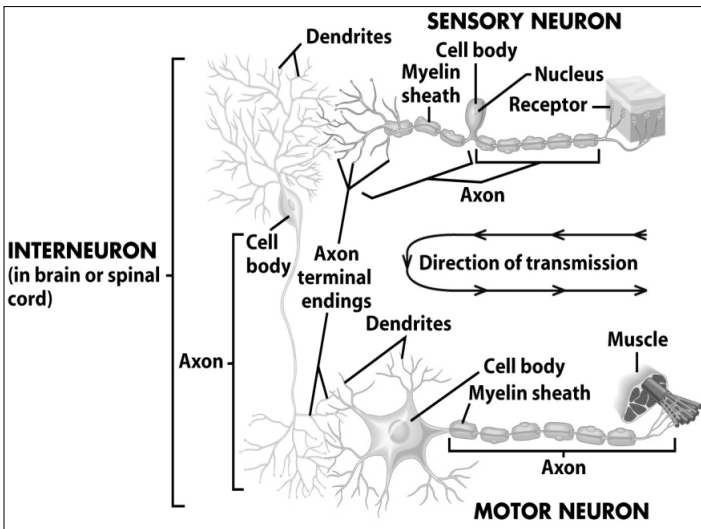


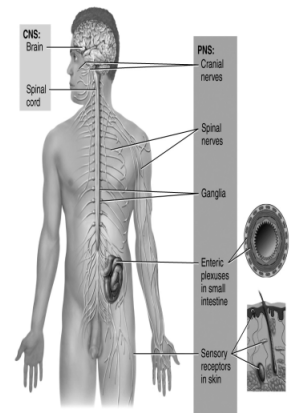
## Overview of the Nervous System

- The nervous system detects environmental changes that impact the body, then works in tandem with the endocrine system to respond to such events
  - It is responsible for all our behaviors, memories, and movement
  - It is able to accomplish all these functions because of the excitable characteristic of nervous tissue, which allows for the generation of nerve impulses (called action potentials)

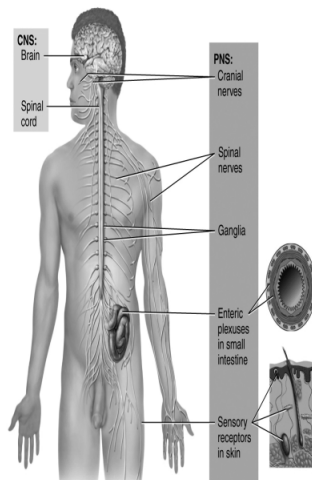


## Organization of the Nervous System

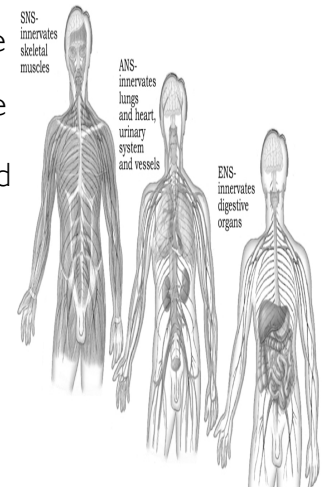
- Over 100 billion neurons and 10–50 times that number of support cells (called neuroglia) are organized into two main subdivisions:
  - The central nervous system (CNS)
  - The peripheral nervous system (PNS)



- The central nervous system (CNS) consists of the brain and spinal cord
- The peripheral nervous system (PNS) consists of all nervous tissue outside the CNS, including nerves, ganglia, enteric plexuses, and sensory receptors



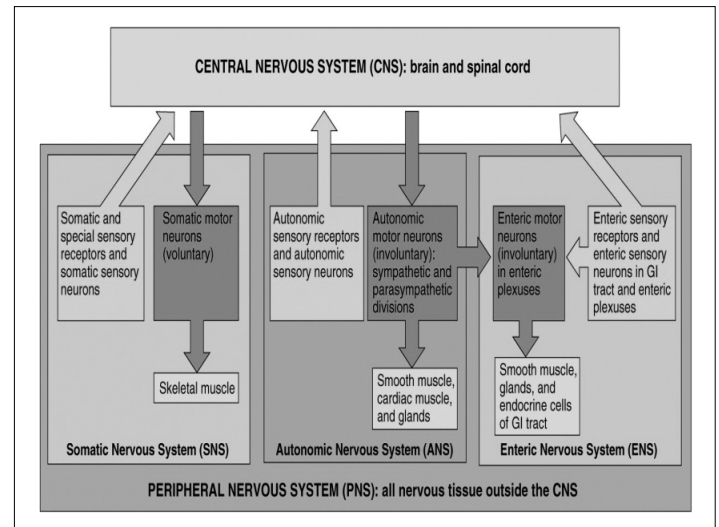
- Most signals that stimulate muscles to contract and glands to secrete originate in the CNS
- The PNS is further divided into:
  - A somatic nervous system (SNS)
  - An autonomic nervous system (ANS)
  - An enteric nervous system (ENS)



- The SNS consists of:
  - Somatic sensory (afferent) neurons that convey information from sensory receptors in the head, body wall and limbs towards the CNS
  - Somatic motor (efferent) neurons that conduct impulses away from the CNS towards the skeletal muscles under voluntary control in the periphery
  - Interneurons are any neurons that conduct impulses between afferent and efferent neurons within the CNS

- The ANS consists of:
  - Sensory neurons that convey information from autonomic sensory receptors located primarily in visceral organs like the stomach or lungs to the CNS
  - Motor neurons under involuntary control conduct nerve impulses from the CNS to smooth muscle, cardiac muscle, and glands
  - The motor part of the ANS consists of two branches which usually have opposing actions:
    - the sympathetic division
    - the parasympathetic division

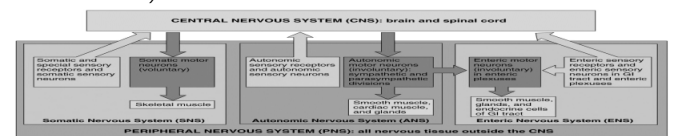
- The operation of the ENS, the “brain of the gut”, involuntarily controls GI propulsion, and acid and hormonal secretions
- Once considered part of the ANS, the ENS consists of over 100 million neurons in enteric plexuses that extend most of the length of the GI tract



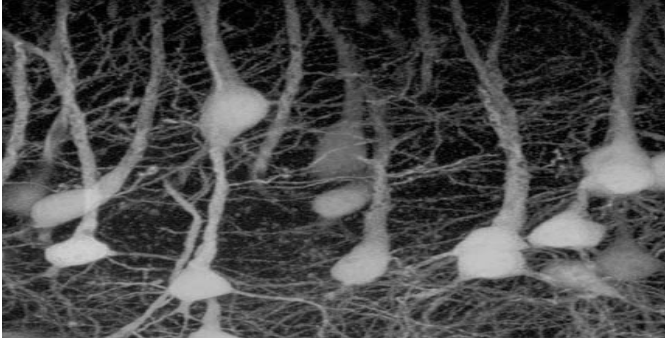
- Ganglia are small masses of neuronal cell bodies located outside the brain and spinal cord, usually closely associated with cranial and spinal nerves
- There are ganglia which are somatic, autonomic, and enteric (that is, they contain those types of neurons)

## Functions of the Nervous System

- Everything done in the nervous system involves 3 fundamental steps:
  - A sensory function detects internal and external stimuli (sensory function)
  - An interpretation is made (analysis - integrative function)
  - A motor response occurs (reaction - motor function)

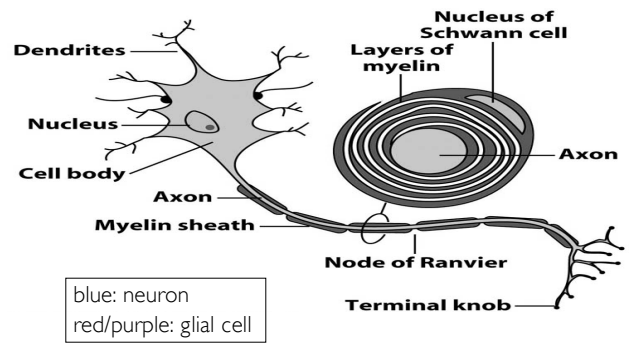


# Histology of Nervous Tissue



Photomicrograph showing neurons in a network

- The Schwann cell depicted in red/purple is one of 6 types of neuroglia that we will study shortly

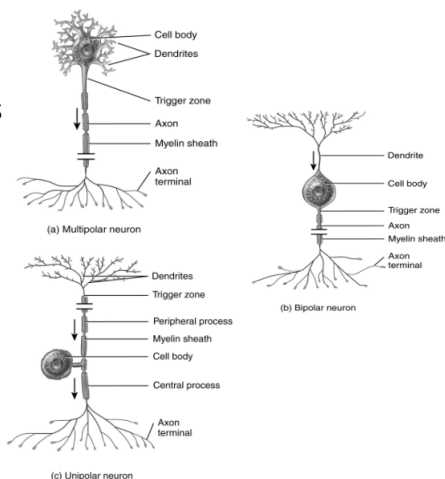


- Neurons and neuroglia combine in a variety of ways in different regions of the nervous system
  - Neurons are the real “functional unit” of the nervous system, forming complex processing networks within the brain and spinal cord that bring all regions of the body under CNS control
  - Neuroglia, though smaller than neurons, greatly outnumber them
    - They are the “glue” that supports and maintains the neuronal networks

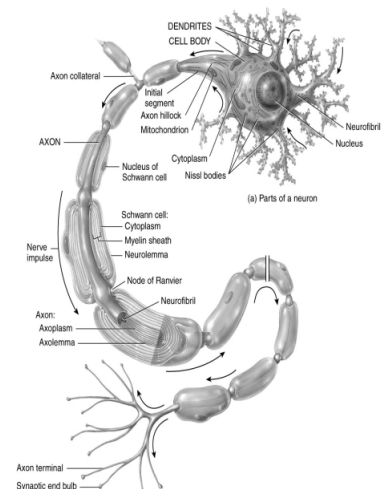
## Neurons

- As the “thinking” cells of the brain, each neuron does, in miniature, what the entire nervous system does as an organ:
  - Receive, process and transmit information by manipulating the flow of charge across their membranes
- Exhibit electrical excitability and are responsible for functions like sensing, thinking, remembering, muscle activity, and regulating glandular secretions

- Though there are several different types of neurons, most have:
  - A cell body
  - An axon
  - Dendrites
  - Axon terminals

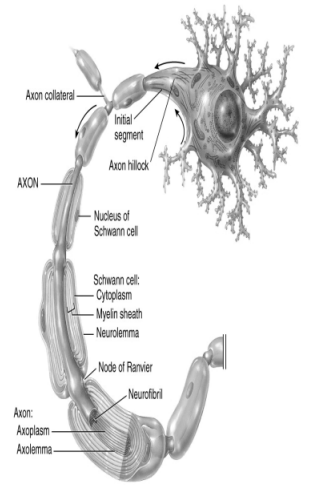


- Neurons gather information at dendrites and process it in the dendritic tree and cell body
- Then they transmit the information down their axon to the axon terminals



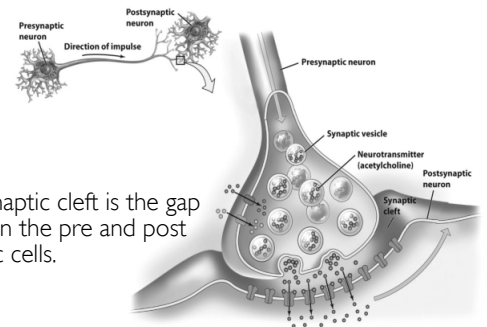
- Dendrites (little trees) are the receiving end of the neuron
  - They are short, highly branched structures that conduct impulses toward the cell body
  - They also contain organelles
- The cell body has a nucleus surrounded by cytoplasm
  - Like all cells, neurons contain organelles such as lysosomes, mitochondria, Golgi complexes, and rough ER for protein production (in neurons, RER is called Nissl bodies) – it imparts a striped “tiger appearance”
  - No mitotic apparatus is present

- Axons conduct impulses away from the cell body toward another neuron or effector cell
  - The “axon hillock” is where the axon joins the cell body
  - The “initial segment” is the beginning of the axon
  - The “trigger zone” is the junction between the axon hillock and the initial segment



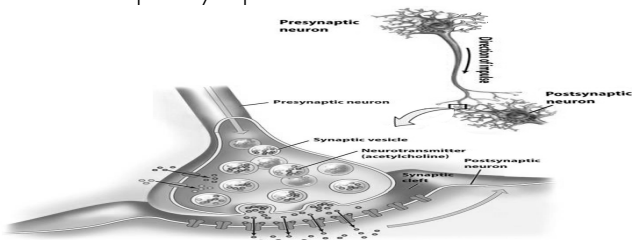
- The axon and its collaterals end by dividing into many fine processes called axon terminals (telodendria)
- Like the dendrites, telodendria may also be highly branched as they interact with the dendritic tree of neurons “downstream”
  - The tips of some axon terminals swell into bulb-shaped structures called synaptic end bulbs

- The site of communication between two neurons or between a neuron and another effector cell is called a synapse



- Synaptic end bulbs and other varicosities on the axon terminals of presynaptic neurons contain many tiny membrane-enclosed sacs called synaptic vesicles that store packets of neurotransmitter chemicals
  - Many neurons contain two or even three types of neuro-transmitters, each with different effects on the postsynaptic cell

- Electrical impulses or action potentials (AP) cannot propagate across a synaptic cleft
- Instead, neurotransmitters are used to communicate at the synapse, and re-establish the AP in the postsynaptic cell



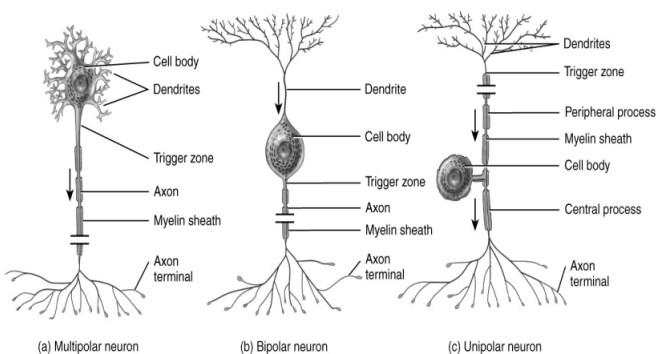
- Substances synthesized or recycled in the neuron cell body are needed in the axon or at the axon terminals
- Two types of transport systems carry materials from the cell body to the axon terminals and back
  - Slow axonal transport conveys axoplasm in one direction only – from the cell body toward the axon terminals
  - Fast axonal transport moves materials in both directions

- Slow axonal transport supplies new axoplasm (the cytoplasm in axons) to developing or regenerating axons and replenishes axoplasm in growing and mature axons
- Fast axonal transport that occurs in an anterograde (forward) direction moves organelles and synaptic vesicles from the cell body to the axon terminals
  - Fast axonal transport that occurs in a retrograde (backward) direction moves membrane vesicles and other cellular materials from the axon terminals to the cell body to be degraded or recycled

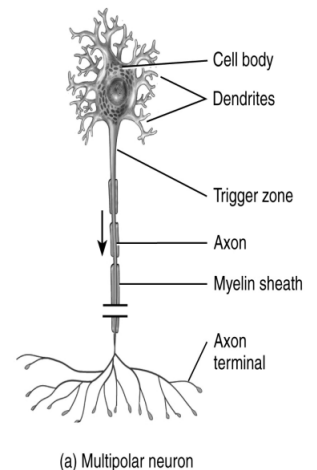
- Substances that enter the neuron at the axon terminals are also moved to the cell body by fast retrograde transport
  - These substances include trophic chemicals such as nerve growth factor, as well as harmful agents such as tetanus toxin and the viruses that cause rabies and polio
    - A deep cut or puncture wound in the head or neck is a more serious matter than a similar injury in the leg because of the shorter transit time for the harmful substance to reach the brain (treatment must begin quickly)

- Neurons display great diversity in size and shape - the longest of them are almost as long as a person is tall, extending from the toes to the lowest part of the brain
  - The pattern of dendritic branching is varied and distinctive for neurons in different parts of the NS
  - Some have very short axons or lack axons altogether
- Both structural and functional features are used to classify the various neurons in the body

- Structural classification is based on the number of processes (axons or dendrites) extending from the cell body

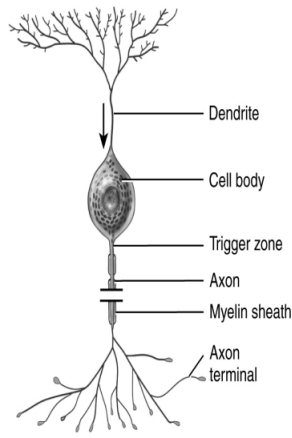


- Multipolar neurons have several dendrites and only one axon and are located throughout the brain and spinal cord
  - The vast majority of the neurons in the human body are multipolar



- Bipolar neurons have one main dendrite and one axon

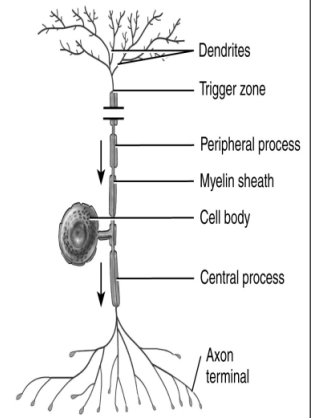
- They are used to convey the special senses of sight, smell, hearing and balance
  - As such, they are found in the retina of the eye, the inner ear, and the olfactory (*olfact* = to smell) area of the brain



(b) Bipolar neuron

- Unipolar (pseudounipolar) neurons contain one process which extends from the body and divides into a central branch that functions as an axon and as a dendritic root

- Unipolar structure is often employed for sensory neurons that convey touch and stretching information from the extremities



(c) Unipolar neuron

- The functional classification of neurons is based on electrophysiological properties (excitatory or inhibitory) and the direction in which the AP is conveyed with respect to the CNS

- Sensory or afferent neurons convey APs into the CNS through cranial or spinal nerves
  - Most are unipolar
- Motor or efferent neurons convey APs away from the CNS to effectors (muscles and glands) in the periphery through cranial or spinal nerves
  - Most are multipolar

- Interneurons or association neurons are mainly located within the CNS between sensory and motor neurons

- Interneurons integrate (process) incoming sensory information from sensory neurons and then elicit a motor response by activating the appropriate motor neurons
  - Most interneurons are multipolar in structure

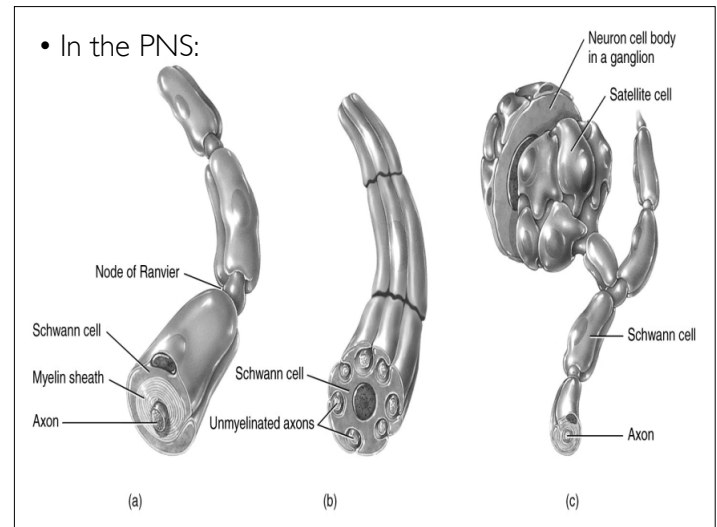
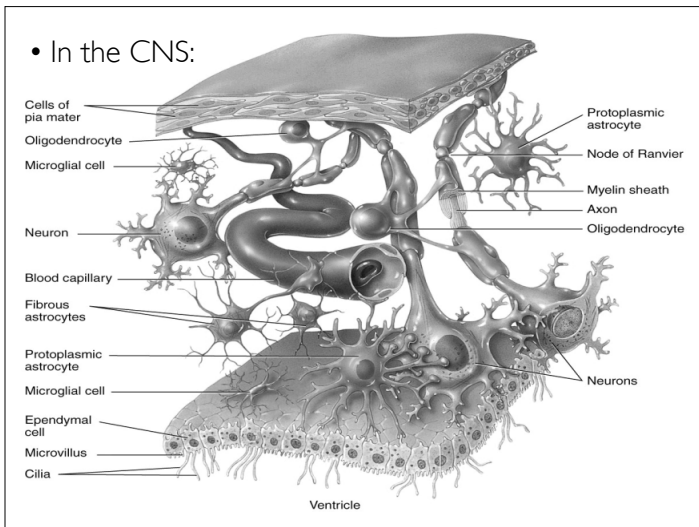
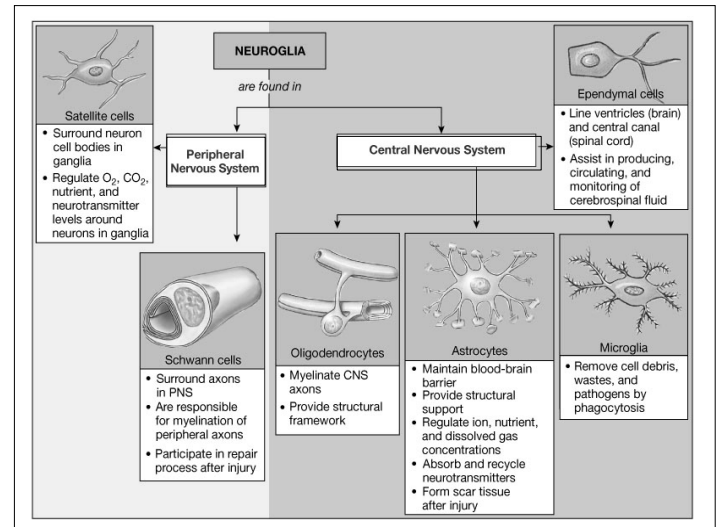
## Neuroglia

- Neuroglia (glial cells) play a major role in support and nutrition of the brain, but they do not manipulate information
  - They maintain the internal environment so that neurons can do their jobs

- Neuroglia do not generate or conduct nerve impulses

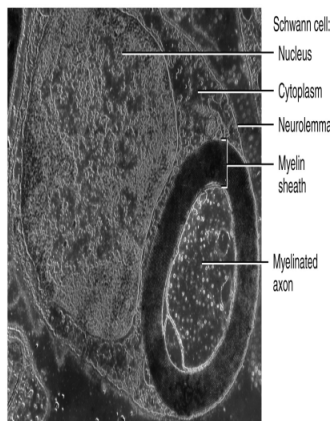
- They support neurons by:
  - Forming the Blood Brain Barrier (BBB)
  - Forming the myelin sheath (nerve insulation) around neuronal axons
  - Making the CSF that circulates around the brain and spinal cord
  - Participating in phagocytosis

- There are 4 types of neuroglia in the CNS:
  - Astrocytes - support neurons in the CNS
    - Maintain the chemical environment ( $\text{Ca}^{2+}$  &  $\text{K}^+$ )
  - Oligodendrocytes - produce myelin in CNS
  - Microglia - participate in phagocytosis
  - Ependymal cells - form and circulate CSF
- There are 2 types of neuroglia in the PNS:
  - Satellite cells - support neurons in PNS
  - Schwann cells - produce myelin in PNS



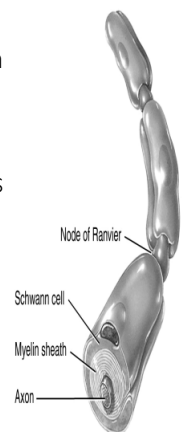
# Myelination

- Myelination is the process of forming a myelin sheath which insulates and increases nerve impulse speed
- It is formed by Oligodendrocytes in the CNS and by Schwann cells in the PNS



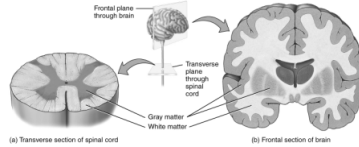
(c) Transverse section of myelinated axon

- Nodes of Ranvier are the gaps in the myelin sheath
  - Each Schwann cell wraps one axon segment between two nodes of Ranvier
  - Myelinated nodes are about 1 mm in length and have up to 100 layers
- The amount of myelin increases from birth to maturity, and its presence greatly increases the speed of nerve conduction
  - Diseases like Multiple Sclerosis result from autoimmune destruction of myelin



# Collections of Nervous Tissue

- White matter of the brain and spinal cord is formed from aggregations of myelinated axons from many neurons
  - The lipid part of myelin imparts the white appearance
- Gray matter (gray because it lacks myelin) of the brain and spinal cord is formed from neuronal cell bodies and dendrites



# Electrical Signals in Neurons

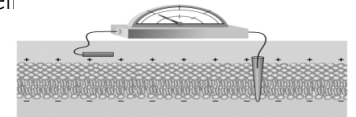
- Like muscle fibers, neurons are electrically excitable
- They communicate with one another using two types of electrical signals:
  - Graded potentials are used for short-distance communication only
  - Action potentials allow communication over long distances within the body



- Producing electrical signals in neurons depends on the existence of a resting membrane potential (RMP) - similar to the electrical potential of this 9v battery which has a gradient of 9 volts from one terminal to another
  - A cell's RMP is created using ion gradients and a variety of ion channels that open or close in response to specific stimuli
  - Because the lipid bilayer of the plasma membrane is a good insulator, ions must flow through these channels

# Ion Channels

- Ion channels are present in the plasma membrane of all cells in the body, but they are an especially prominent component of the nervous system
- Much of the energy expended by neurons, and really all cells of the body, is used to create a net negative charge in the inside of the cell as compared to the outside of the cell



A cell's RMP is created using ion channels to set-up transmembrane ion gradients

- When ion channels are open, they allow specific ions to move across the plasma membrane, down their electrochemical gradient
  - Ions move from areas of higher concentration to areas of lower concentration - the "chemical" (concentration) part of the gradient
  - Positively charged cations move toward a negatively charged area, and negatively charged anions move toward a positively charged area - the electrical aspect of the gradient

- Active channels open in response to a stimulus (they are "gated")
- There are 3 types of active, gated channels:
  - Ligand-gated channels respond to a neurotransmitter and are mainly concentrated at the synapse
  - Voltage-gated channels respond to changes in the transmembrane electrical potential and are mainly located along the neuronal axon
  - Mechanically-gated channels respond to mechanical deformation (applying pressure to a receptor)
- "Leakage" channels are also gated but they are not active, and they open and close randomly



# Resting Membrane Potential

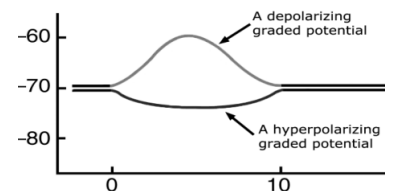
- A neuron's RMP is measured at rest, when it is not conducting a nerve impulse
  - The resting membrane potential exists because of a small buildup of negative ions in the cytosol along the inside of the membrane, and an equal buildup of positive ions in the extracellular fluid along the outside surface of the membrane
  - The buildup of charge occurs only very close to the membrane – the cytosol elsewhere in the cell is electrically neutral

- The RMP is slightly negative because leakage channels favor a gradient where more  $K^+$  leaks out, than  $Na^+$  leaks in (there are more  $K^+$  channels than  $Na^+$  channels)
  - There are also large negatively charged proteins that always remain in the cytosol
- Left unchecked, inward leakage of  $Na^+$  would eventually destroy the resting membrane potential
  - The small inward  $Na^+$  leak and outward  $K^+$  leak are offset by the  $Na^+/K^+$  ATPases (sodium-potassium pumps) which pumps out  $Na^+$  as fast as it leaks in
- In neurons, a typical value for the RMP is  $-70$  mV (the minus sign indicates that the inside of the cell is negative relative to the outside)

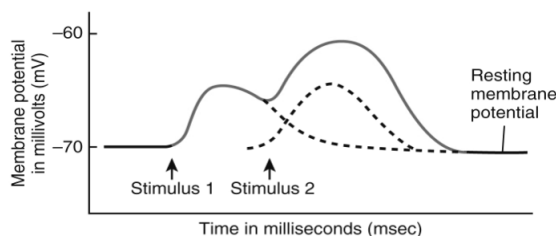
- A cell that exhibits an RMP is said to be polarized
  - In this state, the cell is "primed" - it is ready to produce an action potential
  - In order to do so, graded potentials must first be produced in order to depolarize the cell to threshold
    - A graded potential occurs whenever ion flow in mechanically gated or ligand-gated channels produce a current that is localized – it spreads to adjacent regions for a short distance and then dies out within a few millimeters of its point of origin

# Graded Potentials

- From the RMP, a stimulus that causes the cell to be less negatively charged with respect to the extracellular fluid is a depolarizing graded potential, and a stimulus that causes the cell to be more negatively charged is a hyperpolarizing graded potential



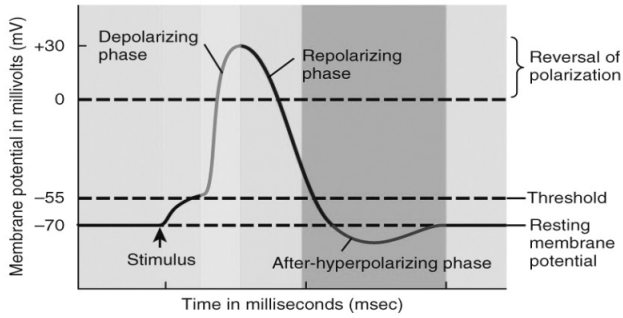
- Graded potentials have different names depending on the type of stimulus and where they occur
- They are voltage variable aptitudes that can be added together (summate) or cancel each other out – the net result is a larger or smaller graded potential
- Graded potentials occur mainly in the dendrites and cell body of a neuron – they do not travel down the axon



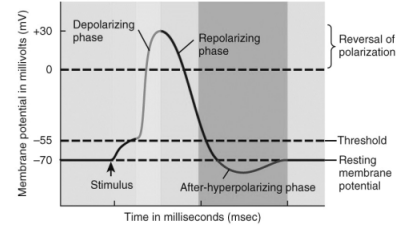
# Generation of Action Potentials

- In contrast to graded potentials, an action potential (AP) or impulse is a signal which travels the length of the neuron
- During an AP, the membrane potential reverses and then eventually is restored to its resting state
  - If a neuron receives a threshold (liminal) stimulus, a full strength nerve impulse is produced and spreads down the axon of the neuron to the axon terminals
  - If the stimulus is not strong enough (subthreshold or subliminal), no nerve impulse will result

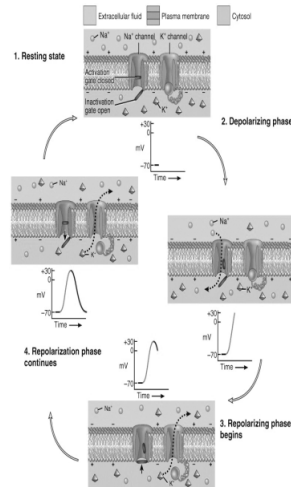
- An AP has two main phases:
  - a depolarizing phase and
  - a repolarizing phase



- Graded potentials that result in depolarization of the neuron from  $-70\text{mV}$  to threshold (about  $-55\text{ mV}$  in many neurons) will cause a sequence of events to rapidly unfold
  - Voltage-gated  $\text{Na}^+$  channels open during the steep depolarization phase allowing  $\text{Na}^+$  to rush into the cell and making the inside of the cell progressively more positive

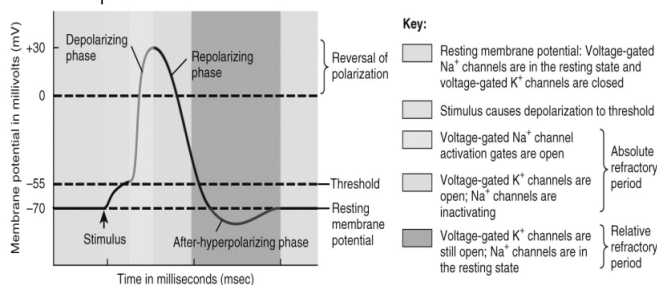


- Only a total of 20,000  $\text{Na}^+$  actually enter the cell in each little area of the membrane, but they change the potential considerably (up to  $+30\text{mV}$ )]
- During the repolarization phase  $\text{K}^+$  channels open and  $\text{K}^+$  rushes outward
  - The cell returns to a progressively more negative state until the RMP of  $-70\text{mV}$  is once again restored



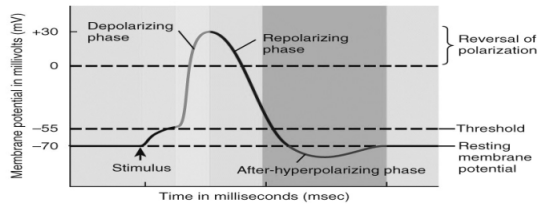
- While the voltage-gated  $\text{K}^+$  channels are open, outflow of  $\text{K}^+$  may be large enough to cause an after-hyperpolarizing phase of the action potential
  - During this phase, the voltage-gated  $\text{K}^+$  channels remain open and the membrane potential becomes even more negative (about  $-90\text{ mV}$ )
  - As the voltage-gated  $\text{K}^+$  channels close, the membrane potential returns to the resting level of  $-70\text{ mV}$

- According to the all-or-none principle, if a stimulus reaches threshold, the action potential is always the same
  - A stronger stimulus will not cause a larger impulse



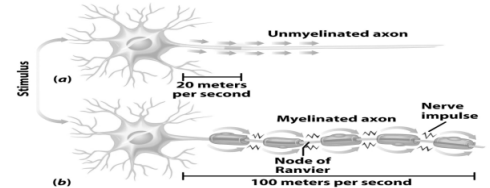
- After initiating an action potential, there is a period of time called the absolute refractory period during which a cell cannot generate another AP, no matter how strong the stimulus
  - This period coincides with the period of  $\text{Na}^+$  channel activation and inactivation (inactivated  $\text{Na}^+$  channels must first return to the resting state)
  - This places an upper limit of 10–1 000 nerve impulses per second, depending on the neuron

- The relative refractory period is the period of time during which a second action potential can be initiated, but only by a larger-than-normal stimulus
  - It coincides with the period when the voltage-gated  $K^+$  channels are still open after inactivated  $Na^+$  channels have returned to their resting state
- In contrast to action potentials, graded potentials do not exhibit a refractory period



## Propagation of Action Potentials

- Propagation of the AP down the length of the axon begins at the trigger zone near the axon hillock
  - By passive spread, the current proceeds by:
    - continuous conduction in unmyelinated axons
    - or by the much faster process of saltatory conduction in myelinated axons (as the AP jumps from one node to the next as shown in this graphic)



- In addition to the nodes of Ranvier that allow saltatory conduction, the speed of an AP is also affected by:
  - The axon diameter
  - The amount of myelination
  - The temperature
- The frequency of AP plays a crucial role in determining the perception of a stimulus, or the extent of our response
  - In addition to this “frequency code,” a second important factor is the number of neurons recruited (activated) to the cause

- The characteristics of the neuronal axon define the “fiber types”
  - A fibers are large, fast (130 m/sec), myelinated neurons that carry touch and pressure sensations; many motor neurons are also of this type
  - B fibers are of medium size and speed (15 m/sec) and comprise myelinated visceral sensory & autonomic preganglionic neurons
  - C fibers are the smallest and slowest (2 m/sec) and comprise unmyelinated sensory and autonomic motor neurons

## Encoding Stimulus Intensity

- The intensity of the stimulus is encoded in the frequency of action potentials and in the number of sensory neurons that are recruited

## Comparison of Electrical Signals Produced by Excitable Cells

- Communication
  - Action Potentials: long distances
  - Graded Potentials: short distances
- Resting Membrane Potential
  - Neuron: -70mV
  - Skeletal and Cardiac Muscle Fiber: -90mV
- Duration of Nerve Impulse
  - Nerve Impulse: 0.5 to 2 msec
  - Skeletal Muscle Fiber: 1 to 5 msec
  - Cardiac and Smooth Muscle Fiber: 10 - 300 msec

- Propagation Speed of Action Potentials
  - 18 times faster along the largest-diameter, myelinated axons, than the propagation speed along the sarcolemma of a skeletal muscle fiber

## Signal Transmission at Synapses

- A synapse is the functional junction between one neuron and another, or between a neuron and an effector such as a muscle or gland
- The two types of synapses are electrical and chemical

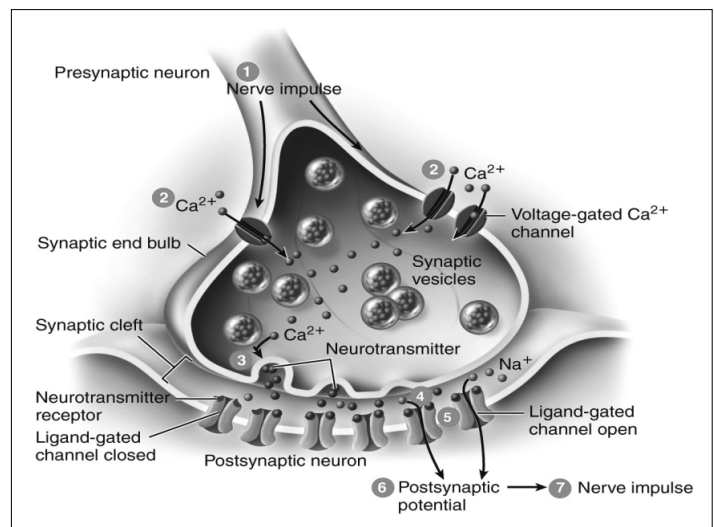
## Electrical Synapses

- Action potentials (impulses) conduct directly between the plasma membranes of adjacent neurons through gap junctions
- Faster communication because the action potential passes directly from the presynaptic cell to the postsynaptic cell
- Can synchronize (coordinate) the activity of a group of neurons or muscle fibers

## Chemical Synapses

- Signal transmission at the synapse is a one-way transfer from a presynaptic neuron to a postsynaptic neuron
  - When an AP reaches the end bulb of axon terminals, voltage-gated  $\text{Ca}^{2+}$  channels open and  $\text{Ca}^{2+}$  flows inward, triggering release of the neurotransmitter
  - The neurotransmitter crosses the synaptic cleft and binds to ligand-gated receptors on the postsynaptic membrane
    - The more neurotransmitter released, the greater the number and intensity of graded potentials in the postsynaptic cell

- In this way, the presynaptic neuron converts an electrical signal (nerve impulse) into a chemical signal (released neurotransmitter)
- The postsynaptic neuron receives the chemical signal and in turn generates an electrical signal (postsynaptic potential)
- The time required for these processes at a chemical synapse produces a synaptic delay of about 0.5 msec



## Excitatory & Inhibitory Postsynaptic Potentials

- A neurotransmitter causes either an excitatory or an inhibitory graded potential:
  - Excitatory postsynaptic potential (EPSP) causes a depolarization of the postsynaptic cell, bringing it closer to threshold. Although a single EPSP normally does not initiate a nerve impulse, the postsynaptic cell does become more excitable
  - Inhibitory postsynaptic potential (IPSP) hyperpolarizes the postsynaptic cell taking it farther from threshold

- Spatial summation occurs when postsynaptic potentials arrive near the same location
- Temporal summation occurs when postsynaptic potentials arrive close to the same time
- Whether or not the postsynaptic cell reaches threshold depends on the net effect after summation of all the postsynaptic potentials

## Structure of Neurotransmitter Receptors

- There are two major types of neurotransmitter receptors
  - Ionotropic
    - Contains a neurotransmitter binding site and an ion channel
  - Metabotropic
    - Contains a neurotransmitter binding site and is coupled to a separate ion channel by a G protein

## Removal of Neurotransmitter

- If a neurotransmitter could linger in the synaptic cleft, it would influence the postsynaptic neuron, muscle fiber, or gland cell indefinitely – removal of the neurotransmitter is essential for normal function
  - Removal is accomplished by diffusion out of the synaptic cleft, enzymatic degradation, and re-uptake by cells.
    - An example of a common neurotransmitter inactivated through enzymatic degradation is acetylcholine
    - The enzyme acetylcholinesterase breaks down acetylcholine in the synaptic cleft

## Spatial & Temporal Summation of Postsynaptic Potentials

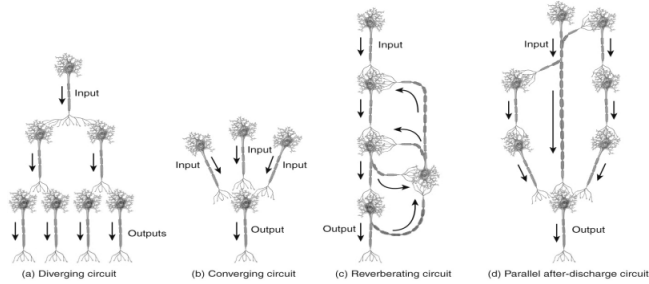
- If several presynaptic end bulbs release their neurotransmitter at about the same time, the combined effect may generate a nerve impulse due to summation
  - May be spatial or temporal
- The postsynaptic neuron is an integrator
  - It receives excitatory and inhibitory signals, integrates them, and responds accordingly

## Neurotransmitters

- Both excitatory and inhibitory neurotransmitters are present in the CNS and the PNS
- A given neurotransmitter may be excitatory in some locations and inhibitory in others
- Neurotransmitters can be divided into two classes based on size
  - Small- Molecule Neurotransmitters
  - Neuropeptides



- A neuronal network may contain thousands or even millions of neurons
  - Types of circuits include diverging, converging, reverberating, and parallel after-discharge

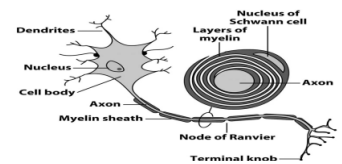


- In a diverging circuit, a small number of neurons in the brain stimulate a much larger number of neurons in the spinal cord
  - A converging circuit is the opposite
- In a reverberating circuit, impulses are sent back through the circuit time and time again
  - Used in breathing, coordinated muscular activities, waking up, and short-term memory
- Parallel after-discharge circuits involve a single presynaptic cell that stimulates a group of neurons, which then synapse with a common postsynaptic cell
  - Used in precise activities such as mathematical calculations

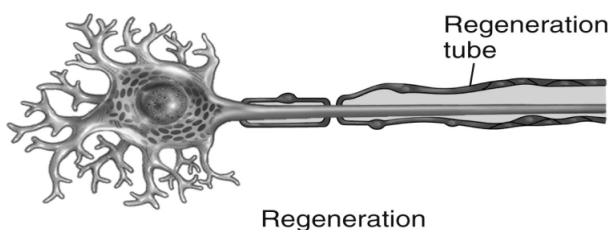
## Regeneration & Repair of Nervous Tissue

- The nervous system exhibits plasticity, the capability to change based on experience
- But has very limited powers of regeneration, the capability to replicate or repair damaged neurons
- Neurogenesis, the birth of new neurons from undifferentiated stem cells, is normally very limited
- Damaged axons does not occur in most regions of the CNS

- The cell bodies of neurons lose their mitotic features at birth and can only be repaired through regeneration after an injury (they are never replaced by daughter cells as occurs with epithelial tissues)
- Nerve tissue regeneration is largely dependent on the Schwann cells in the PNS and essentially doesn't occur at all in the CNS where astrocytes just form scar tissue



- The outer nucleated cytoplasmic layer of the Schwann cell, which encloses the myelin sheath, is the neurolemma (sheath of Schwann)
  - When an axon is injured, the neurolemma aids regeneration by forming a regeneration tube that guides and stimulates regrowth of the axon



- To do any regeneration, neurons must be located in the PNS, have an intact cell body, and be myelinated by functional Schwann cells having a neurolemma
  - Demyelination refers to the loss or destruction of myelin sheaths around axons
    - It may result from disease, or from medical treatments such as radiation therapy and chemotherapy
    - Any single episode of demyelination may cause deterioration of affected nerves