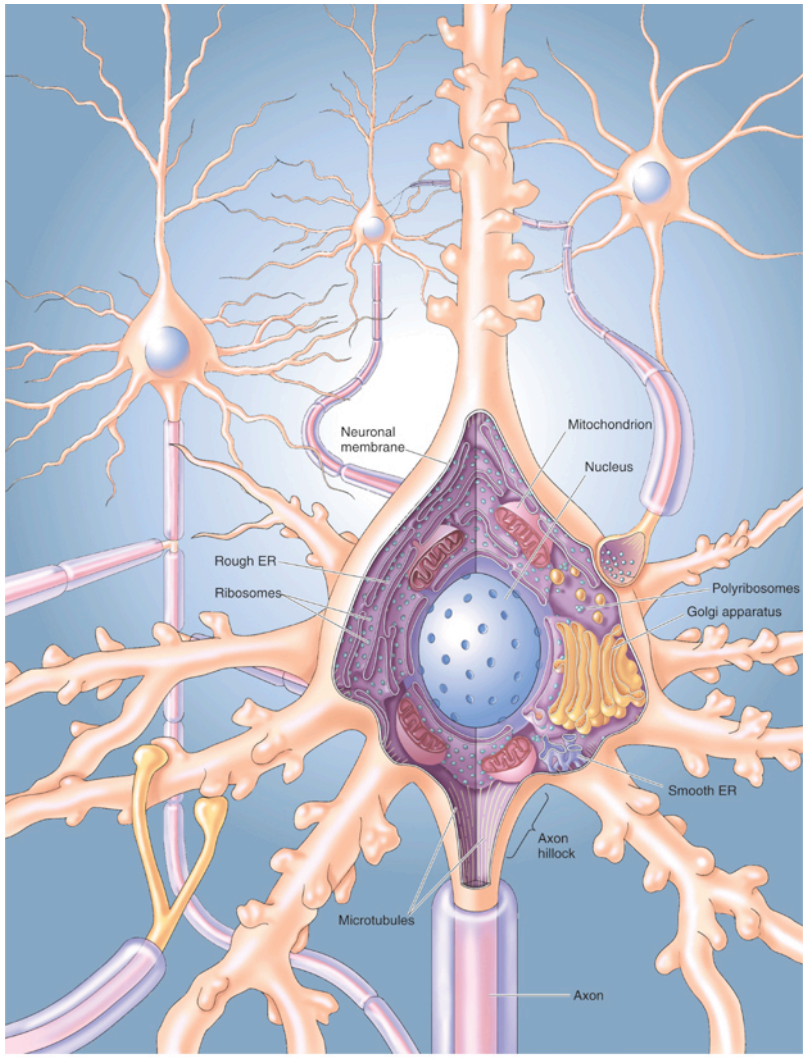
Chapter 2: Neurons and Glia

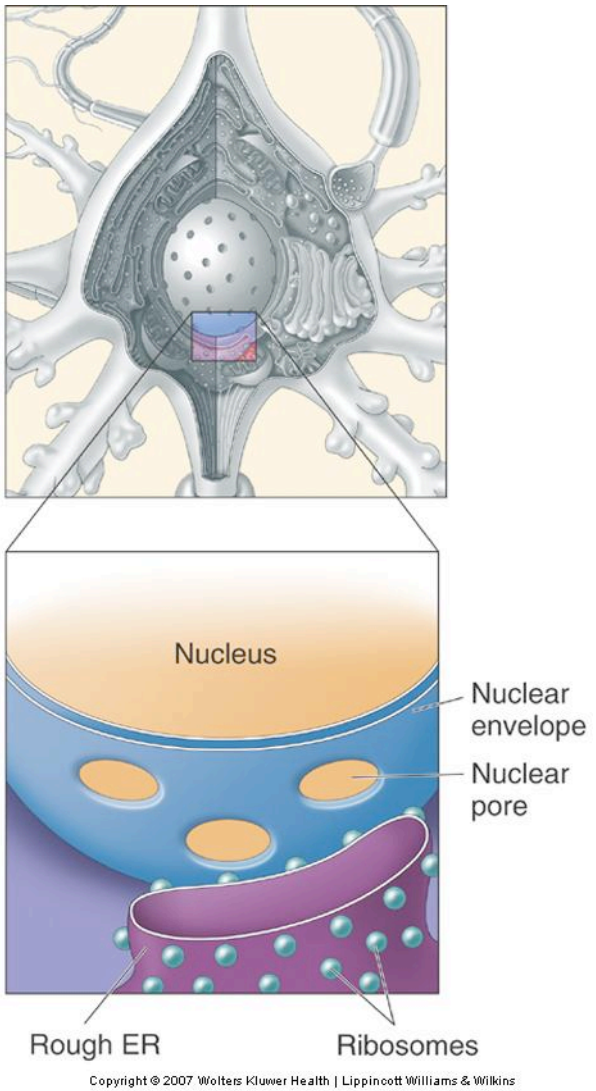
The Prototypical Neuron

- The Soma
  - Cytosol: watery fluid inside the cell
  - Organelles: membrane-enclosed structures within the soma
  - Cytoplasm: contents within a cell membrane, *e.g.*, organelles, excluding the nucleus



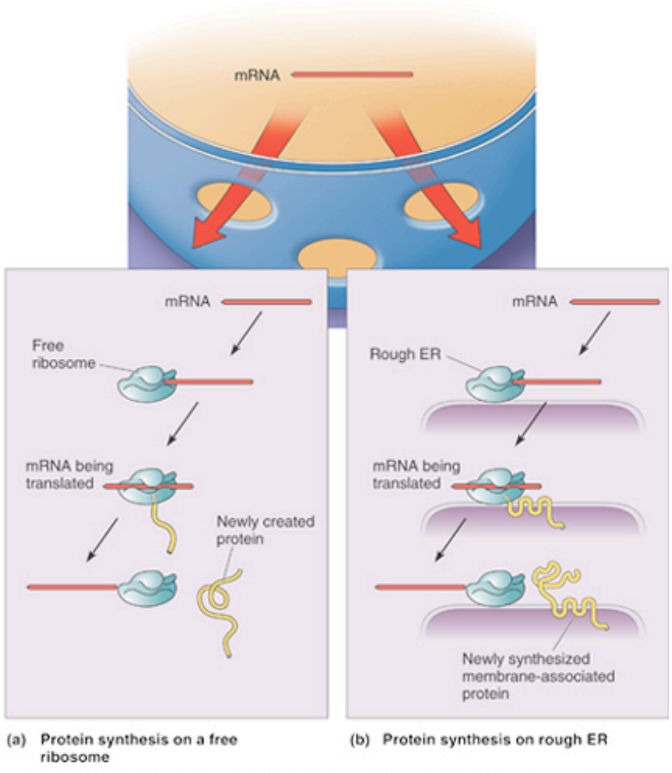
The Prototypical Neuron

- The Soma
  - Major site for protein synthesis
    - Rough endoplasmic reticulum



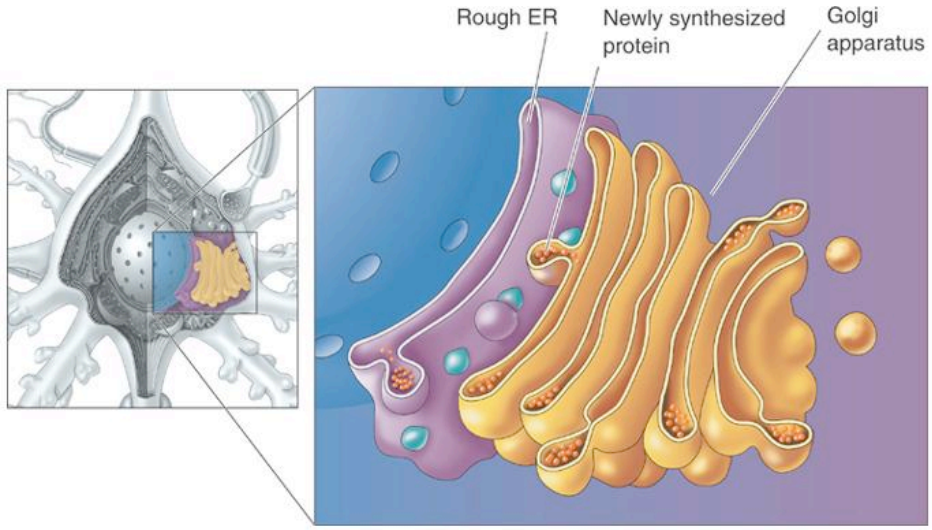
The Prototypical Neuron

- The Soma
  - Protein synthesis also on free ribosomes; polyribosomes



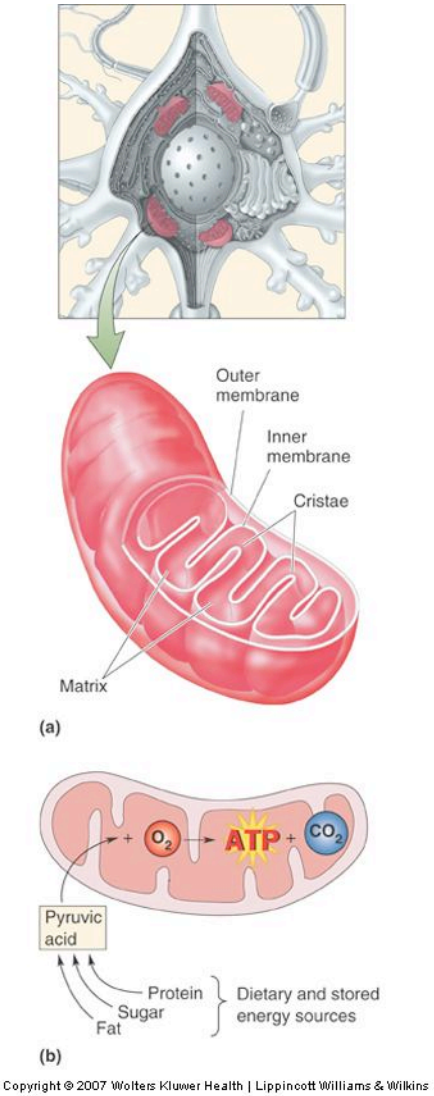
The Prototypical Neuron

- The Soma
  - Smooth ER and Golgi Apparatus
    - Sites for preparing and sorting proteins for delivery to different cell regions — trafficking — and regulating substances



The Prototypical Neuron

- The Soma
  - Mitochondrion
    - Site of cellular respiration — "inhale and exhale"
    - Krebs cycle
    - ATP — cell's energy source

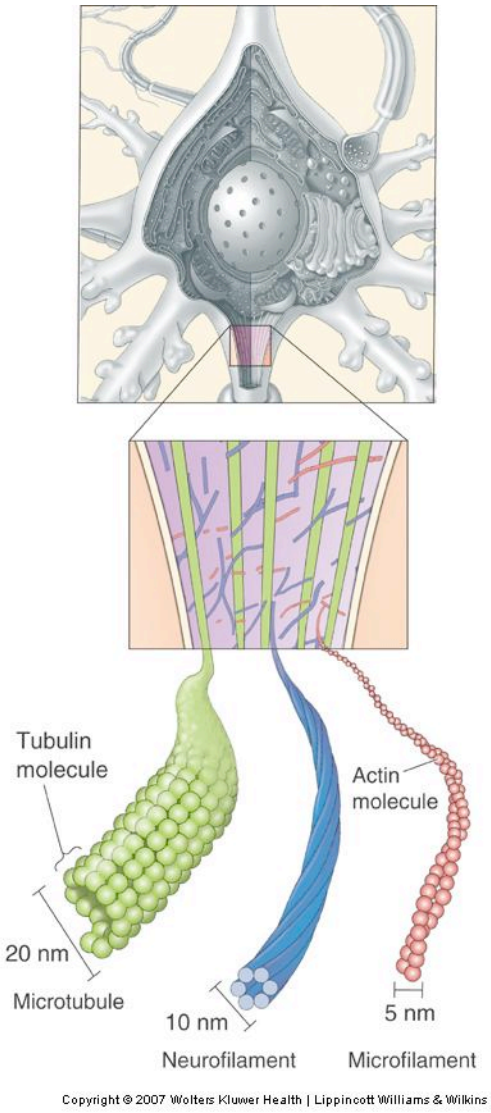


The Prototypical Neuron

- The Neuronal Membrane
  - Barrier that encloses cytoplasm
  - Approximately 5 nm thick
  - Protein concentration in membrane varies
  - Structure of discrete membrane regions influences neuronal function

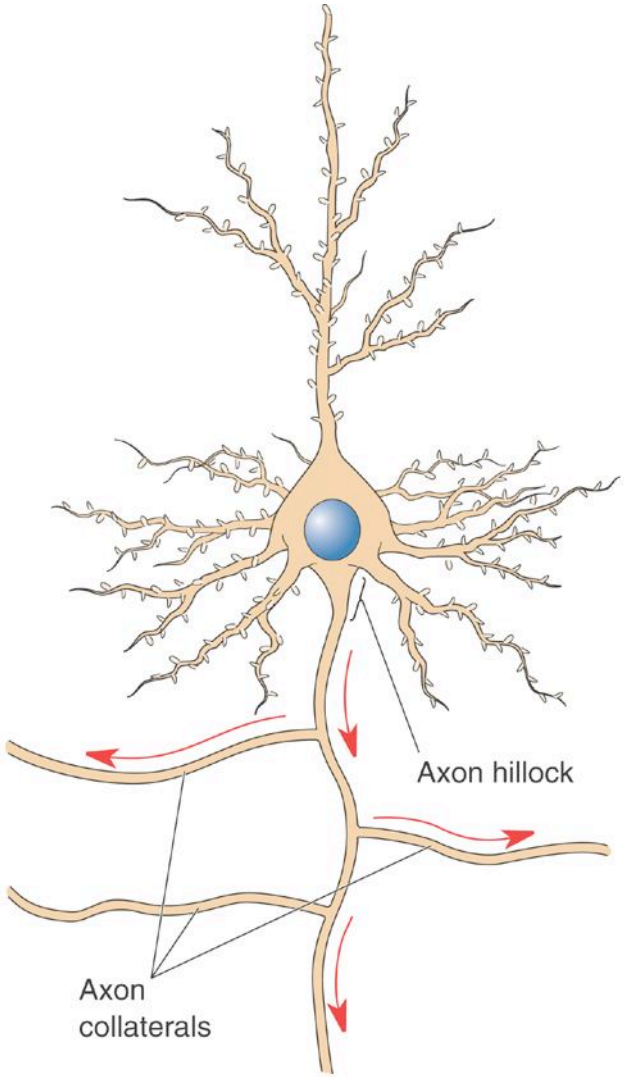
The Prototypical Neuron

- The Cytoskeleton
  - Not static
  - Internal scaffolding of neuronal membrane
  - Three "bones"
    - Microtubules
    - Microfilaments
    - Neurofilaments



The Prototypical Neuron

- The Axon
  - Axon hillock (beginning)
  - Axon proper (middle)
  - Axon terminal (end)
- Differences between axon and soma
  - ER does not extend into axon
  - Protein composition: Unique

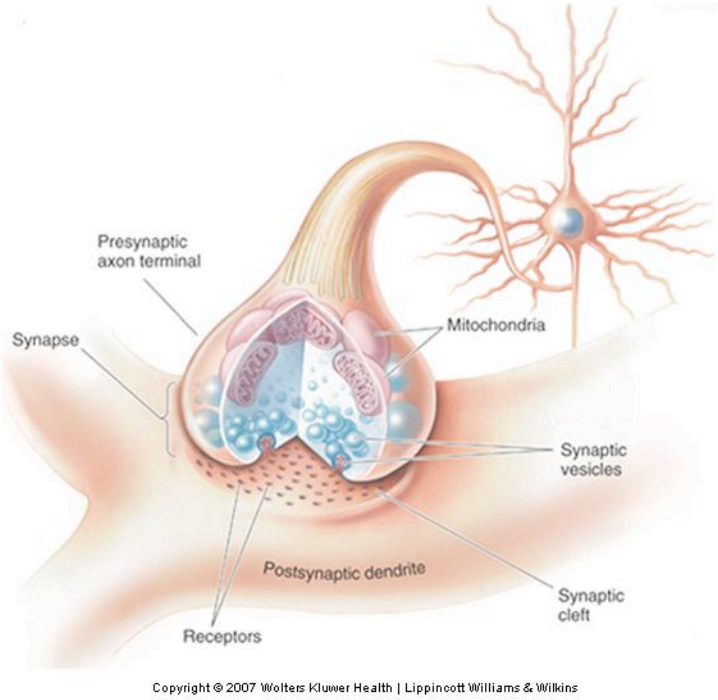


The Prototypical Neuron

- The Axon
  - The Axon Terminal
    - Differences between the cytoplasm of axon terminal and axon
      - No microtubules in terminal
      - Presence of synaptic vesicles
      - Abundance of membrane proteins
      - Large number of mitochondria

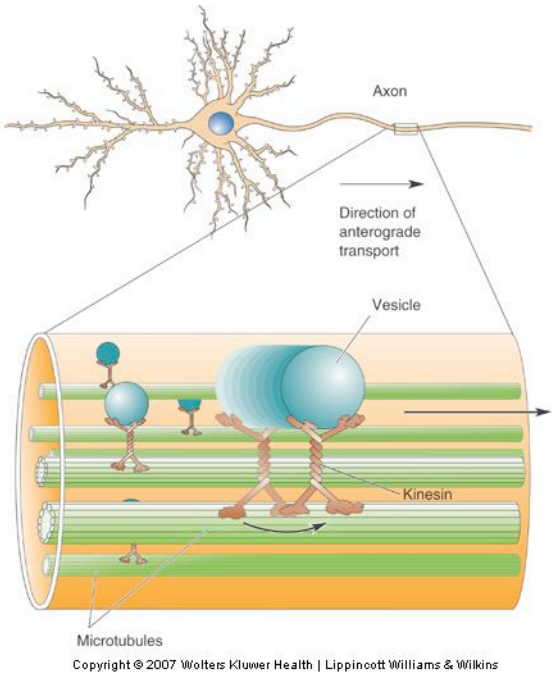
The Prototypical Neuron

- The Axon
  - Synapse
    - Synaptic transmission
    - Electrical-to-chemical-to-electrical transformation
    - Synaptic transmission dysfunction
      - Mental disorders



The Prototypical Neuron

- The Axon
  - Axoplasmic transport
  - Anterograde (soma to terminal) vs. Retrograde (terminal to soma) transport

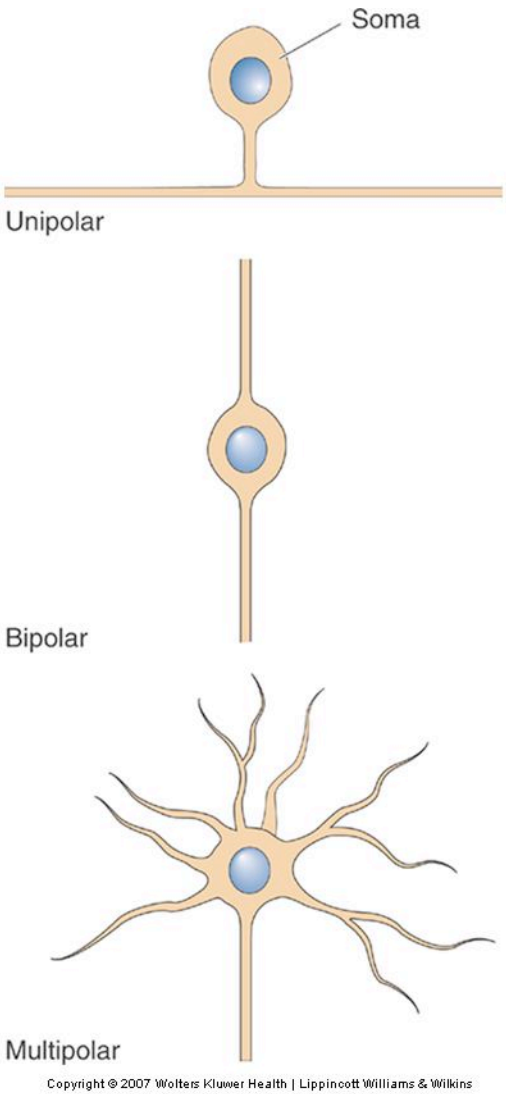


The Prototypical Neuron

- Dendrites
  - "Antennae" of neurons
  - Dendritic tree
  - Synapse — receptors
  - Dendritic spines
    - Postsynaptic: receives signals from axon terminal

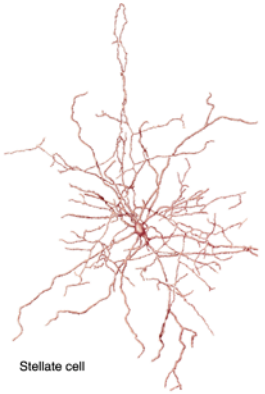
Classifying Neurons

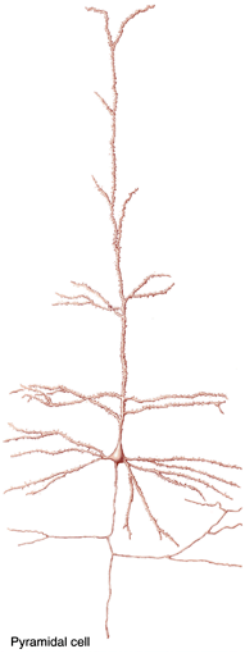
- Classification Based on the Number of Neurites
  - Single neurite
    - Unipolar
  - Two or more neurites
    - Bipolar — two
    - Multipolar — > two



Classifying Neurons

- Classification Based on Dendritic and Somatic Morphologies
  - Stellate cells (star-shaped) and pyramidal cells (pyramid-shaped)
  - Spiny or aspinous



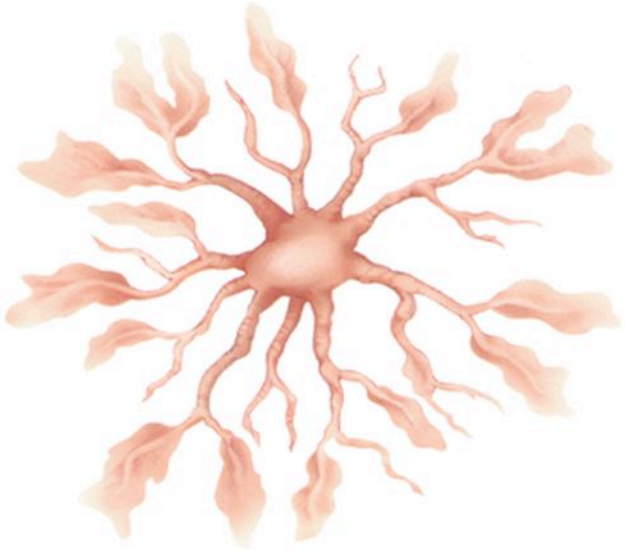


Classifying Neurons

- Further Classification
  - By connections within the CNS
    - Primary sensory neurons, motor neurons, interneurons
  - Based on axonal length
    - Golgi Type I
    - Golgi Type II
  - Based on neurotransmitter type
    - *e.g.,* Cholinergic = Acetycholine at synapses

Glia

- Function of Glia
  - Supports neuronal functions
- Astrocytes
  - Most numerous glia in the brain
  - Fill spaces between neurons
  - Influence neurite growth
  - Regulate chemical content of extracellular space

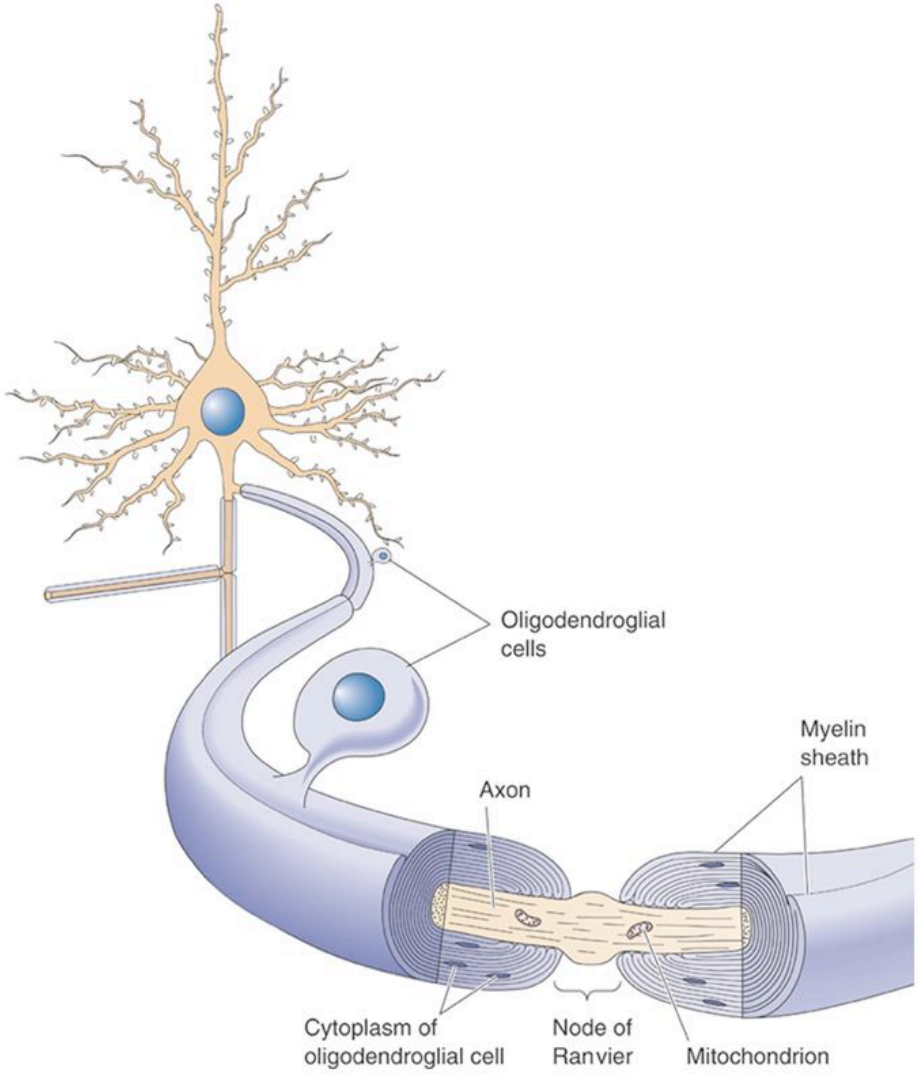


Glia

- Myelinating Glia
  - Oligodendroglia (in CNS)
  - Schwann cells (in PNS)
  - Insulate axons

Glia

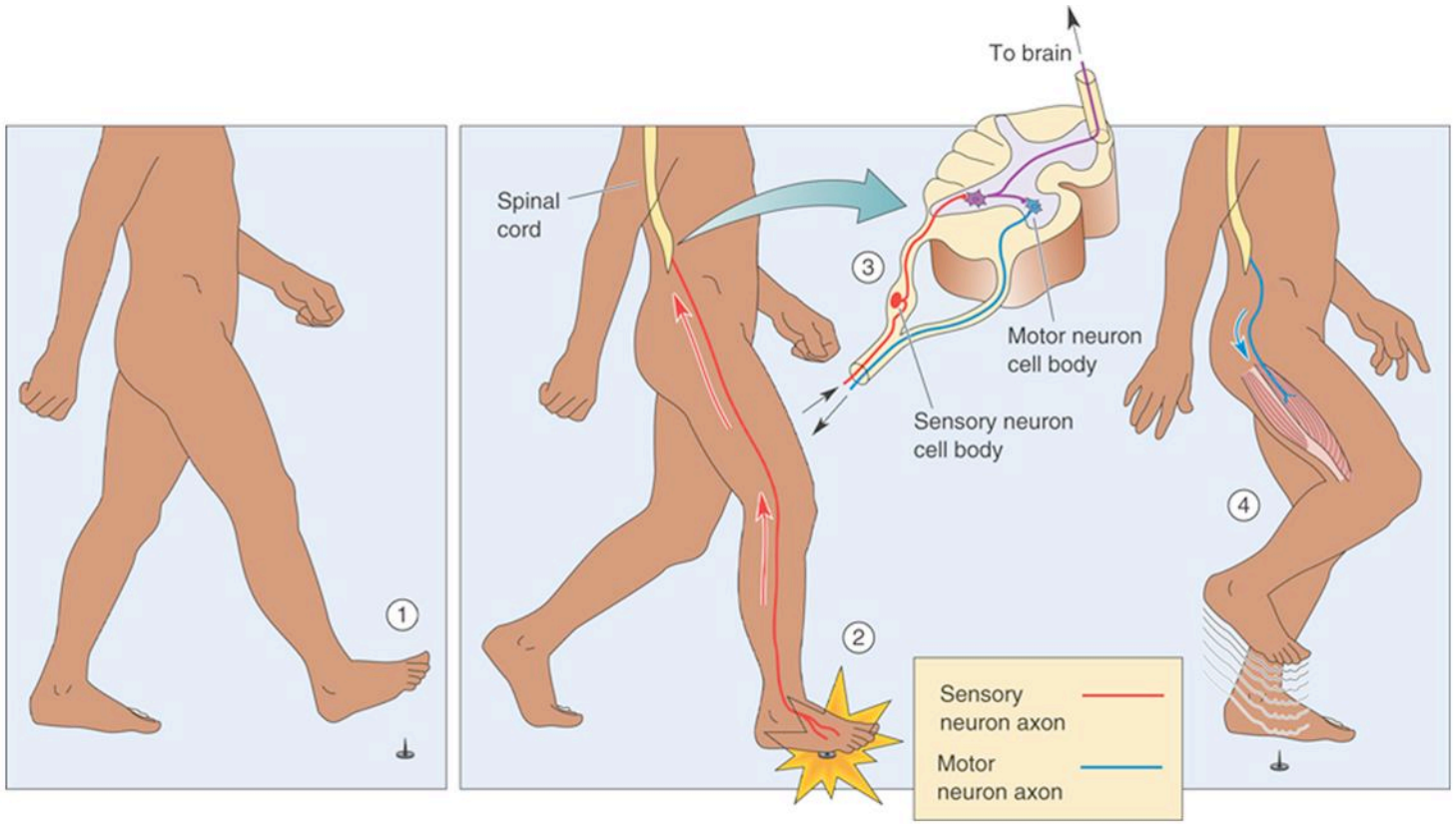
- Myelinating Glia
  - Oligodendroglial cells
  - Node of Ranvier
    - Region where the axonal membrane is exposed



Chapter 3: Neuronal Membrane at Rest

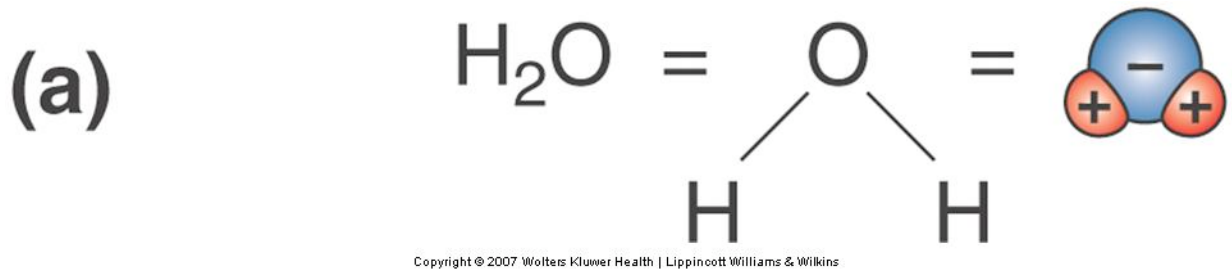
Introduction

- Action potential in the nervous system
  - Action potential versus resting potential



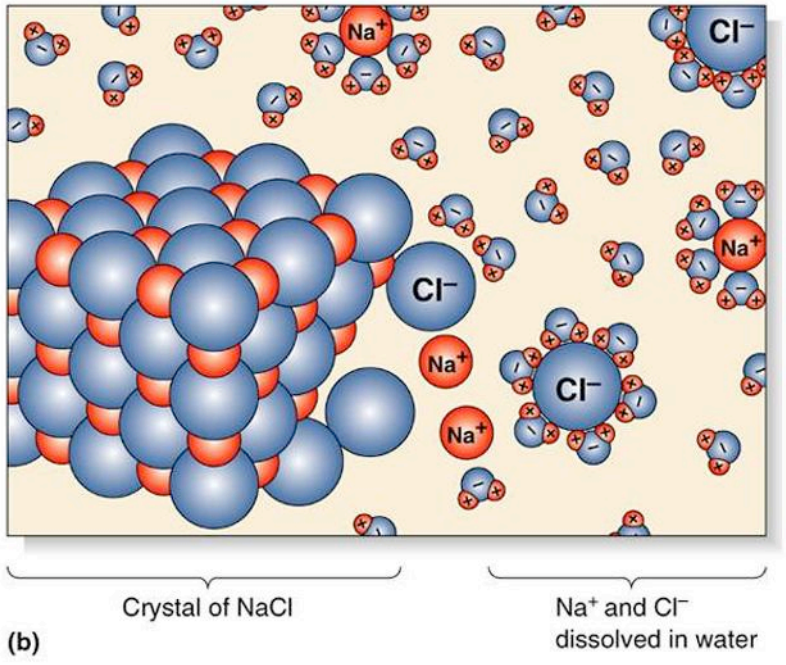
The Cast of Chemicals

- Cytosolic and Extracellular Fluid
  - Water
    - Key ingredient in intracellular and extracellular fluid
    - Key feature — water is a polar solvent
      - Oxygen acquires a net positive charge
      - Hydrogen acquires a net negative charge



The Cast of Chemicals

- Cytosolic and Extracellular Fluid
  - Ions: atoms or molecules with a net electrical charge
    - Cations: positive charge
    - Anions: negative charge
    - Spheres of hydration

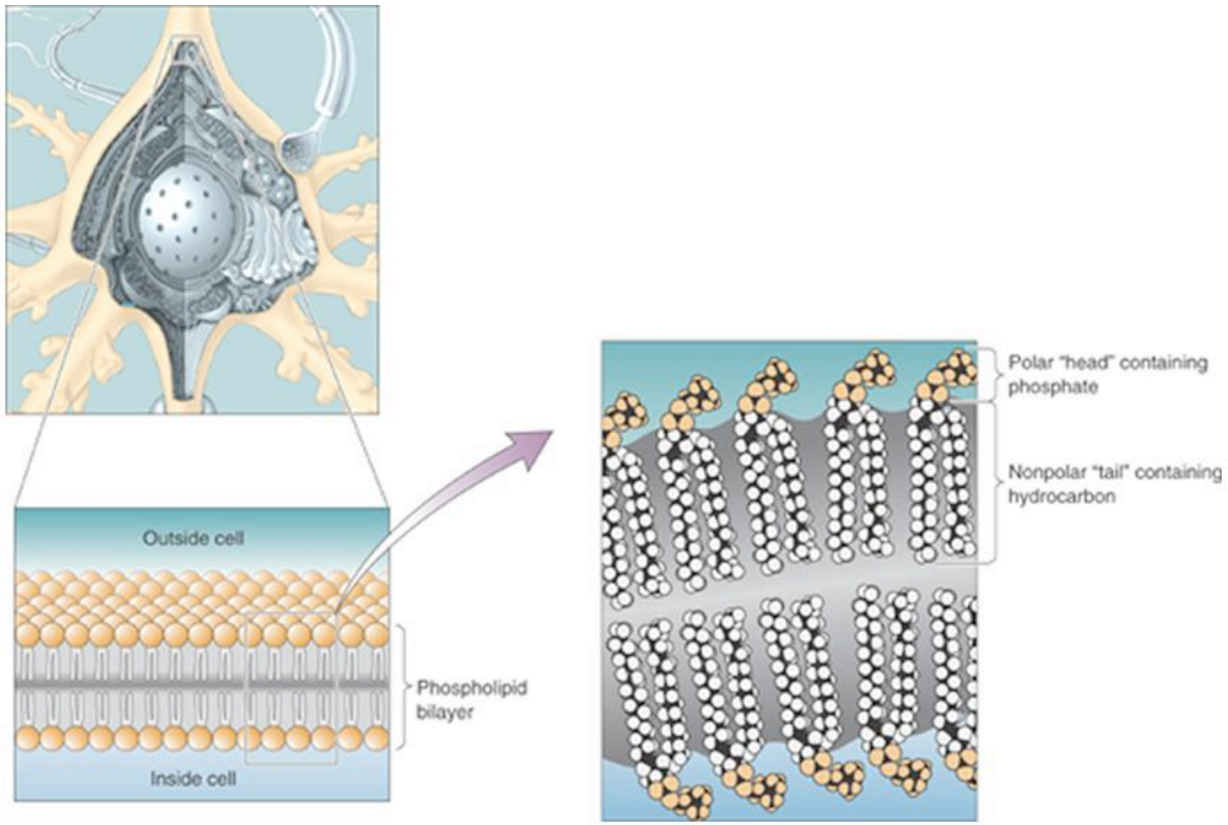


The Cast of Chemicals

- The Phospholipid Membrane
  - Hydrophilic
    - Dissolve in water due to uneven electrical charge, *e.g.,* salt
  - Hydrophobic
    - Does not dissolve in water due to even electrical charge, *e.g.,* oil
  - Lipids are hydrophobic
    - Contribute to resting and action potentials

The Cast of Chemicals

- The Phospholipid Membrane
  - The Phospholipid Bilayer

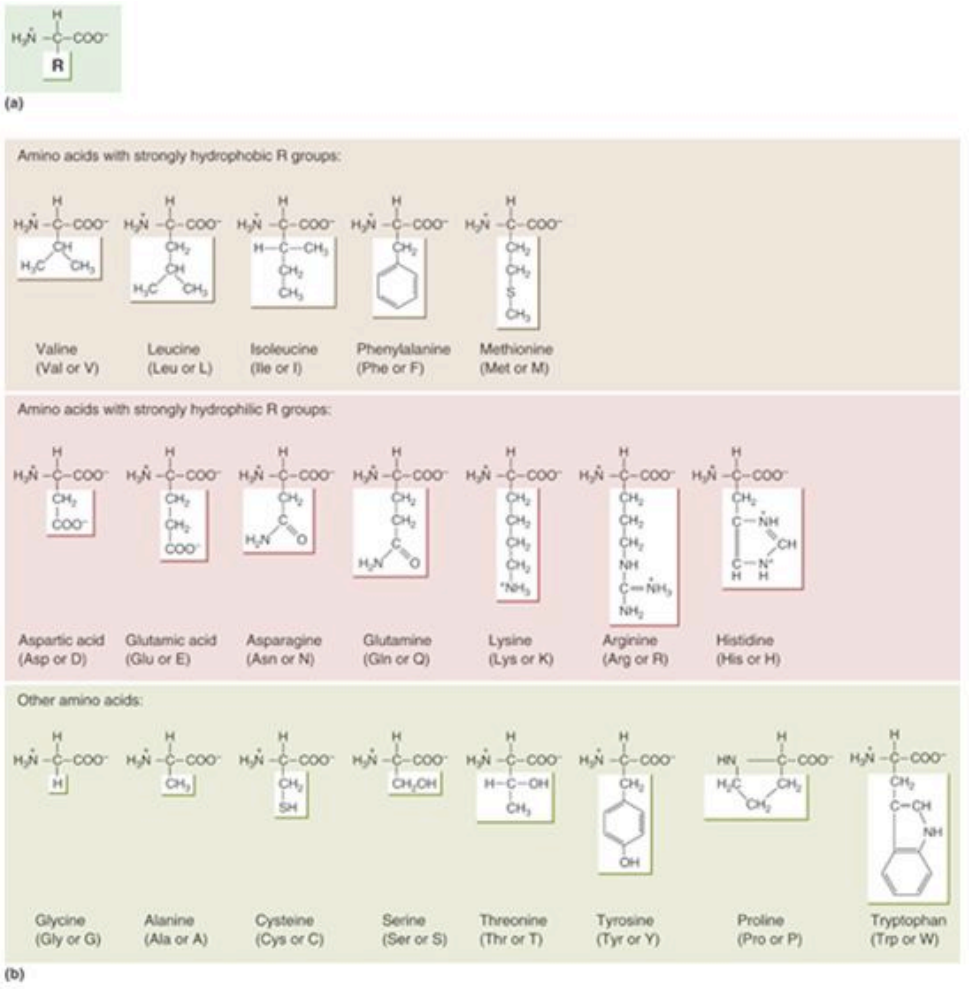


The Cast of Chemicals

- Protein
  - Molecules
    - Enzymes
    - Cytoskeletal elements
    - Receptors
    - Special transmembrane proteins
      - Control resting and action potentials

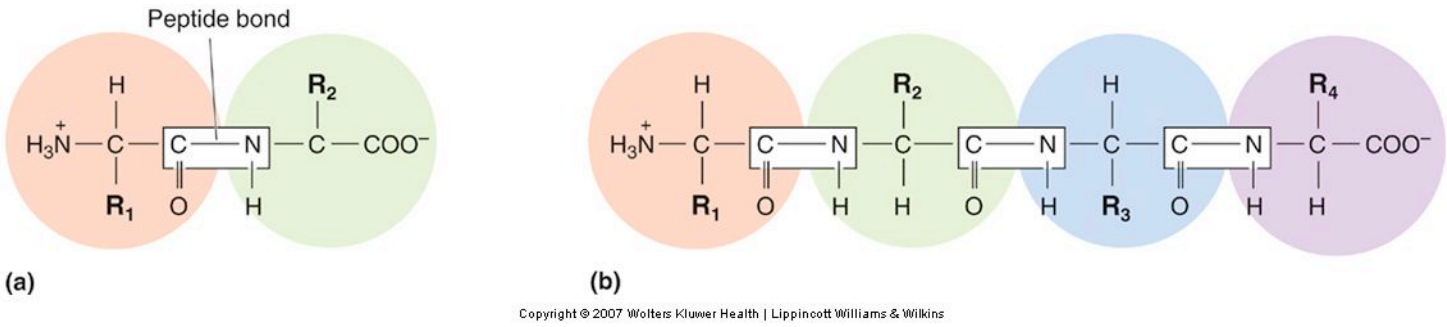
The Cast of Chemicals

- Protein
  - Structure
    - Amino acids
    - Alpha carbon and R groups



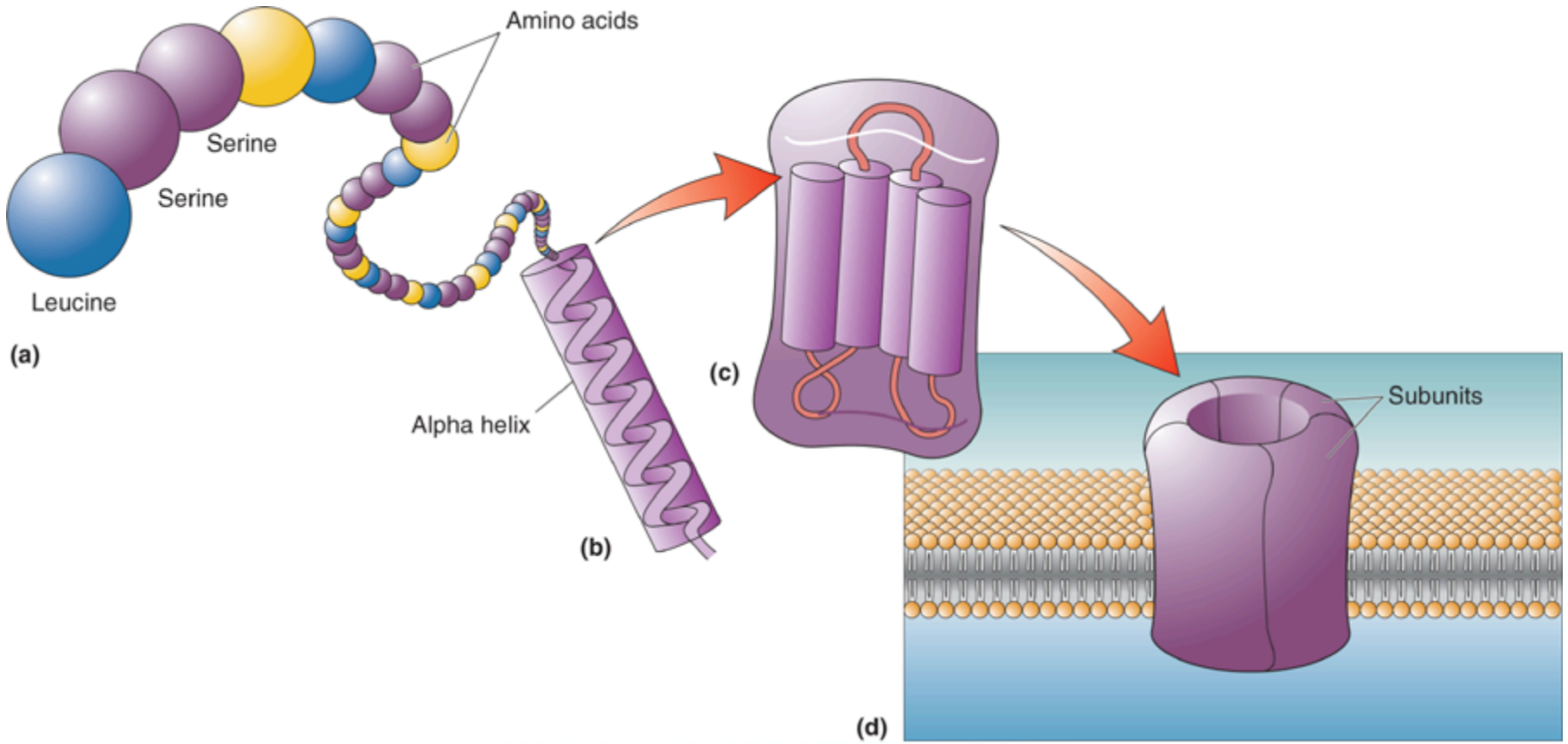
The Cast of Chemicals

- Protein
  - Structure (Cont'd)
    - Peptide bonds and polypeptides



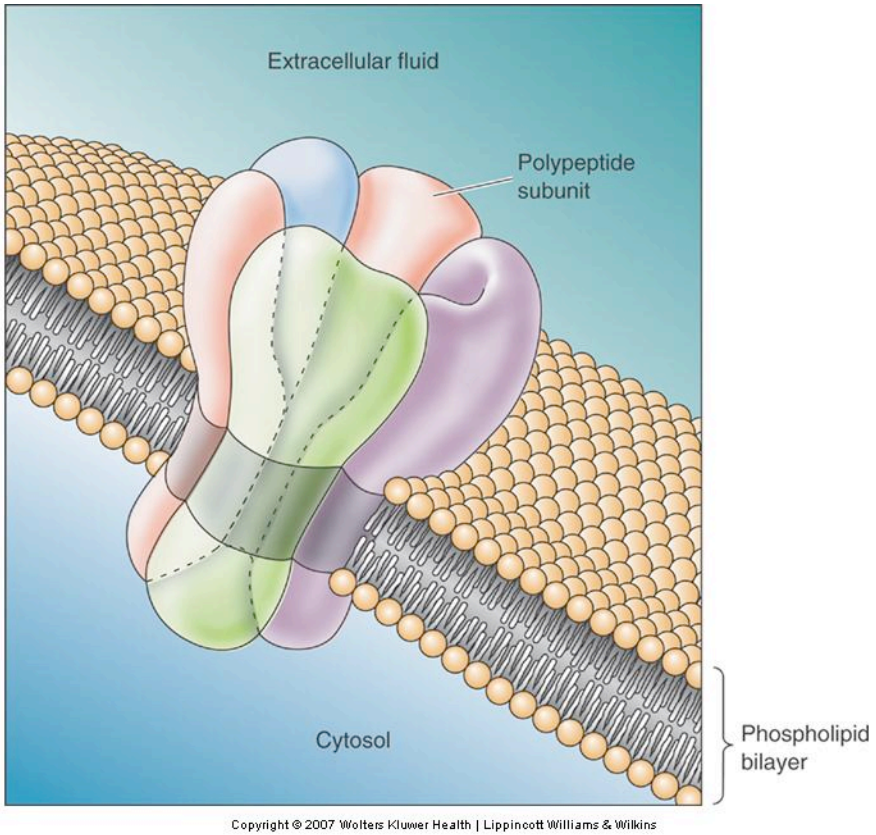
The Cast of Chemicals

- Protein
  - Structure (Cont'd)
    - Four levels of protein structure
    - Primary, Secondary, Tertiary, Quaternary



The Cast of Chemicals

- Protein
  - Channel proteins
    - Polar R groups and nonpolar R groups
    - Ion selectivity and gating

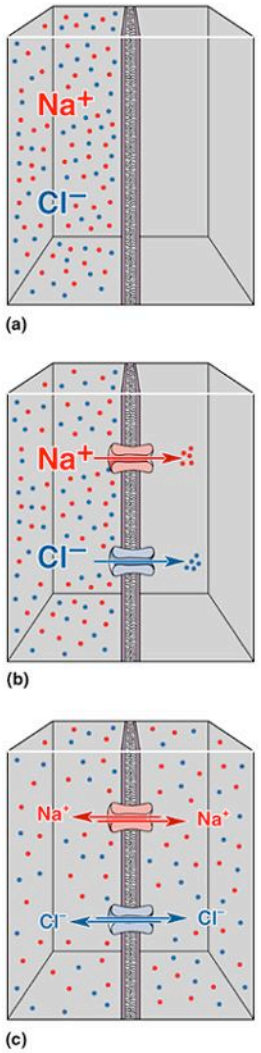


The Cast of Chemicals

- Protein
  - Ion pumps
    - Formed by membrane spanning proteins
    - Uses energy from ATP breakdown
    - Neuronal signaling

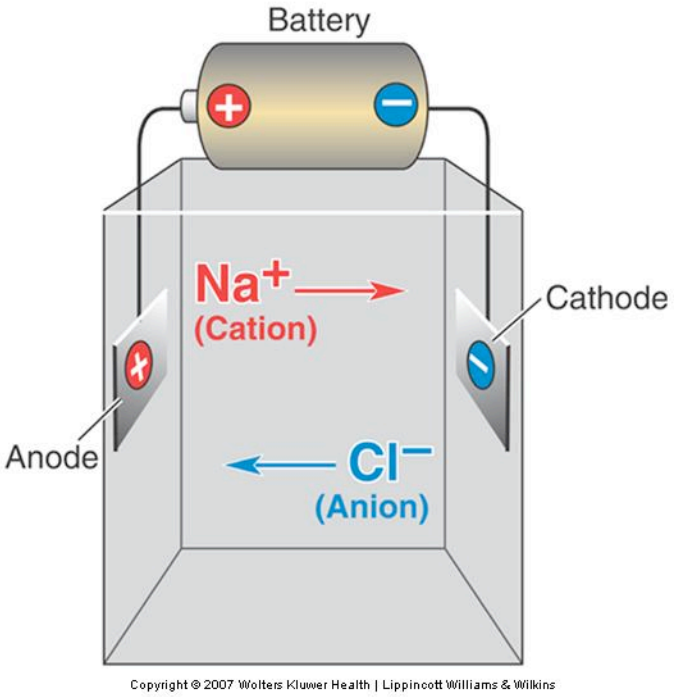
The Movement of Ions

- Diffusion
  - Dissolved ions distribute evenly
  - Ions flow down concentration gradient when:
    - Channels permeable to specific ions
    - Concentration gradient across the membrane



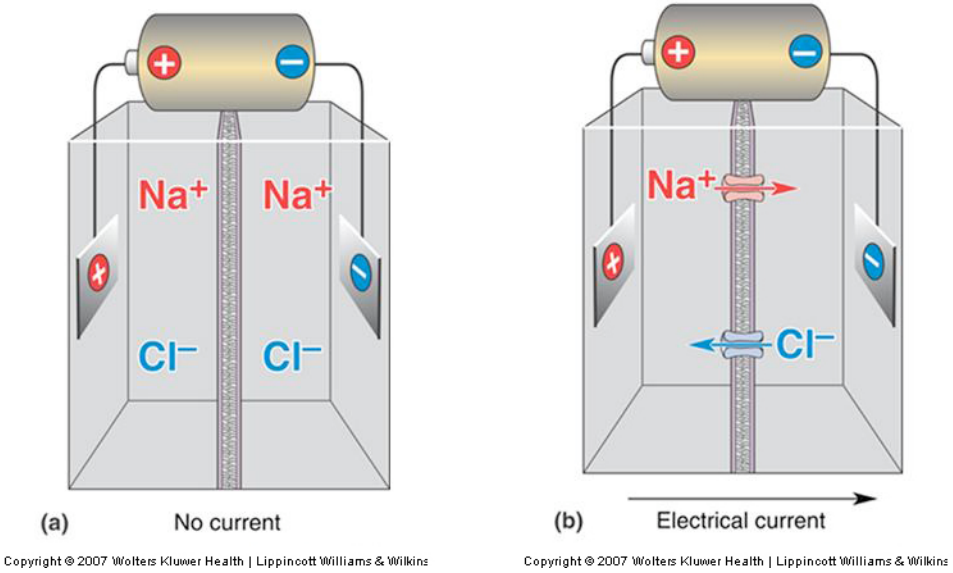
The Movements of Ions

- Electricity
  - Electrical current influences ion movement
  - Electrical conductance (g) and resistance (R); R = 1/g
  - Electrical potential (voltage)



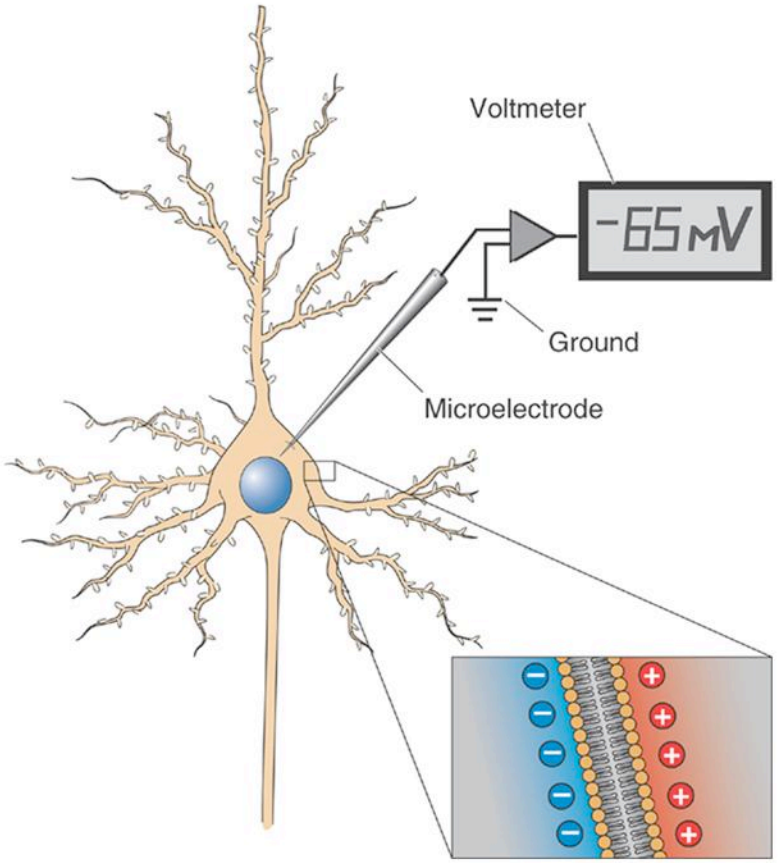
The Cast of Chemicals

- Electricity
  - Electrical current flow across a membrane
  - Ohm's law I = gV



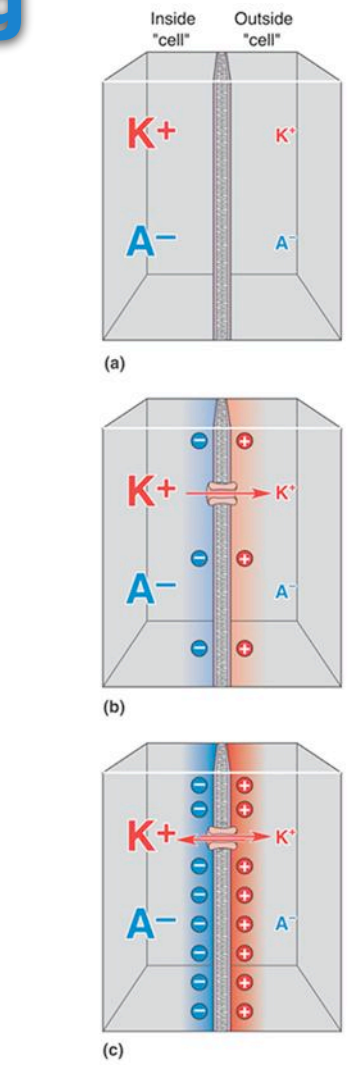
The Ionic Basis of The Resting Membrane Potential

- Membrane potential: voltage across the neuronal membrane



The Ionic Basis of The Resting Membrane Potential

- Equilibrium Potential (E_{ion})
  - No net movement of ions when separated by a phospholipid membrane
  - Equilibrium reached when K^+ channels inserted into the phospholipid bilayer
  - Electrical potential difference that exactly balances ionic concentration gradient

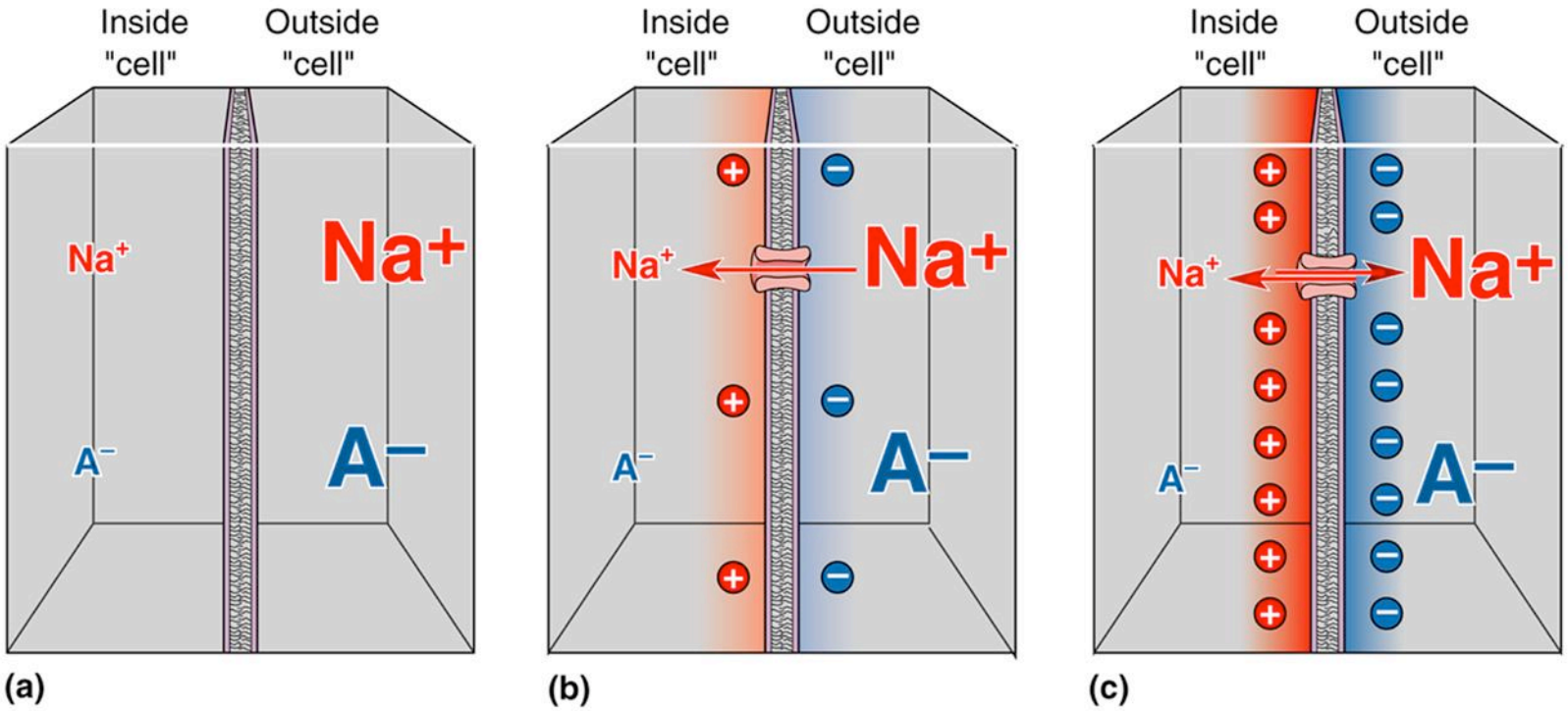


The Ionic Basis of The Resting Membrane Potential

- Equilibrium Potentials (Cont'd)
  - Four important points
    - Large changes in V_m
      - Minuscule changes in ionic concentrations
    - Net difference in electrical charge
      - Inside and outside membrane surface
    - Rate of movement of ions across membrane
      - Proportional $V_m - E_{ion}$
    - Concentration difference known: equilibrium potential can be calculated

The Ionic Basis of The Resting Membrane Potential

- Equilibrium Potential (Cont'd)
  - Inside positively charged relative to outside



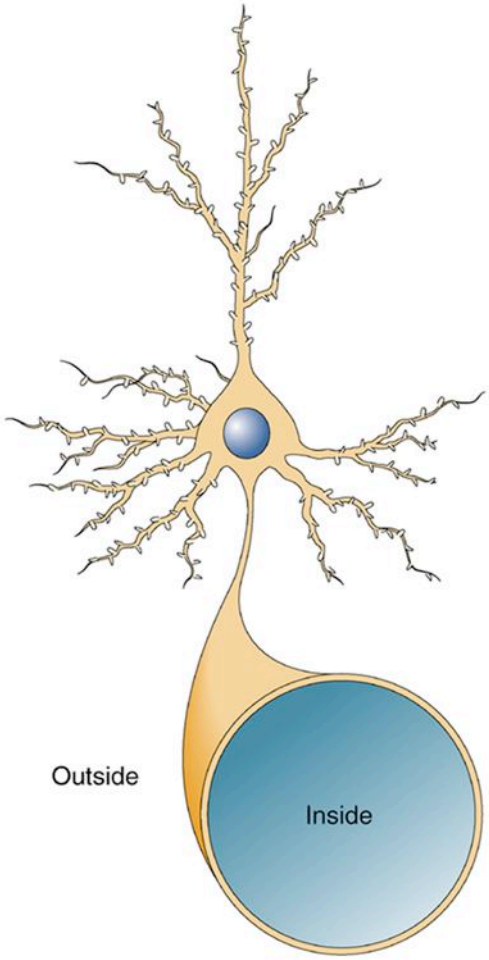
The Ionic Basis of The Resting Membrane Potential

- Equilibrium Potentials (Cont'd)
  - The Nernst Equation
    - Calculates the *exact* value of the equilibrium potential for each ion in mV
    - Takes into consideration:
      - Charge of the ion
      - Temperature
      - Ratio of the external and internal ion concentrations

The Ionic Basis of The Resting Membrane Potential

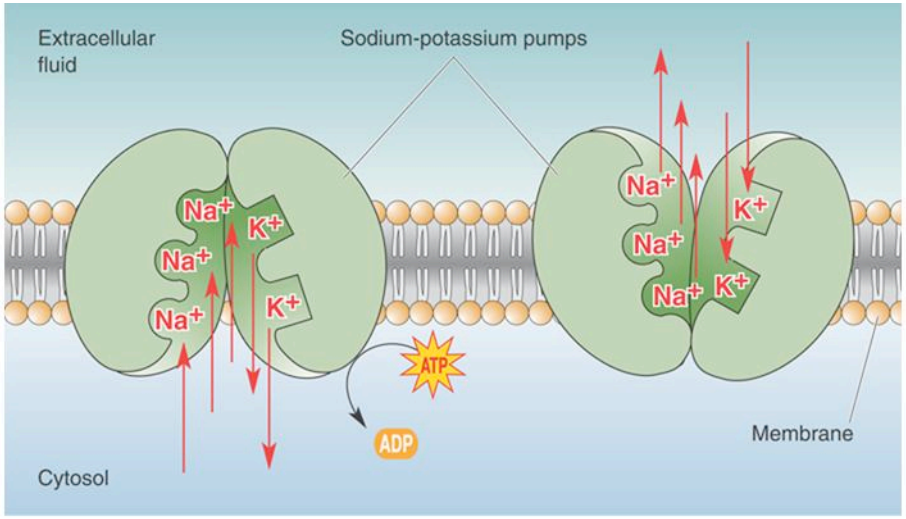
- The Distribution of Ions Across The Membrane
  - K^+ more concentrated on inside, Na^+ and Ca^{2+} more concentrated outside

Ion	Concentration outside (in mM)	Concentration inside (in mM)	Ratio Out : In	E_{ion} (at 37°C)
K^+	5	100	1 : 20	−80 mV
Na^+	150	15	10 : 1	62 mV
Ca^{2+}	2	0.0002	10,000 : 1	123 mV
Cl^-	150	13	11.5 : 1	−65 mV



The Ionic Basis of The Resting Membrane Potential

- The sodium-potassium pump
  - Enzyme - breaks down ATP when Na present
  - Calcium pump: Actively transports Ca^{2+} out of cytosol



The Ionic Basis of The Resting Membrane Potential

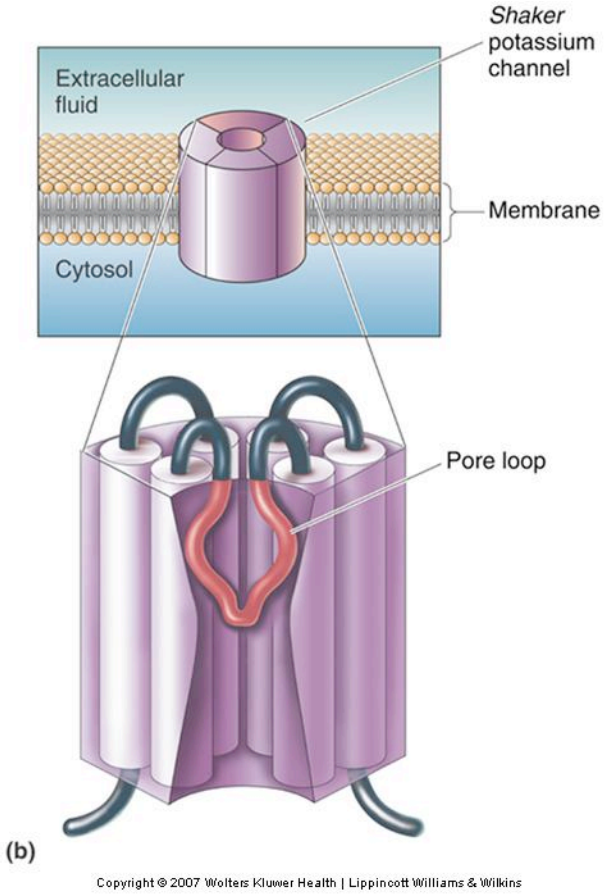
- Relative Ion Permeabilities of the Membrane at Rest
  - Neurons permeable to more than one type of ion
  - Membrane permeability determines membrane potential
  - Goldman equation
    - Takes into account permeability of membrane to different ions

The Ionic Basis of The Resting Membrane Potential

- Relative Ion Permeabilities of the Membrane at Rest
  - Selective permeability of potassium channels — key determinant in resting membrane potential
  - Many types of Potassium Channel
    - Lily and Yuh Nung Jan — amino acid sequences; family of K^+ channels
    - *e.g.,* Shaker Potassium Channel

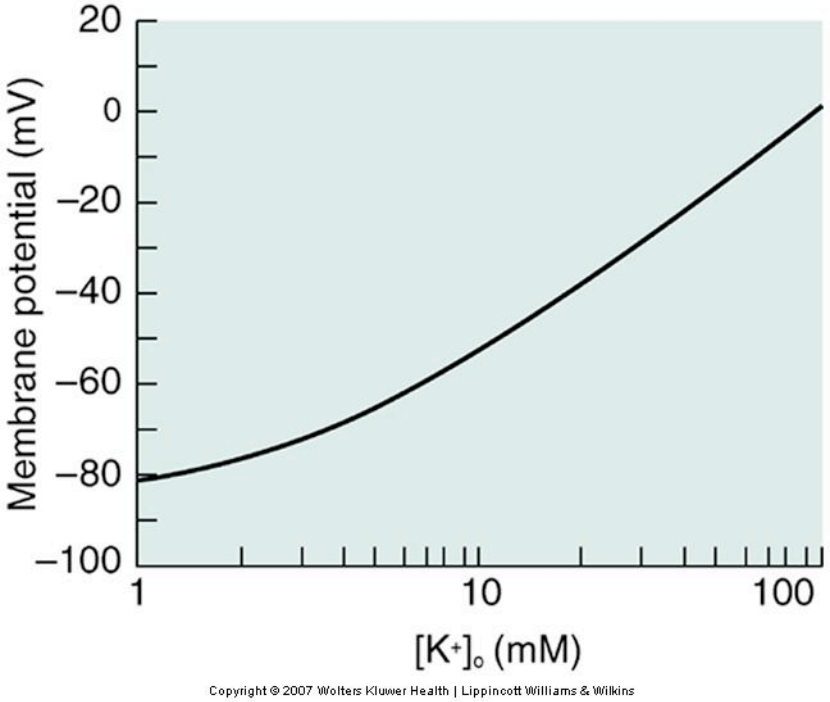
The Ionic Basis of The Resting Membrane Potential

- Relative Ion Permeabilities of the Membrane at Rest
  - K^+ channels: 4 subunits
  - Channel selectively permeable to K^+ ions
  - MacKinnon — 2003 Nobel Prize
    - Mutations of specific K^+ channels; inherited neurological disorders



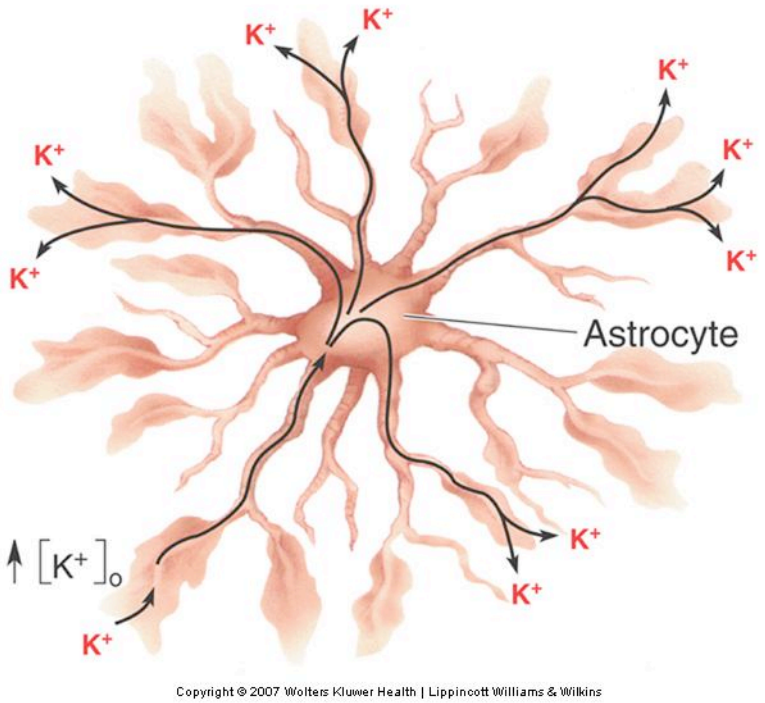
The Ionic Basis of The Resting Membrane Potential

- Relative Ion Permeabilities of the Membrane at Rest
  - Resting membrane potential is close to E_K because it is mostly permeable to K^+
  - Membrane potential sensitive to extracellular K^+
  - Increased extracellular K^+ depolarizes membrane potential



The Ionic Basis of The Resting Membrane Potential

- Relative Ion Permeabilities of the Membrane at Rest
  - Regulating the External Potassium Concentration
    - Blood-Brain barrier
    - Potassium spatial buffering



Concluding Remarks

- Activity of the sodium-potassium pump
- Large K^+ concentration gradient
- Electrical potential difference across the membrane
  - Similar to a battery
- Potassium channels
  - Contribute to resting potential
- Roles of ion pumps

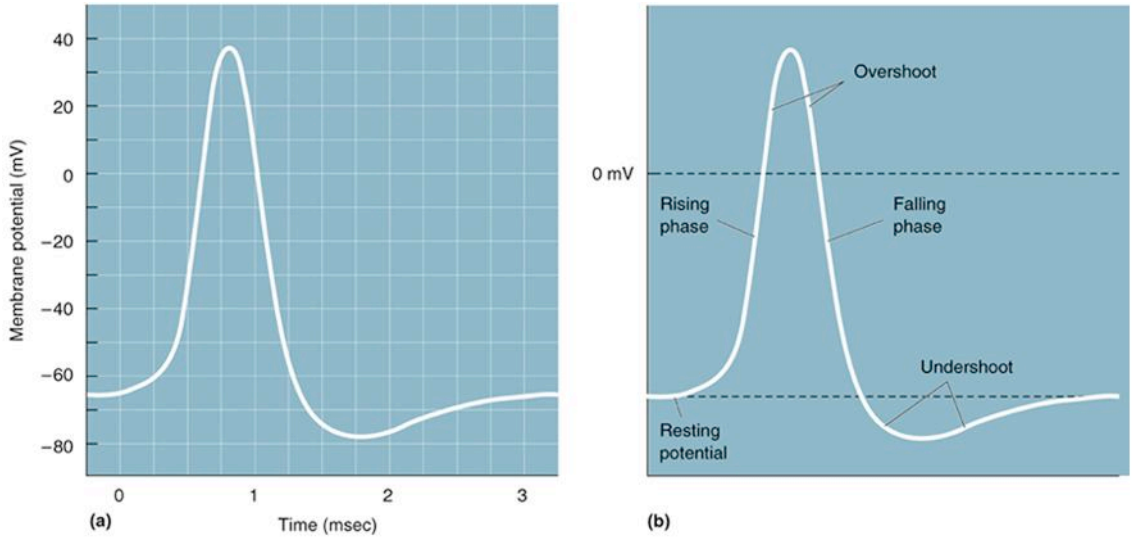
Chapter 4: The Action Potential

Introduction

- Action Potential in the Nervous System
  - Conveys information over long distances
  - Cytosol has negative charge relative to extracellular space
  - Neural code — frequency and pattern
  - Action potential
    - Spike
    - Nerve impulse
    - Discharge

Properties of the Action Potential

- The Ups and Downs of an Action Potential
  - Oscilloscope to visualize an AP
    - Rising phase, overshoot, falling phase, and undershoot

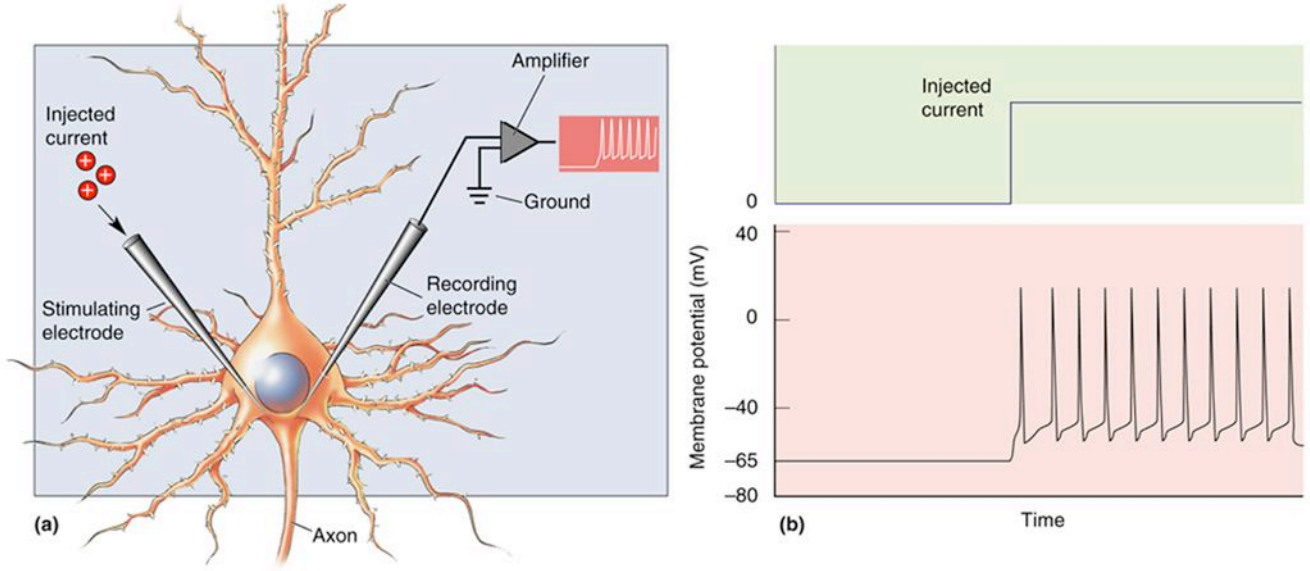


Properties of the Action Potential

- The Generation of an Action Potential
  - Caused by depolarization of membrane beyond threshold
  - "All-or-none"
  - Chain reaction
    - *e.g.,* puncture foot, stretch membrane of nerve fibers
      - 0pens Na^+-permeable channels→ Na^+ influx→ depolarized membrane→ reaches threshold→ action potential

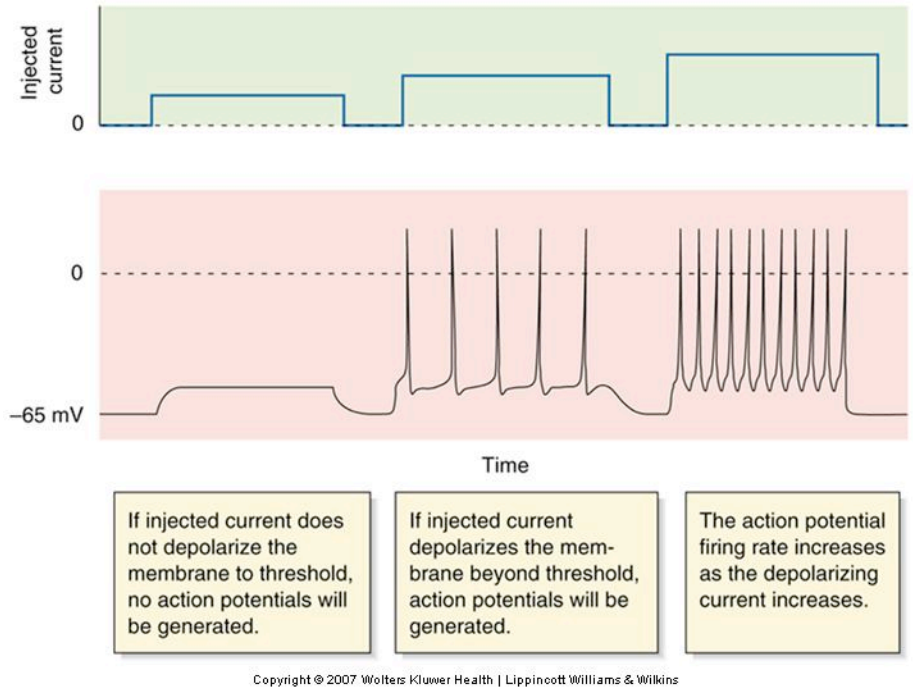
Properties of the Action Potential

- The Generation of Multiple Action Potentials
  - Artificially inject current into a neuron using a microelectrode



Properties of the Action Potential

- The Generation of Multiple Action Potentials (Cont'd)
  - Firing frequency reflects the magnitude of the depolarizing current

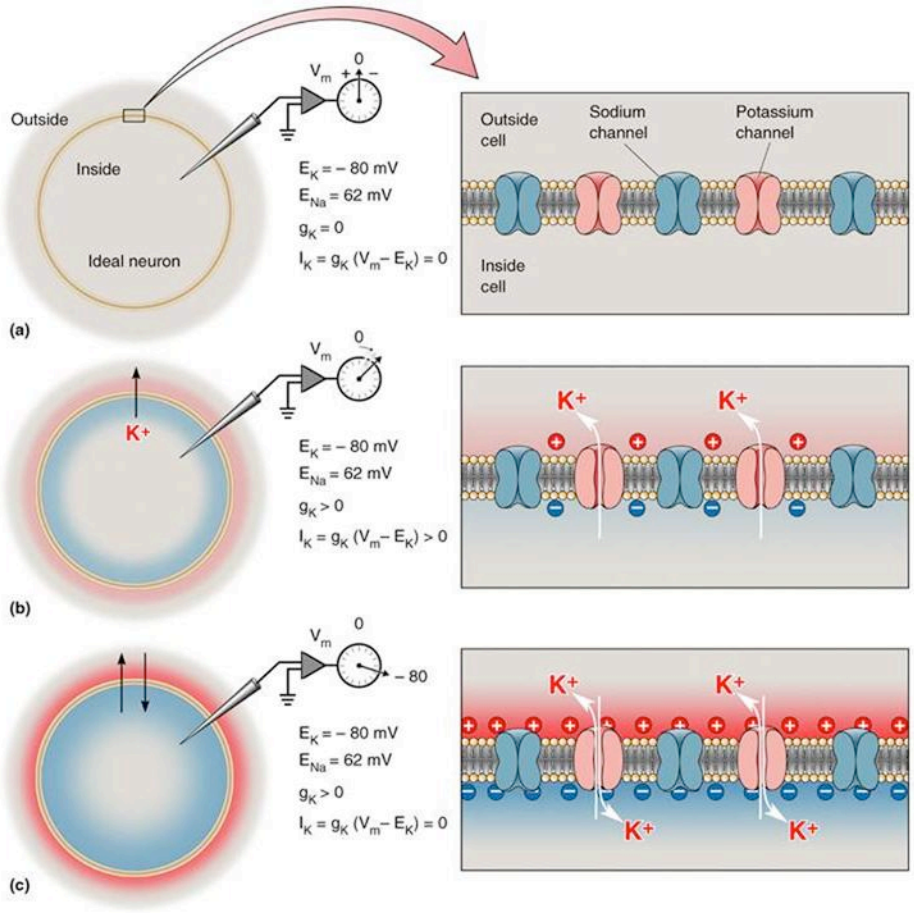


The Action Potential, In Theory

- Depolarization — influx of Na^+ — and repolarization — efflux of K^+
- Membrane Currents and Conductances
  - Current
    - The net movement of K^+ across membrane
  - Potassium channel number
    - Proportional to electrical conductances
  - Membrane potassium current
    - Flow and driving force

The Action Potential, In Theory

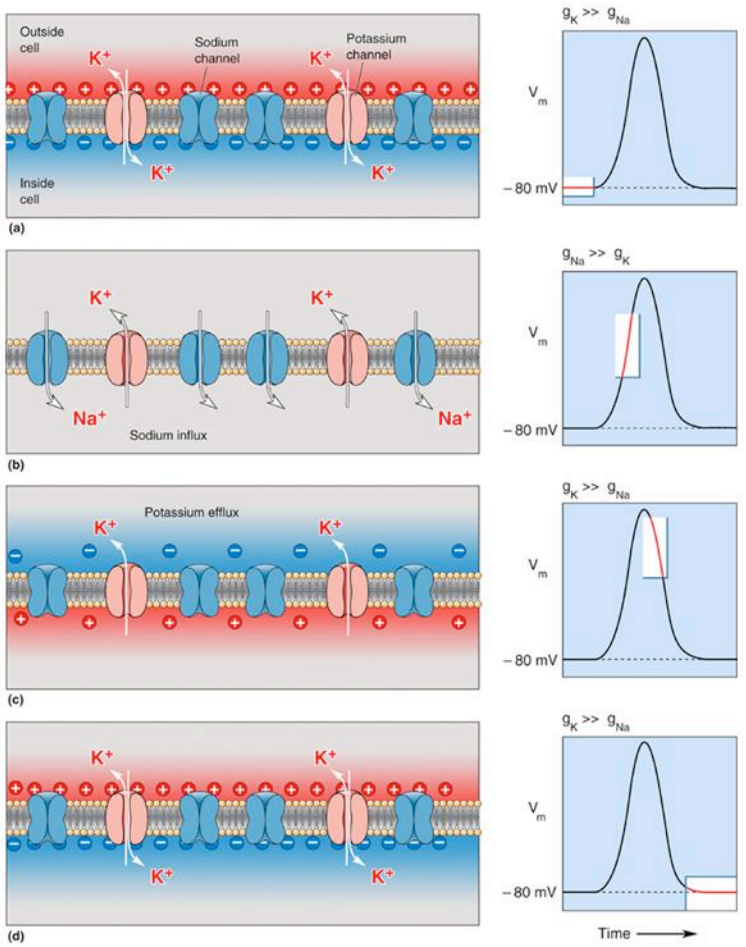
- Membrane Currents and Conductances (Cont'd)



The Action Potential, In Theory

- The *ins* and *outs* of an action potential

- Rising phase: inward sodium current
  - Falling phase: Outward potassium current

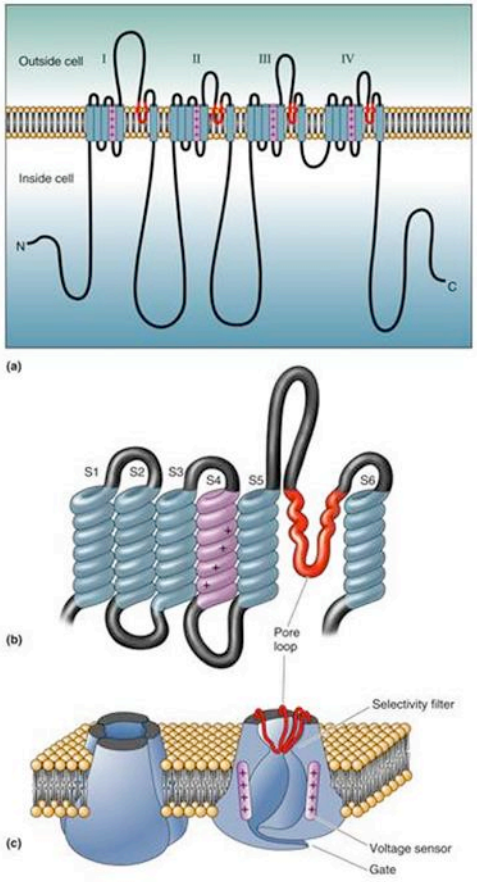


The Action Potential, In Reality

- The Generation of an Action Potential
  - Hodgkin and Huxley
    - Voltage Clamp: "Clamp" membrane potential at any chosen value
    - Rising phase → transient increase in g_{Na}, influx of Na^+ ions
    - Falling phase → increase in g_K, efflux of K^+ ions
    - Existence of sodium "gates" in the axonal membrane

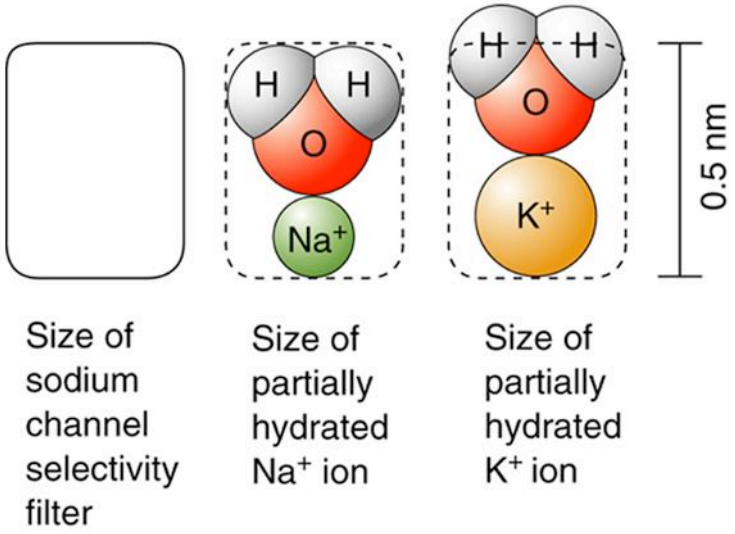
The Action Potential, In Reality

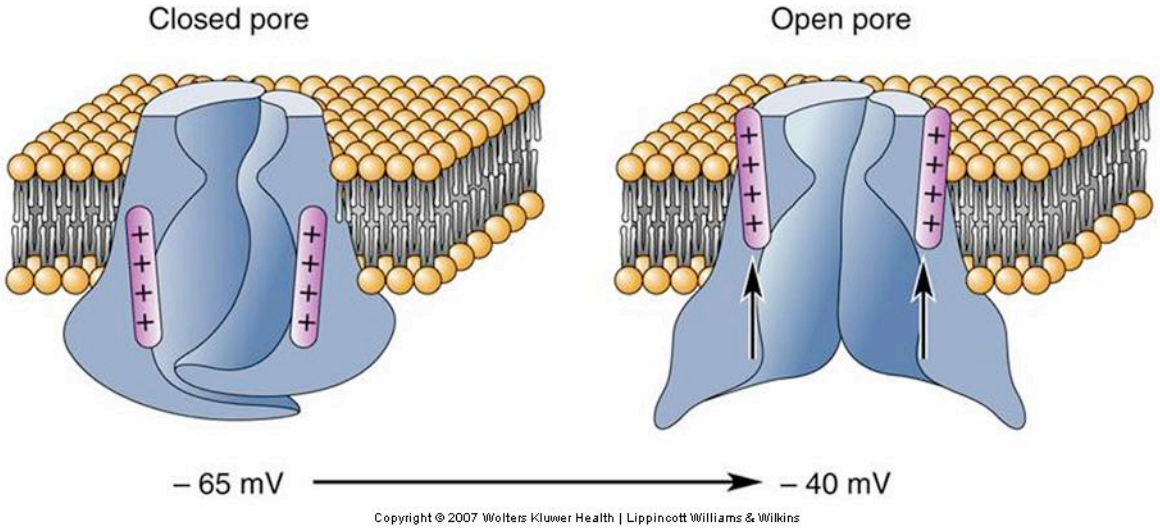
- The Voltage-Gated Sodium Channel
  - Structure — transmembrane domains and ion-selective pore



The Action Potential, In Reality

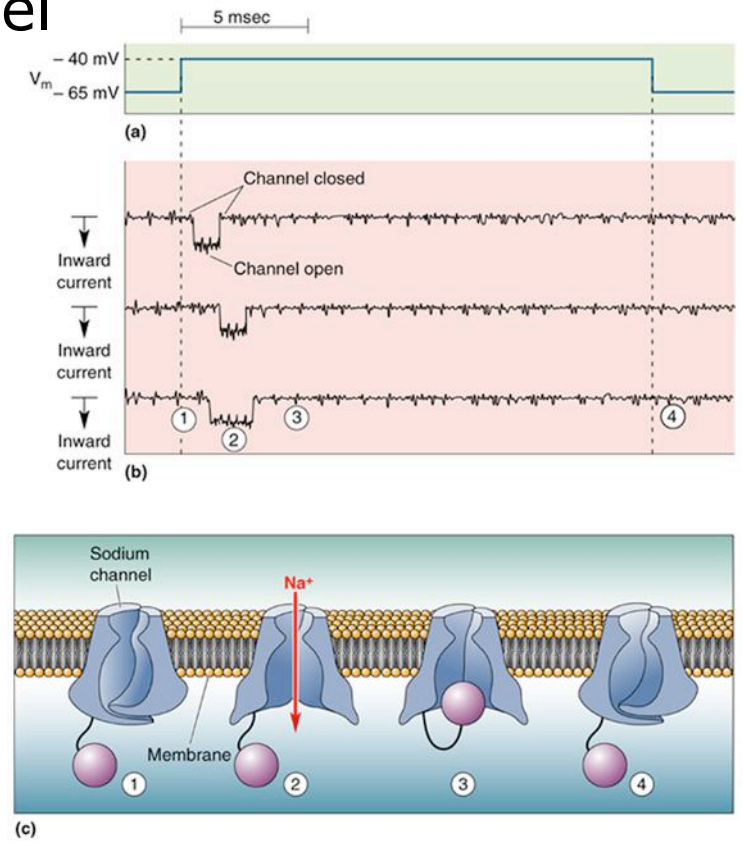
- The Voltage-Gated Sodium Channel (Cont'd)
  - Structure – gating and pore selectivity





The Action Potential, In Reality

- The Voltage-Gated Sodium Channel
  - Patch-clamp method (Erwin Neher)



The Action Potential, In Reality

- The Voltage-Gated Sodium Channel (Cont'd)
  - Functional Properties of the Sodium Channel
    - Open with little delay
    - Stay open for about 1 msec
    - Cannot be open again by depolarization
- Absolute refractory period: Channels are inactivated

The Action Potential, In Reality

- The Voltage-Gated Sodium Channel (Cont'd)
  - In genetic disease — channelopathies
    - *e.g.,* Generalized epilepsy with febrile seizures
  - Toxins as experimental tools
    - Toshio Narahashi — ion channel pharmacology
    - Puffer fish: Tetrodotoxin — clogs Na^+ permeable pore
    - Red Tide: Saxitoxin — Na^+ channel-blocking toxin

The Action Potential, In Reality

- The Voltage-Gated Sodium Channel (Cont'd)
  - Varieties of toxins
    - Batrachotoxin (frog): Blocks inactivation so channels remain open
    - Veratridine (lilies): Inactivates channels
    - Aconitine (buttercups): Inactivates channels
  - Differential toxin binding sites: clues about 3-D structure of channels

The Action Potential, In Reality

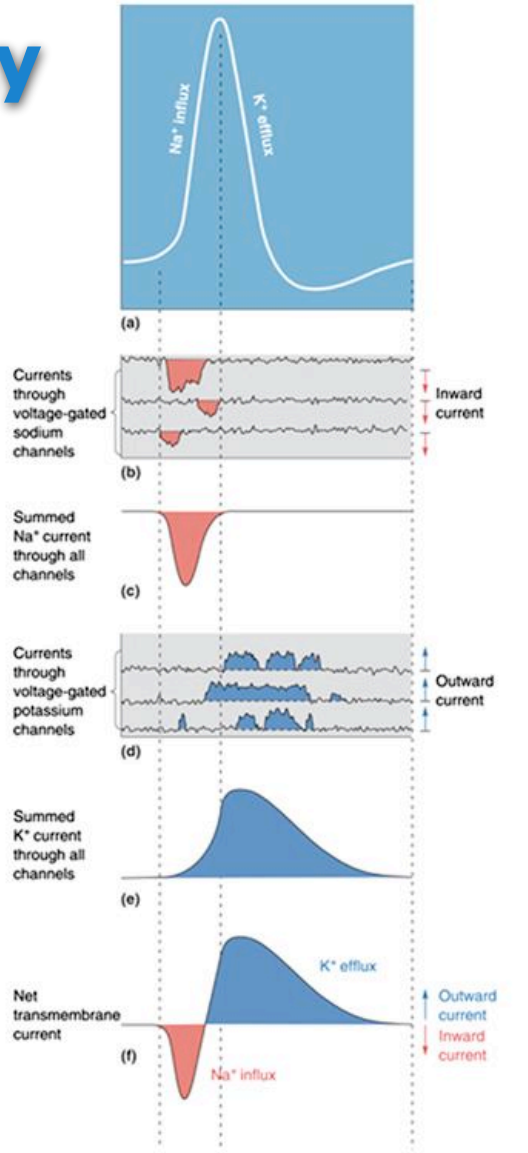
- Voltage-Gated Potassium Channels
  - Potassium vs. sodium gates
    - Both open in response to depolarization
    - Potassium gates open later than sodium gates
  - Delayed rectifier
    - Potassium conductance serves to rectify or reset membrane potential
  - Structure: four separate polypeptide subunits join to form a pore

The Action Potential, In Reality

- Key Properties of the Action Potential
  - Threshold
  - Rising phase
  - Overshoot
  - Falling phase
  - Undershoot
  - Absolute refractory period
  - Relative refractory period

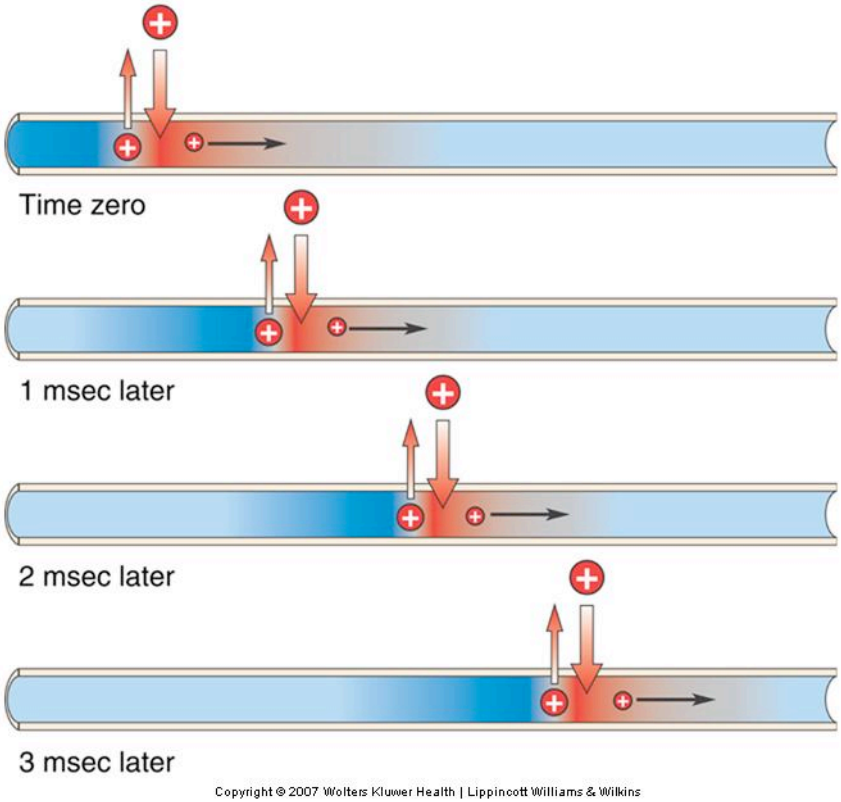
The Action Potential, In Reality

- Molecular basis of action potentials



Action Potential Conduction

- Propagation



Action Potential Conduction

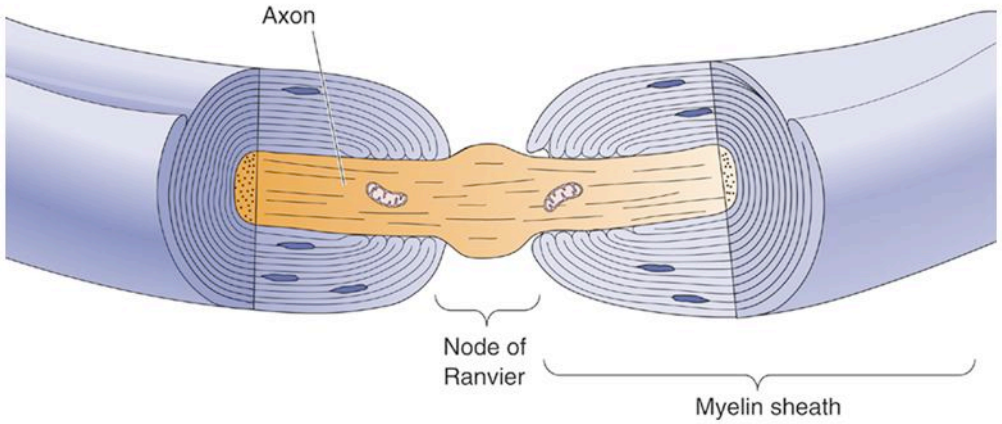
- Propagation of the action potential
  - Orthodromic: action potential travels in one direction - down axon to the axon terminal
  - Antidromic (experimental): Backward propagation
  - Typical conduction velocity: 10 m/sec
  - Length of action potential: 2 msec

Action Potential Conduction

- Factors Influencing Conduction Velocity
  - Spread of action potential along membrane
    - Dependent upon axon structure
  - Path of the positive charge
    - Inside of the axon (faster)
    - Across the axonal membrane (slower)
  - Axonal excitability
    - Axonal diameter (bigger = faster)
    - Number of voltage-gated channels

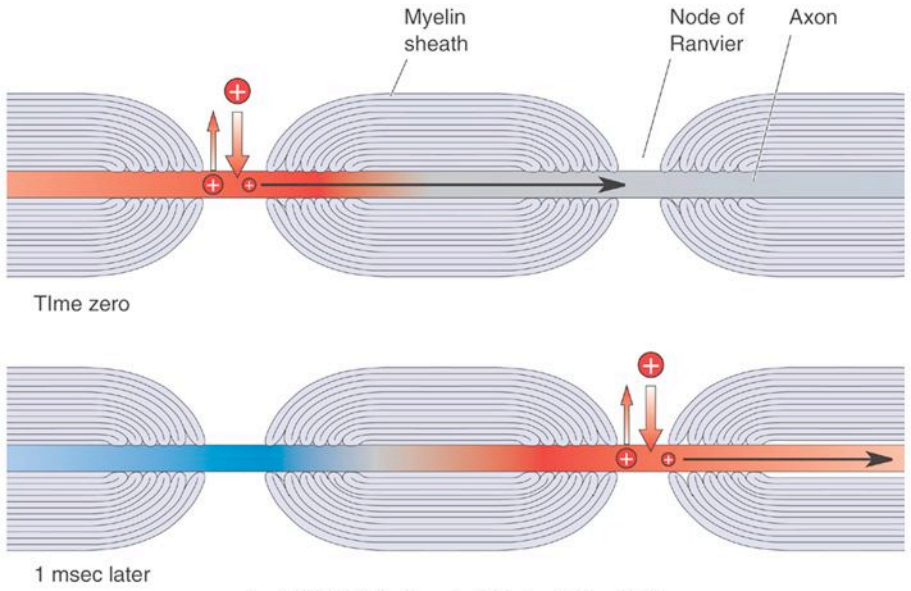
Action Potential Conduction

- Factors Influencing Conduction Velocity
  - Myelin: Layers of myelin sheath facilitate current flow
    - Myelinating cells
      - Schwann cells in the PNS
      - Oligodendroglia in CNS



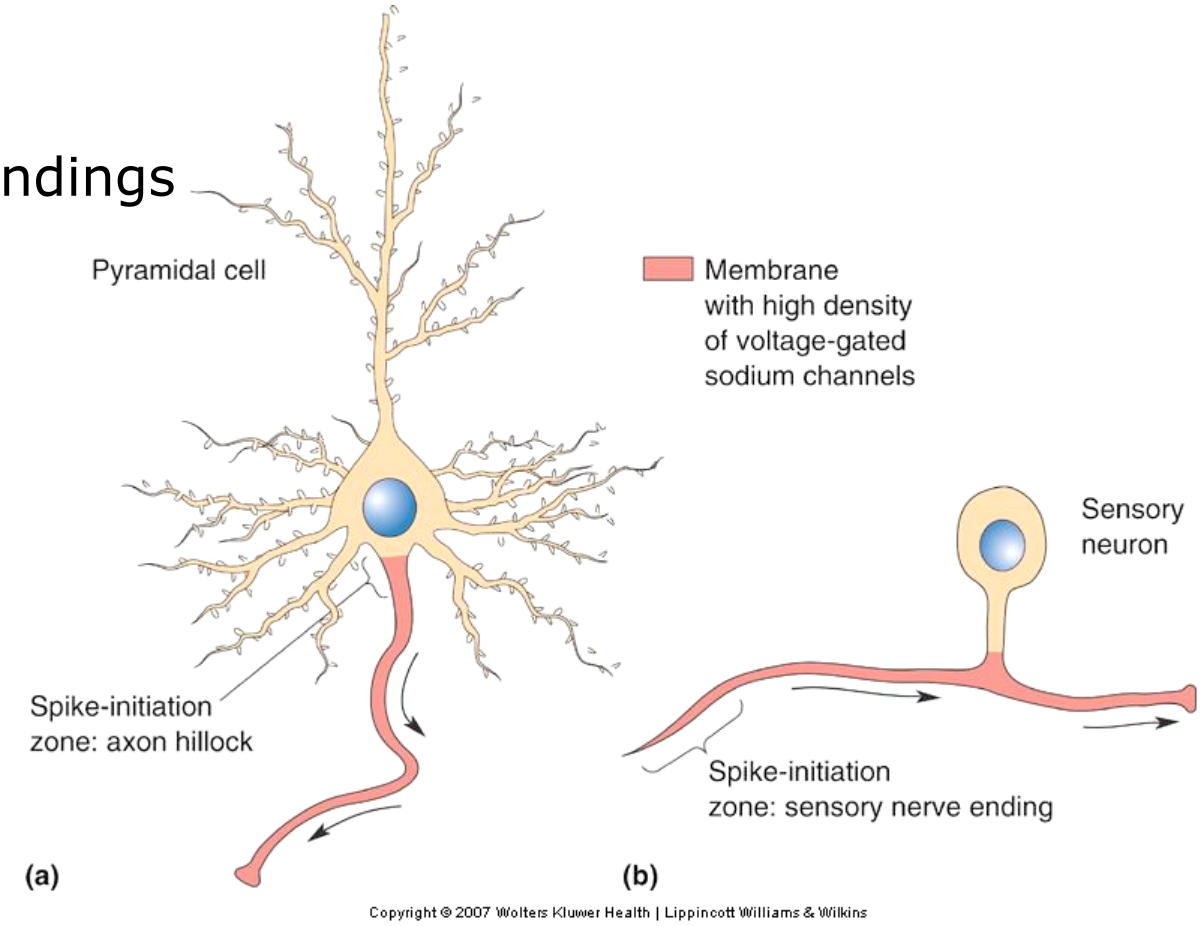
Action Potential Conduction

- Factors Influencing Conduction Velocity
  - Saltatory conduction at Nodes of Ranvier
  - Voltage gated sodium channels concentrated at nodes



Action Potentials, Axons, and Dendrites

- Spike-initiation zone
  - Sensory nerve endings
  - Axon hillock



Concluding Remarks

- Neuronal signal transmitted as the generation and regeneration of APs
  - *e.g.,* puncture the skin→ nerves stretch→ Na^+-channels open→ AP initiated and propagated→ information is "communicated" to next neuron across the membrane (synaptic transmission)
  - Emerging picture: the brain as an interconnected mesh of membranes
- Next: synaptic transmission-information transfer