraine

	Na^+	K^+	Ca^{2+}	$GABA_A$	Nicotinic
Epilepsy	*SCN1A* *SCN1B* *SCN2A*	*KCNQ2* *KCNQ3* *KCNMA1*	*CACNA1H*	*GABRA1* *GABRB3* *GABRG2*	*CHRNA2* *CHNRA4* *CHRNB2*
Migraine	*SCN1A*		*CACNA1A*		

Neuromuscular disorders

	Na^+	K^+	Ca^{2+}	Cl^-	Nicotinic
Myasthenia **Fetal akinesia**					*CHRNA1* *CHRNB1* *CHRNG* *CHRND* *CHRNE*
Myotonia	*SCN4A*			*CLCN1*	
Periodic paralysis	*SCN4A*	*KCNJ2*	*CACNA1S*		
Pain **Erythema**	*SCN9A*				



Cerebellar ataxia and excessive startle

	K^+	Ca^{2+}	Glycine
Ataxia	*KCNA1* *KCNC3*	*CACNA1A*	
Hyperexplexia			*GLRA1* *GLRB*

Ataxia is typically defined as the presence of abnormal, uncoordinated movements

Table 1. The neurological channelopathies

		Gene	Channel subunit	Disease
CNS	Sodium channels	*SCN1A*	α subunit of Nav1.1	Epilepsy, migraine
		SCN1B	β1	Epilepsy
		SCN2A	α subunit of Nav1.2	Epilepsy
	Potassium channels	*KCNQ2*	Kv7.2	Epilepsy
		KCNQ3	Kv7.3	Epilepsy
		KCNMA1	BK	Epilepsy with dyskinesia
		KCNA1	Kv1.1	Episodic ataxia
		KCNC3	Kv3.3	Ataxia
	Calcium channels	*CACNA1H*	α1H subunit of Cav3.2	Epilepsy
		CACNA1A	α1A subunit of Cav2.1	Episodic or progressive ataxia, migraine, epilepsy
	$GABA_A$ receptors	*GABRA1*	α1	Epilepsy
		GABRB3	β3	Epilepsy
		GABRG2	γ2	Epilepsy
	Nicotinic ACh receptors	*CHRNA2*	α2	Epilepsy
		CHNRA4	α4	Epilepsy
		CHRNB2	β2	Epilepsy
	Glycine receptors	*GLRA1*	α1	Hyperekplexia
		GLRB	β	Hyperekplexia
Peripheral nerve	Sodium channel	*SCN9A*	α subunit of Nav1.7	Excessive pain, insensitivity to pain
Muscle	Sodium channel	*SCN4A*	α subunit of Nav1.4	Periodic paralysis, myotonia
	Potassium channels	*KCNJ2*	Kir2.1	Periodic paralysis
		KCNJ18	Kir2.6	Periodic paralysis
	Calcium channel	*CACNA1S*	α1S subunit of CaV1.1	Periodic paralysis
	Chloride channel	*CLCN1*	CLC-1	Myotonia
	Nicotinic ACh receptors	*CHRNA1*	α1	Congenital myasthenic syndromes
		CHRNB1	β1	Congenital myasthenic syndromes
		CHRNG	γ	Congenital myasthenic syndromes
		CHRND	δ	Congenital myasthenic syndromes
		CHRNE	ε	Congenital myasthenic syndromes

Table 2 Classification of neurological channelopathies according to channel

Channel	Muscle	Gene	CNS	Gene
Sodium channel	Hypokalaemic periodic paralysis	SCN4A	Generalised epilepsy with febrile seizures plus syndrome (GEFS+), severe myoclonic epilepsy of infancy	SCN1A SCN1B SCN2A
	Hyperkalaemic periodic paralysis	SCN4A		
	Paramyotonia congenita	SCN4A		
	Potassium aggravated myotonia	SCN4A		
Chloride channel	Myotonia congenita: Thomsen's, Becker's	CLCN1		
Calcium channel	Hypokalaemic periodic paralysis	CACNA1S	Episodic ataxia type 2	CACNA1A
	Malignant hyperthermia	CACNA1S CACNL2A	Familial hemiplegic migraine	
			Childhood absence epilepsy	CACNA1H
Potassium channel	Andersen's syndrome	KCNJ2	Episodic ataxia type 1	KCNA1
	Hypokalaemic periodic paralysis	KCNE3	Benign familial neonatal convulsions	KCNQ2 KCNQ3
	Hyperkalaemic periodic paralysis	KCNE3		
Ryanodine receptor	Malignant hyperthermia	RYR1		
	Central core disease	RYR1		
Glycine receptor			Hyperekplexia	GLRA1
Acetylcholine receptor			Autosomal dominant frontal lobe epilepsy	CHRNB2 CHRNA4
GABA receptor			GEFS+, juvenile myoclonic epilepsy	GABRG2

- Pages 84 & 85 in

  Neuroscience 3rd edition by Dale *Purves*

Ion Channel Neurotoxins

Synapses and Neurotransmitters

Communication Between Neurons

- **Synapse:**

Communication Between Neurons

- **Synapse: A specialized site of contact, and transmission of information between a neuron and an effector cell**

Anterior Motor Neuron

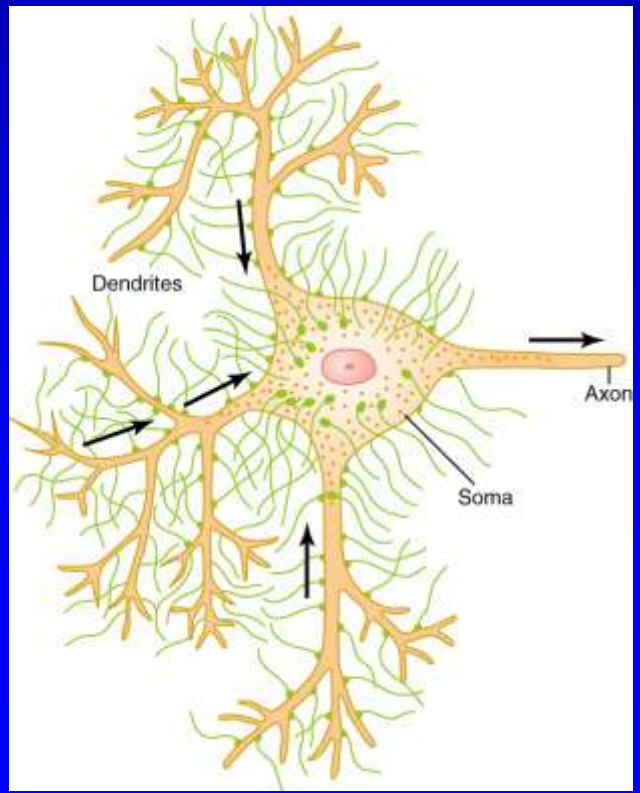
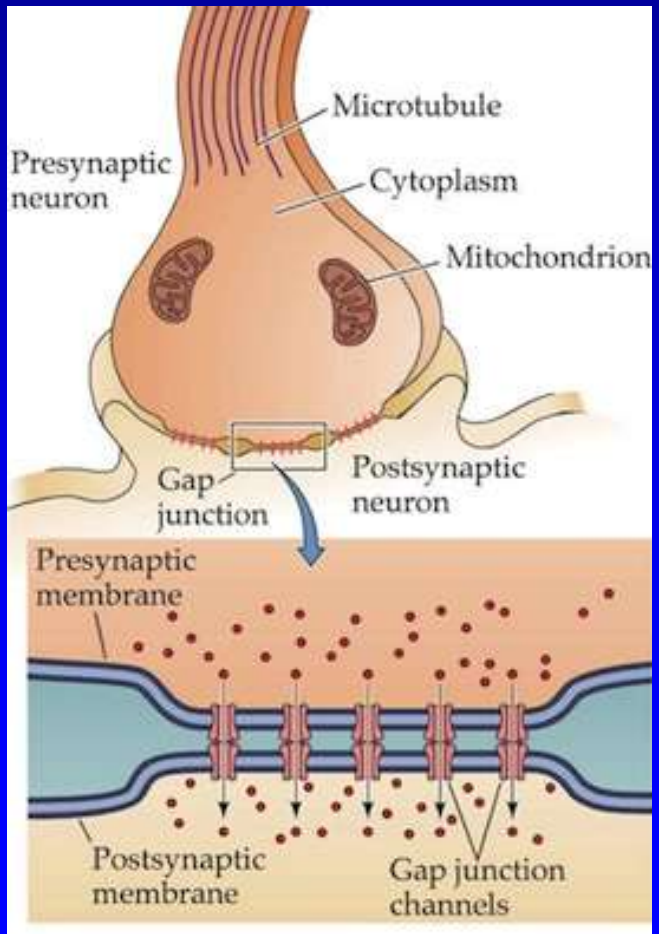


Figure 45-5

Communication Between Neurons

- Electrical synapse



Communication Between Neurons

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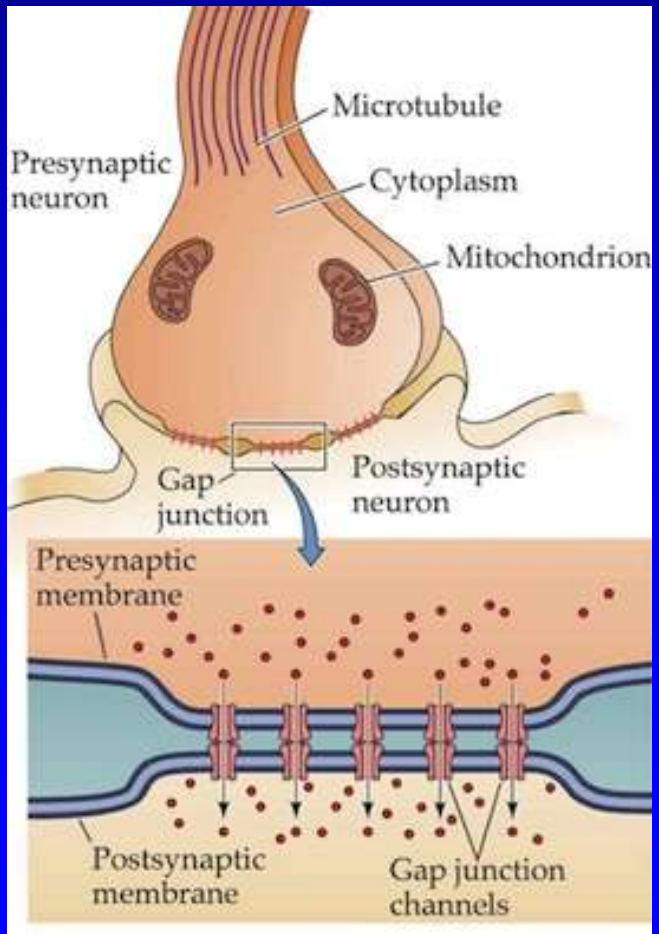
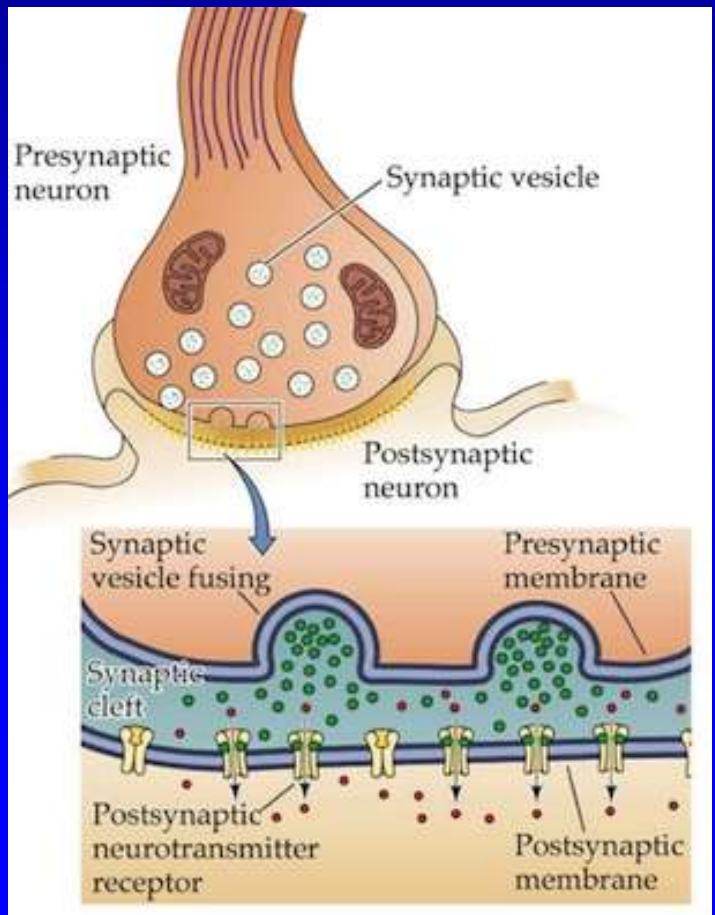
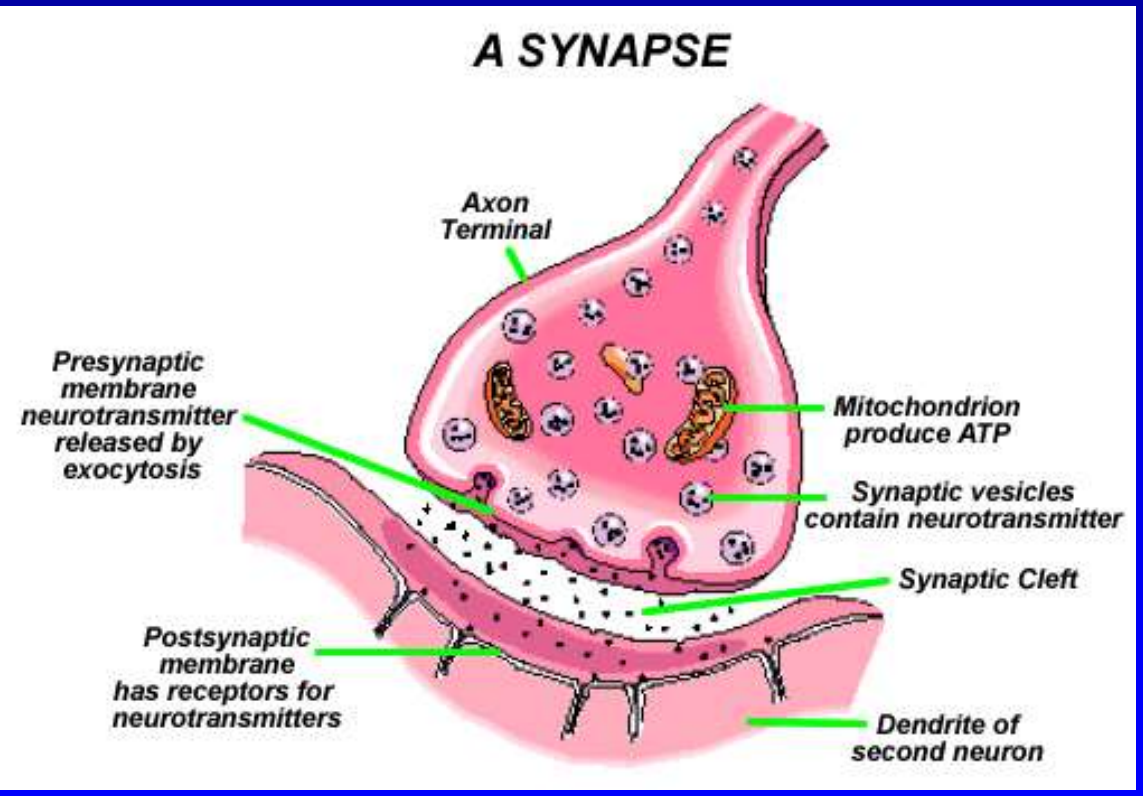


Chemical synapse

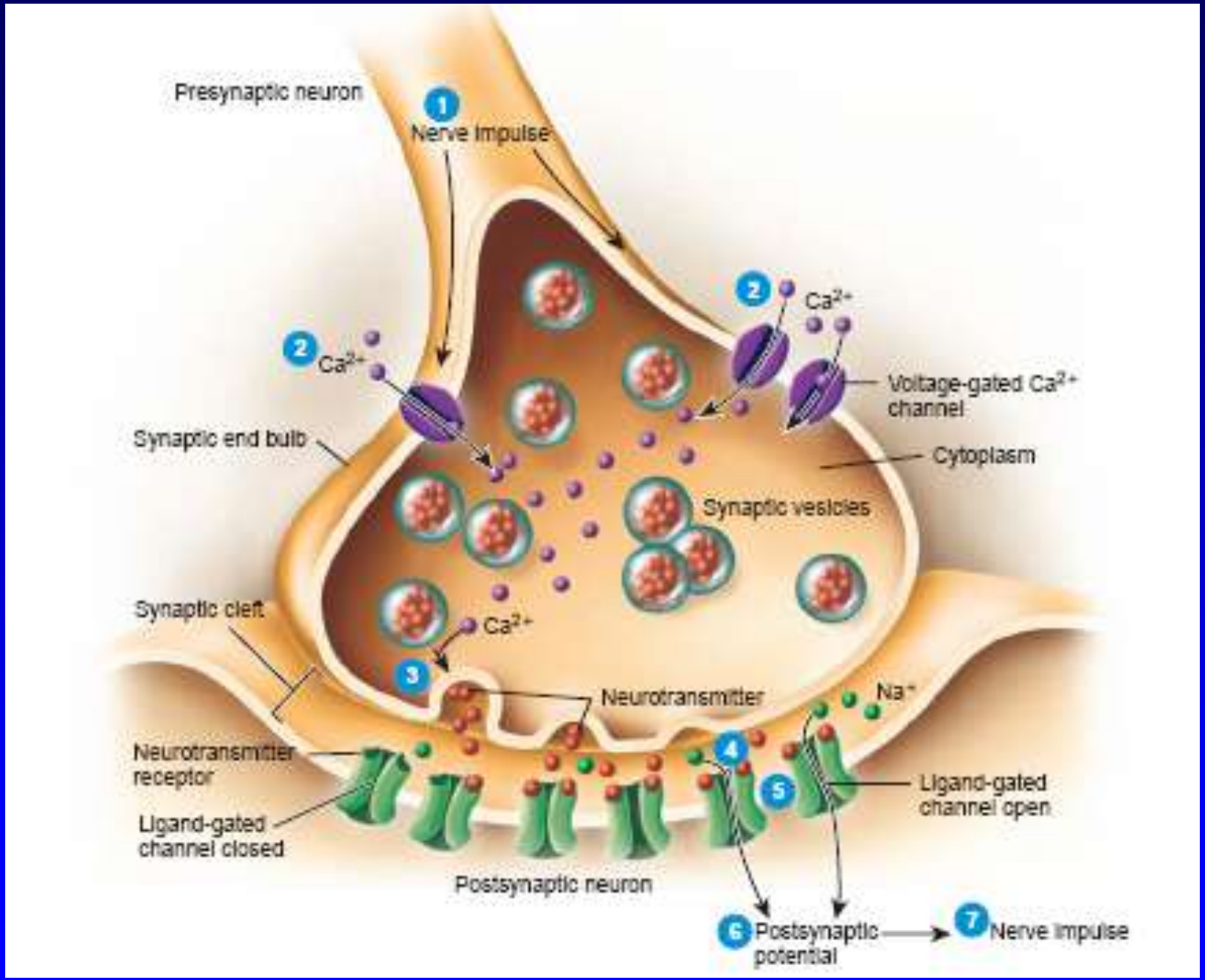


Communication Between Neurons

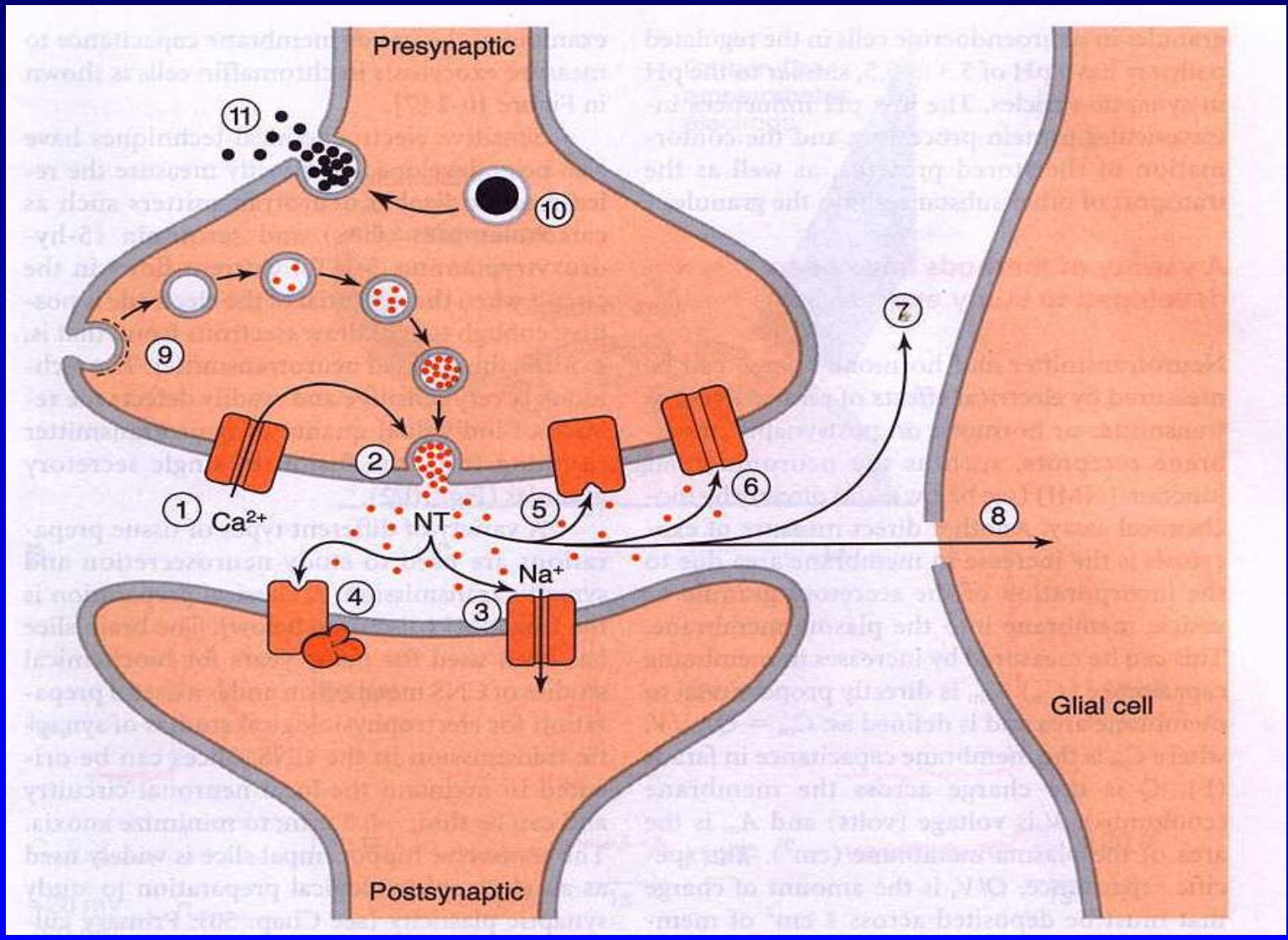
- Chemical synapse



Neurotransmitter: is a messenger of neurologic information from one cell to another.


Presynaptic neuron
1
Nerve impulse
2
Ca^{2+}
2
Ca^{2+}
Voltage-gated Ca^{2+} channel
Synaptic end bulb
Cytoplasm
Synaptic vesicles
Synaptic cleft
Ca^{2+}
3
Neurotransmitter
Na^+
Neurotransmitter receptor
4
5
Ligand-gated channel open
Ligand-gated channel closed
Postsynaptic neuron
6
Postsynaptic potential
7
Nerve impulse

Synaptic Transmission

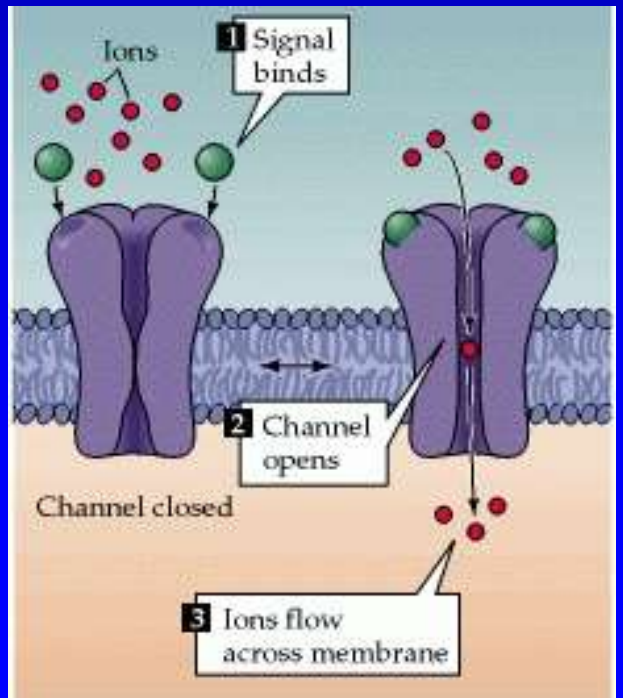


Action of Neurotransmitter on Postsynaptic Neuron

- postsynaptic membrane contains receptor proteins for the transmitter released from the presynaptic terminal.
- The effect of neurotransmitter on the post synaptic neuron depend on the type of the receptor

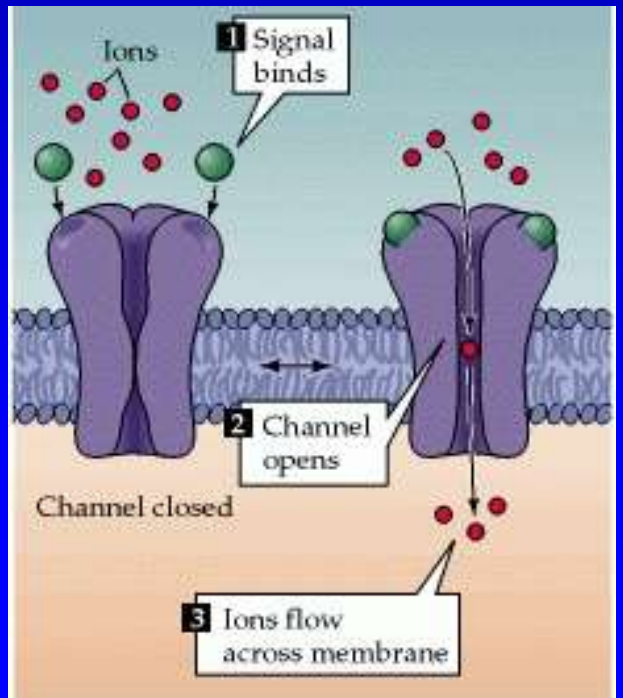
Action of Neurotransmitter on Postsynaptic Neuron

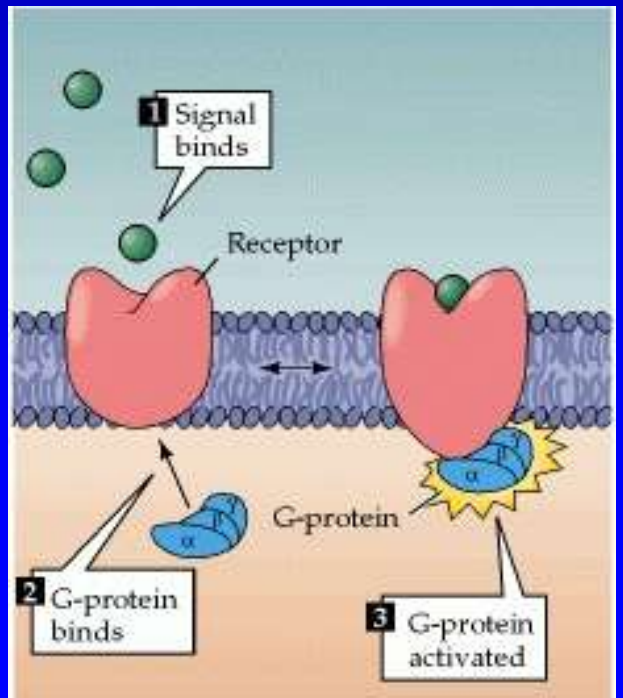
- Two types of receptors
  - Ion channels receptors



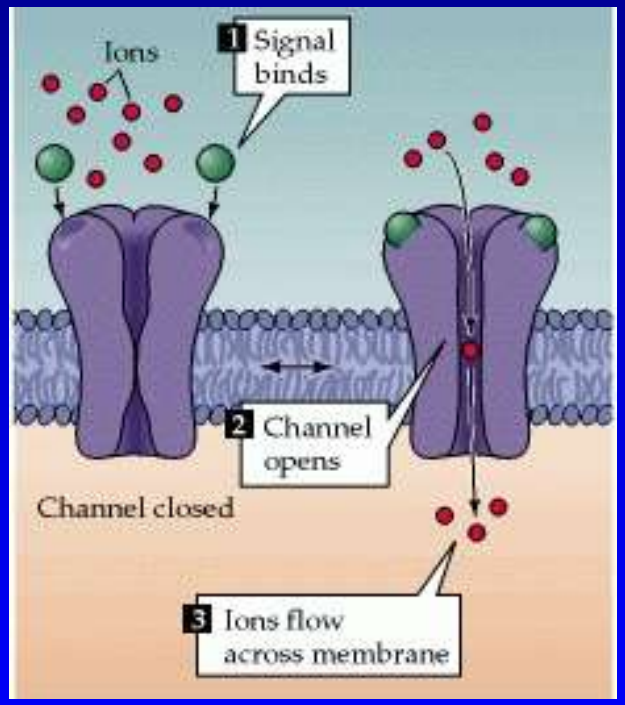
Action of Neurotransmitter on Postsynaptic Neuron

- Two types of receptors
  - Ion channels receptors
  - Second messenger receptors





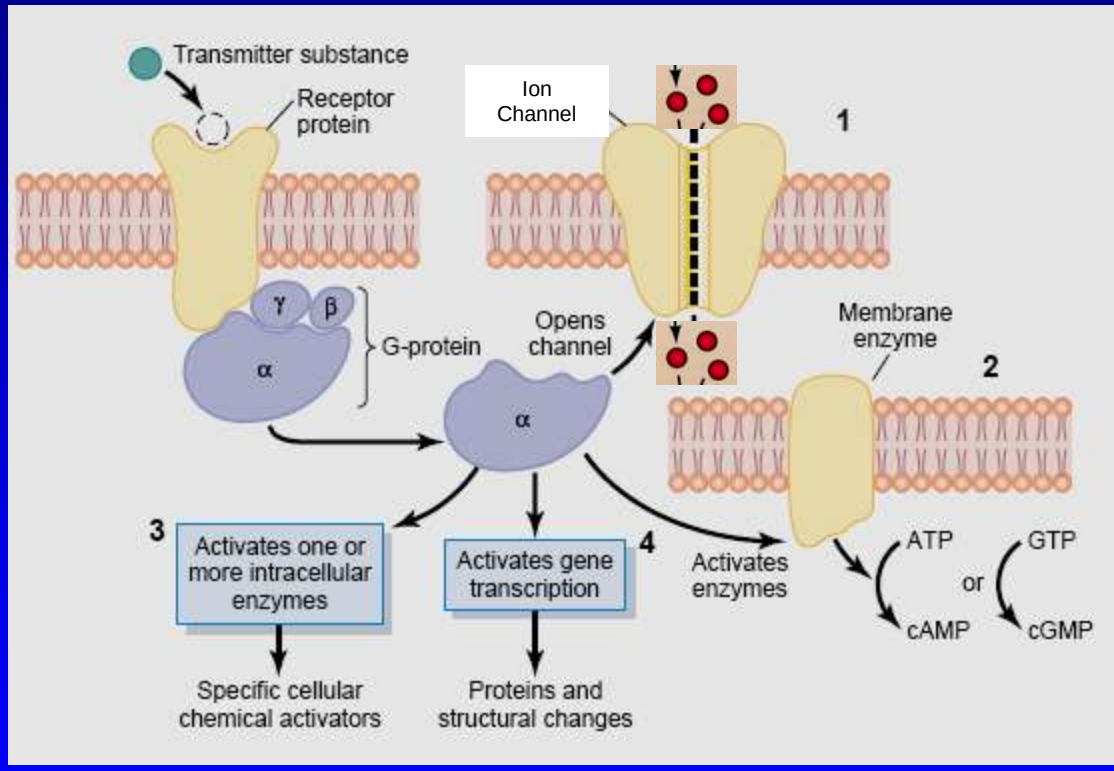
Ion Channels receptors



- transmitters that open sodium channels excite the postsynaptic neuron.
- transmitters that open chloride channels inhibit the postsynaptic neuron.
- transmitters that open potassium channels inhibit the postsynaptic neuron.

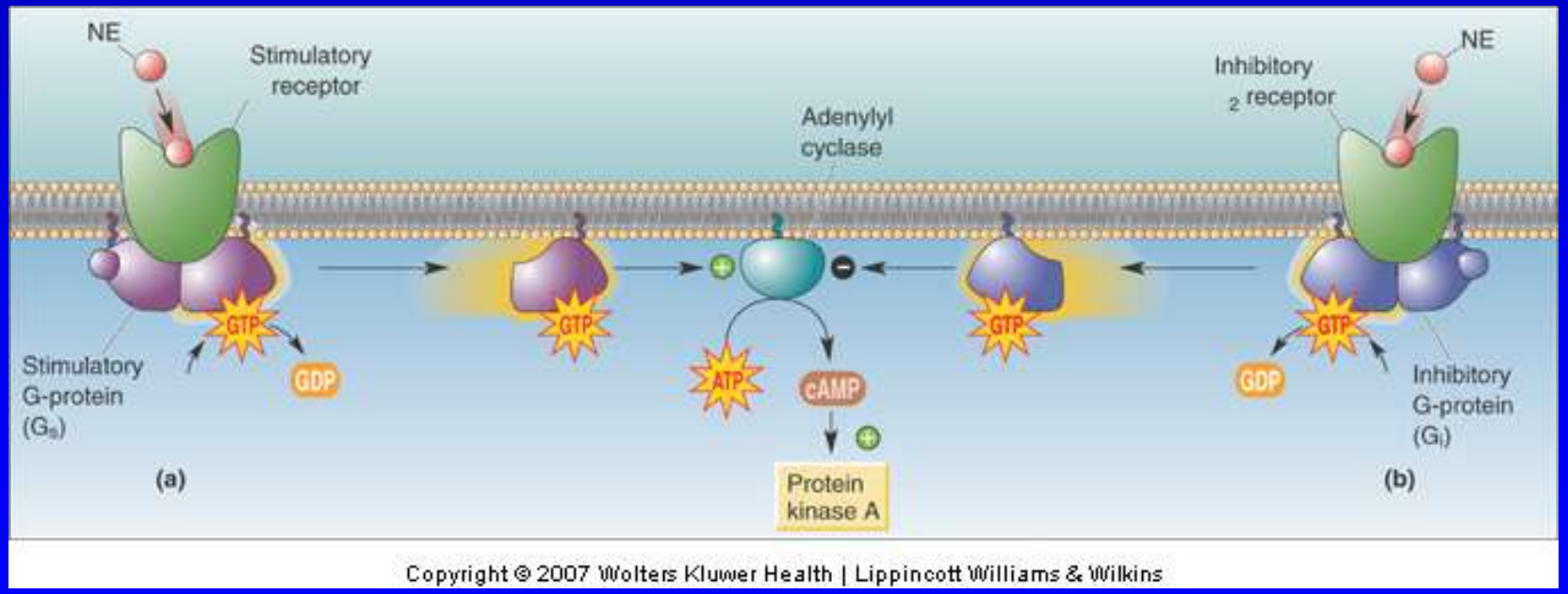
Seconded messenger receptors (as example G-protein)

1. *Opening specific ion channels*
2. *Activation of cAMP or cGMP*
3. *Activation of one or more intracellular enzymes*
4. *Activation of gene transcription.*



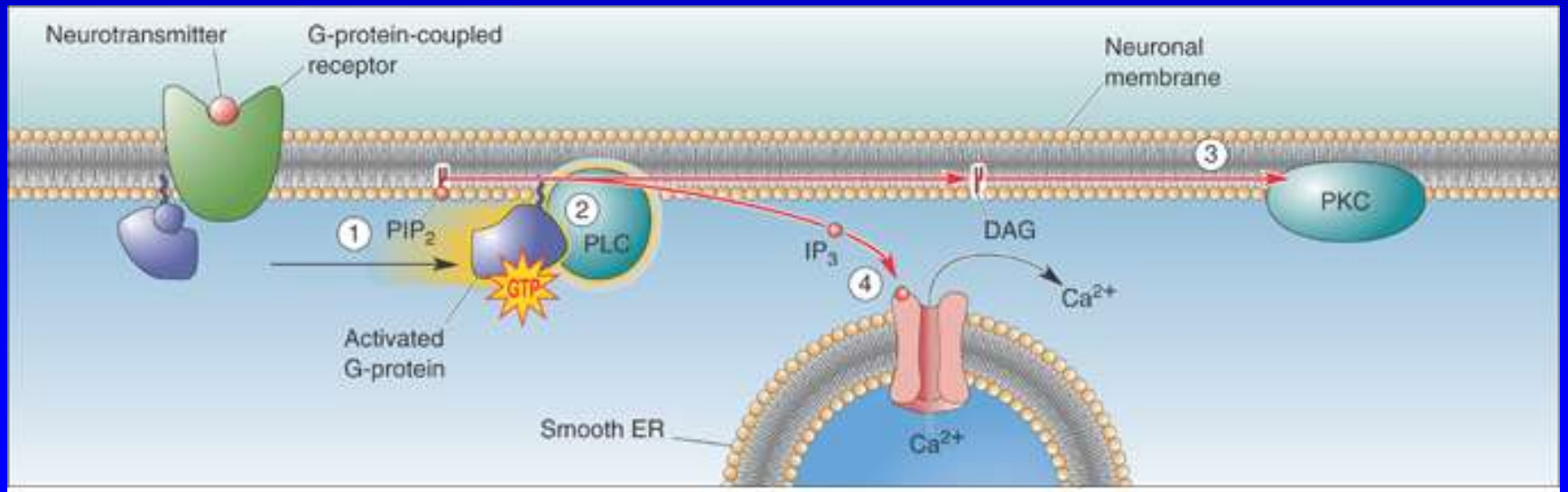
G-Protein-Coupled Receptors and Effectors

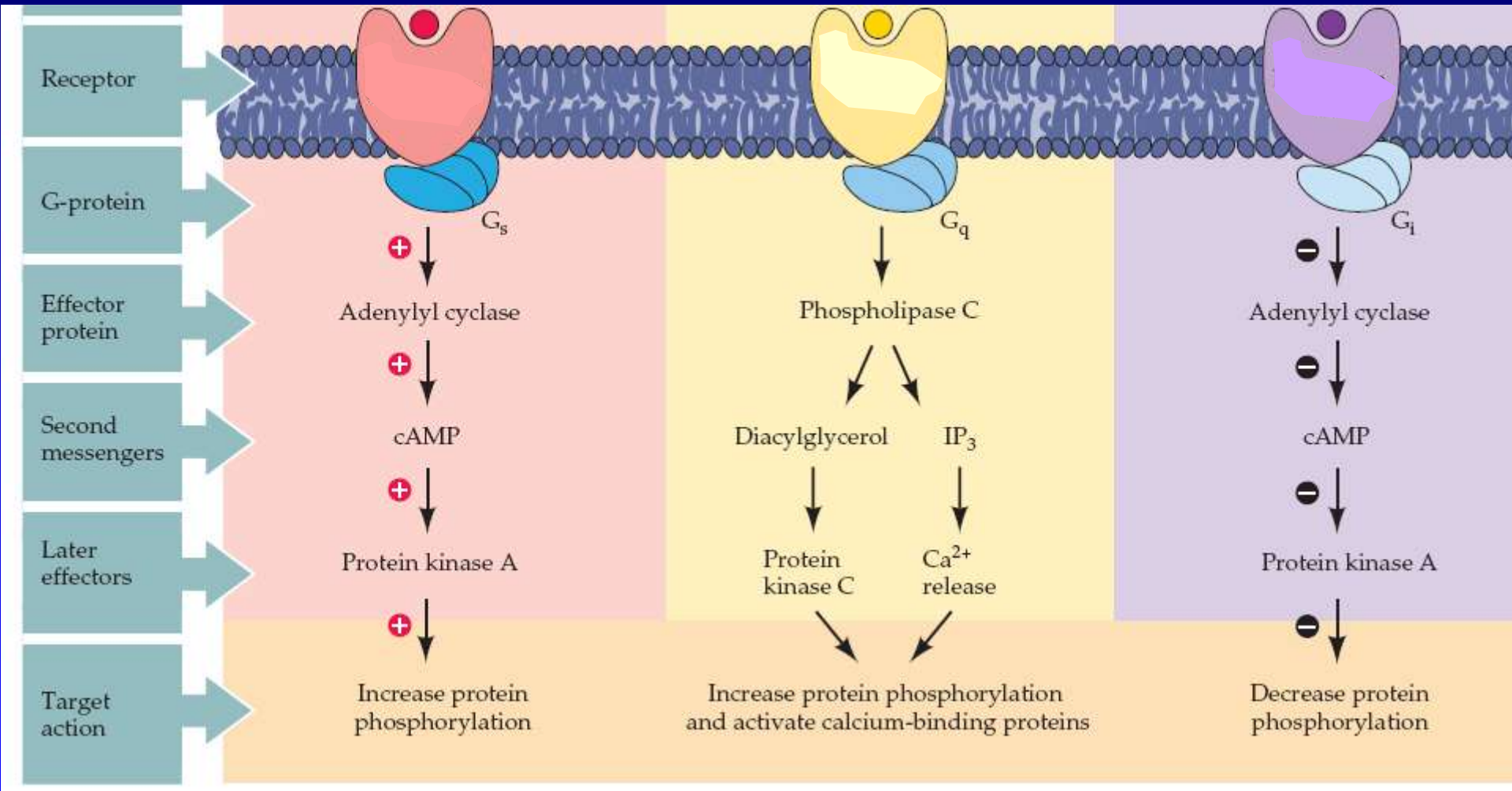
- GPCR Effector Systems (Cont'd)
  - Push-pull method (e.g., different G proteins for stimulating or inhibiting adenylyl cyclase)

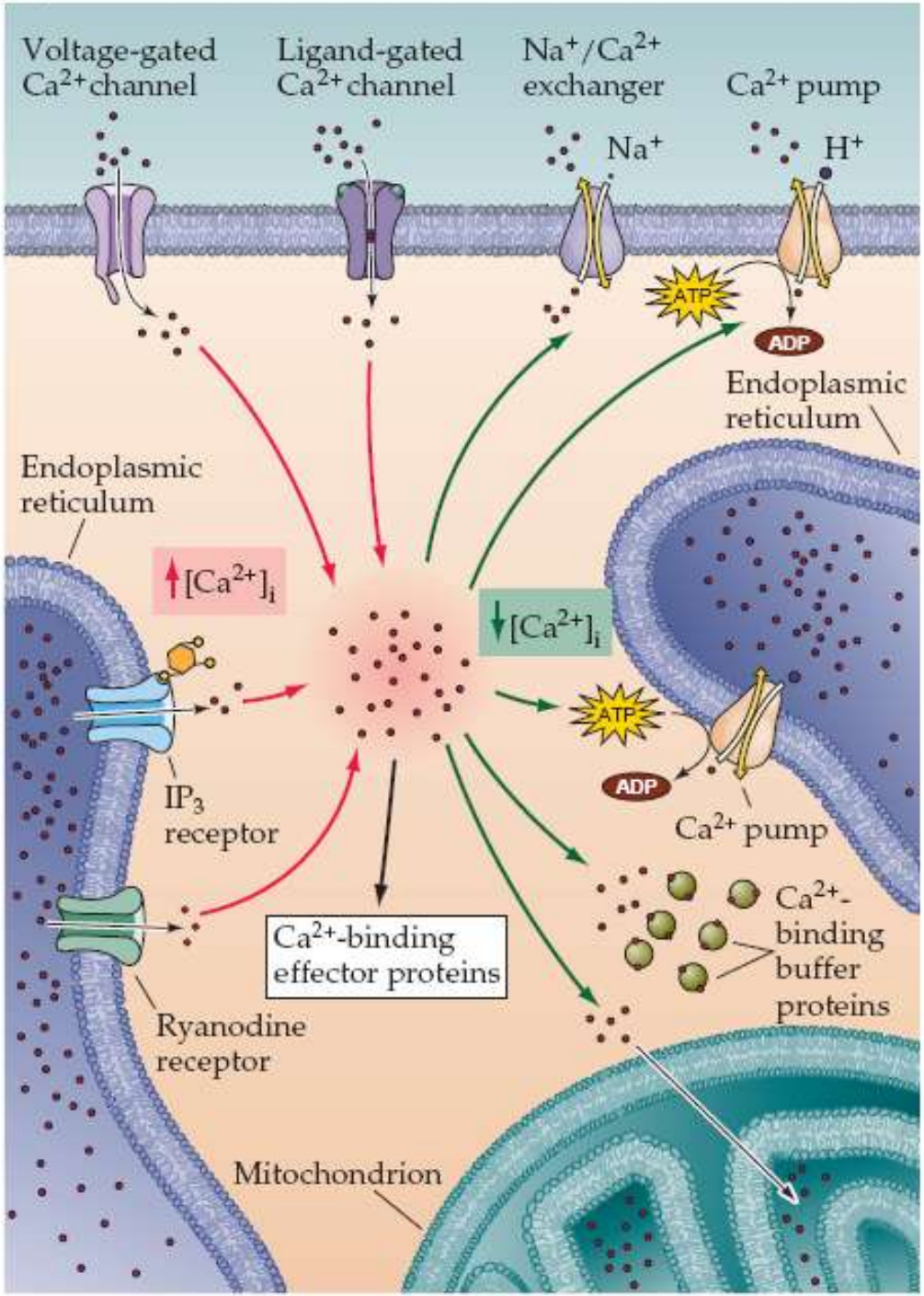


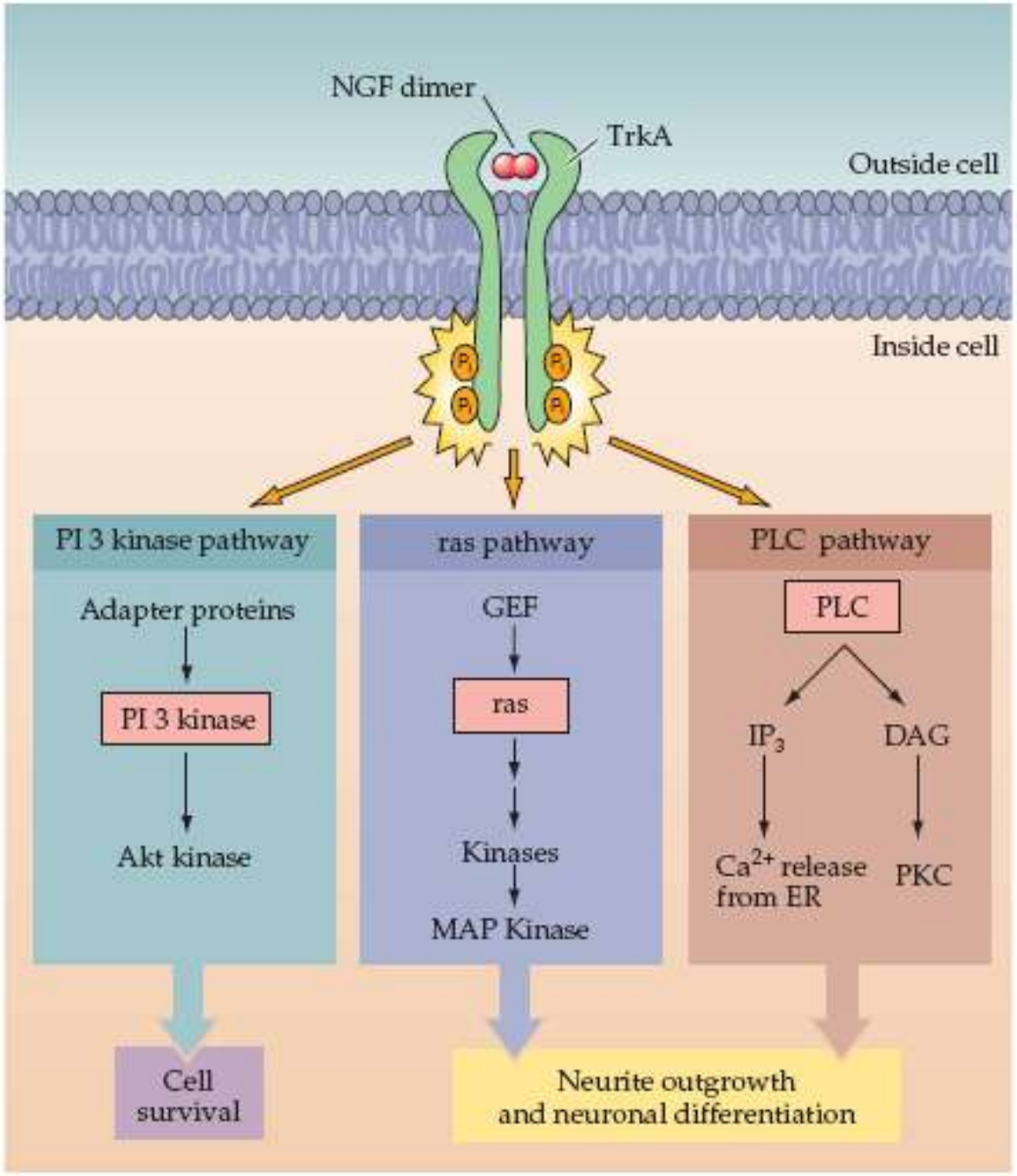
G-Protein-Coupled Receptors and Effectors

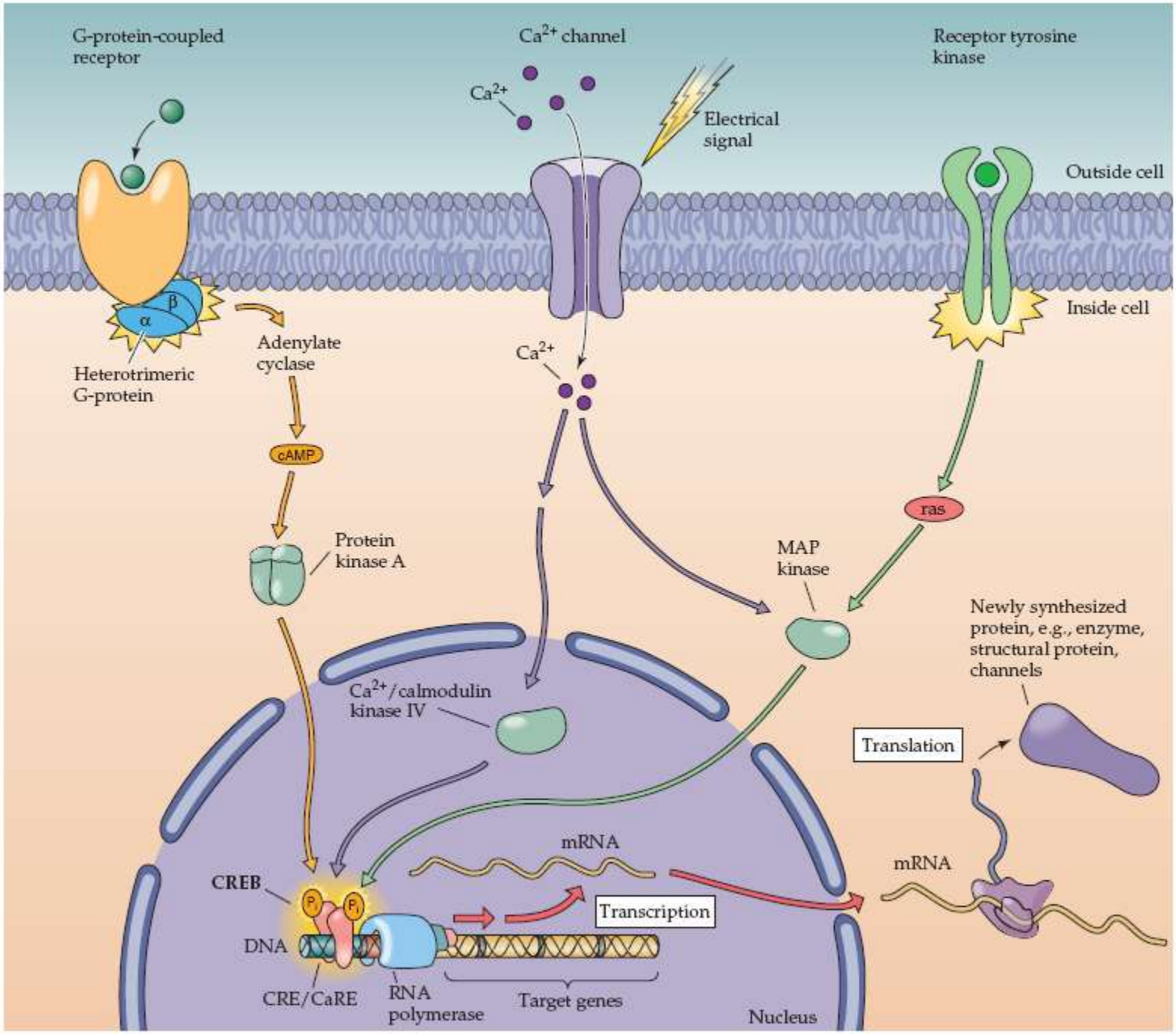
- GPCR Effector Systems (Cont'd)
  - Some cascades split
    - G-protein activates PLC→ generates DAG and IP3→ activate different effectors




Receptor
G-protein
Effector protein
Second messengers
Later effectors
Target action
G_s
G_q
G_i
Adenylyl cyclase
Phospholipase C
Adenylyl cyclase
cAMP
Diacylglycerol
IP_3
cAMP
Protein kinase A
Protein kinase C
Ca^{2+} release
Protein kinase A
Increase protein phosphorylation
Increase protein phosphorylation and activate calcium-binding proteins
Decrease protein phosphorylation


Voltage-gated Ca^{2+} channel
Ligand-gated Ca^{2+} channel
Na^+/Ca^{2+} exchanger
Ca^{2+} pump
Na^+
H^+
ATP
ADP
Endoplasmic reticulum
Endoplasmic reticulum
$\uparrow[Ca^{2+}]_i$
$\downarrow[Ca^{2+}]_i$
ATP
ADP
IP_3 receptor
Ca^{2+} pump
Ca^{2+}-binding effector proteins
Ca^{2+}-binding buffer proteins
Ryanodine receptor
Mitochondrion


NGF dimer
TrkA
Outside cell
Inside cell
P
PI 3 kinase pathway
Adapter proteins
PI 3 kinase
Akt kinase
ras pathway
GEF
ras
Kinases
MAP Kinase
PLC pathway
PLC
IP3
DAG
Ca2+ release from ER
PKC
Cell survival
Neurite outgrowth and neuronal differentiation


G-protein-coupled receptor
Ca^{2+} channel
Receptor tyrosine kinase
Ca^{2+}
Electrical signal
Outside cell
Inside cell
β
α
Heterotrimeric G-protein
Adenylate cyclase
cAMP
Ca^{2+}
ras
Protein kinase A
MAP kinase
Newly synthesized protein, e.g., enzyme, structural protein, channels
Ca^{2+}/calmodulin kinase IV
Translation
mRNA
mRNA
CREB
P
P
DNA
Transcription
CRE/CaRE
RNA polymerase
Target genes
Nucleus

G-Protein-Coupled Receptors and Effectors

- GPCR Effector Systems (Cont'd)
  - Signal amplification