Lecture 11b.

Neurophysiology

Review from 12b.

- CNS – brain and spinal cord
- PNS – nerves
  - SNS (somatic)
  - ANS (autonomic)
    - Sympathetic NS
    - Parasympathetic NS
  - Afferent vs efferent (SAME)
- Cells of the nervous system:
  - Neurons (most are multipolar shape)
  - Glia (6 types: 4 in CNS, 2 in PNS)

Topics in neurophysiology

- Resting potential
  - how the neuron maintains an electrical charge at rest
- Action Potential
  - how electrical activity gets from the dendrites to the synaptic terminals
- Neurotransmission
  - how the message gets from one cell to the next

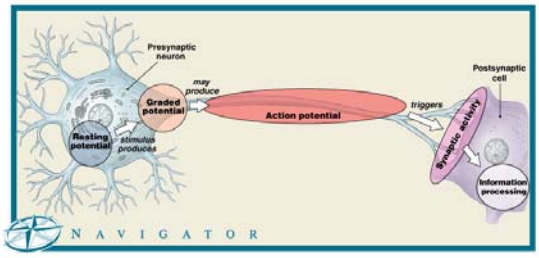
Information flow

- Through **one neuron**:
  - dendrites
  - cell body
  - axon hillock
  - axon
  - synaptic terminals
  - synaptic knobs

From **one neuron to the next**:

- Synapse
  - presynaptic cell
  - postsynaptic cell
  - synaptic cleft
- Neurotransmitters

Overview



Big Picture

- Don' t lose sight of the larger significance of what we are talking about:
  - the ability to move, think, and feel, everything that makes us human, everything that makes all animals live and breathe…

  All of these things are caused by the movement of a ions into and out of the membranes of neural cells.

If neurons are excitable cells…

- What does this mean?
- Have we talked about a model in another cell for propagation of an impulse?

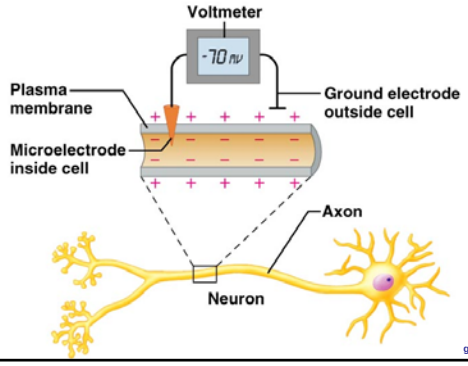
Electricity Definitions

- Voltage (V) – measure of potential energy generated by separated charge
- Potential difference – voltage measured between two points
- Current (I) – the flow of electrical charge between two points (carried by **ions**)
- Resistance (R) – hindrance to charge flow
- Insulator – substance with high electrical resistance (e.g. myelin)
- Conductor – substance with low electrical resistance (e.g. cytoplasm)

Transmembrane Potential

- All cells have an excess of negative and charges inside versus outside (in the extracellular fluid)
- This transmembrane potential is particularly important to neurons because *changes* in the membrane potential can be used for signaling or transmitting information
- In neurons, it is abround -70mV (millivolts)

Resting Membrane Potential



gure 11.7

Ion Movements and Electrical Signals

- **Ion movements**, or changes in the distribution of ions on either side of a cell membrane cause changes in the membrane potential which propagate (spread) along cells = action potentials
- To understand this, we first must look at the resting conditions, when no changes are occuring

Resting Membrane Potential (V_r)

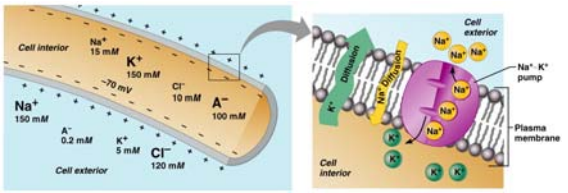


Figure 11.8

Requirements for Resting Membrane Potential

For a cell to have a resting potential, it must have:

1. Concentration gradient of ions (Na^+, K^+)
2. **Selectively** permeable membrane that allows limited movement of ions through channels

This creates and maintains a charge difference across membrane (*resting potential* ~ -70 mV)

Potential Energy

- Energy can be stored in a form that can later be released = turned into active energy, energy that does something
- This stored energy = potential energy
- Examples: waterfall, raised book

The semipermeable cell membrane is key.

- Remember that the membrane allows for the separation of ions because it is selectively permeable.
- Which ions are in greater concentration **inside** the cell? **Outside** the cell?

Membrane concentrations

- INSIDE cells:
- High [K+]
- High [proteins] (negatively charged)
- Low [Cl-]
- Low [Na+]

- OUTSIDE cells:
- High [Na+]
- High [Cl-]
- Low [K+]

So far we know the following:

- Intracellular fluid contains a high concentration of K+ and negatively charged proteins)
- Extracellular fluid contains a high concentration of Na+ and Cl- ions
- What would happen if the cell membrane were freely permeable? Gradients? Potential?

Key to resting potential

- Membrane is selectively permeable: at rest, the membrane is **more permeable to K+ than to Na+**

So what does this mean?

How does K+ move?

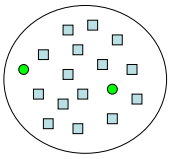
What charge will the cell develop?

Resting Potential – the simple story

The Cell membrane is more permeable to K+ ions than Na+ ions (because it has more K+ channels than Na+ channels) so the cell loses more positively charged ions (K+) than it gains (Na+). Thus, the cell at rest is negative

● = Na+ channel

□ = K+ channel



Patch of cell membrane

Resting Membrane Potential (V_r)

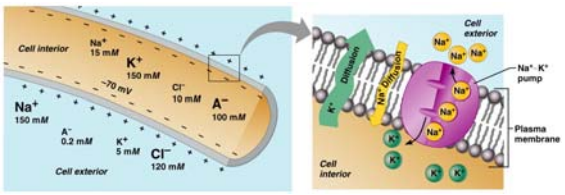


Figure 11.8

Resting potential overview

- At rest, the cell is almost exclusively permeable to K+
- So K+ leaves the cell continuously, but will it reach **concentration** equilibrium (same conc. on both sides)?
- NO, because as + ions leave, they leave behind an excess of negative charge and an **electrical** potential develops (due to separation of + and – charges) which is EQUAL and OPPOSITE to the concentration force.
- This balance point is called the equilibrium potential.

Two types of gradients

1. Chemical (concentration) gradient: caused by different concentrations of a **single ion** on either side of the plasma membrane
   - e.g. high potassium concentration inside the cell tends to make K+ ions want to leave the cell

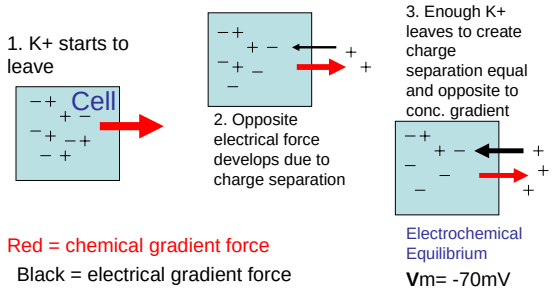
Two types of gradients

2. Electrical gradient: caused by different total numbers of positively and negatively charged particles on either side of membrane
   - Excess negative charge inside cells causes cells to be negatively charged inside. Note that K+ is still more concentrated inside than outside, but it is the TOTAL balance of charges that matters (there are more total + charges outside than inside)

Cell model

- Imagine a cell with high K+ inside and high Na+ outside.
- At time = 0, the membrane is impermeable
- Say that we now put K+ channels in the cell, making it permeable to only K+. What happens to K+?
- Will it continue to move until it is the same on both sides (in and out)?

Electrical and Chemical Forces



Red = chemical gradient force

Black = electrical gradient force

Equilibrium = balance

- Chemical equilibrium: The point at which diffusion causes equal amounts of a particular ion on either side of the membrane
- Electrical equilibrium: The point at which the TOTAL number of + and – ions is equal on both sides of the membrane (potential = 0)

The **electrochemical gradient**

- The sum of the two gradients, chemical and electrical. This "overall" gradient is valid for an individual ion (e.g. "the electrochemical gradient for Na+" or "the electrochemical gradient for K+")
- The electrochemical gradient tells you **which direction** an ion will tend to move (into or out of a cell)
- At **electrochemical equilibrium**, neither the concentration nor the electrical force is zero. Instead, they are **equal** and **opposite**.

Electrochemical equilibrium and the equilibrium potential

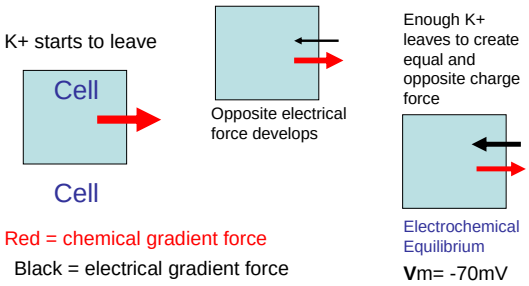
- Electrochemical equilibrium = The point at which an electrical charge balances out the chemical gradient (Note that neither chemical nor electrical equilibrium is required).
- Equilibrium Potential for a given ion is the **electrical charge that must develop in order to balance the opposite tendency for that ion to move**, resulting in an equilibrium.
- For example: it is the negative charge that develops inside the cell that is *so negative* that it balances the tendency of K+ to leave down its concentration gradient

Equilibrium Potential

Put another way:

- It's the transmembrane potential at which there is no **net** movement of a particular ion across the cell membrane
- For K+ = -90mV (close to the resting pot'l)
- For Na+ = +65mV (we'll see why in a minute)

Summary of forces



Red = chemical gradient force

Black = electrical gradient force

Resting potential summary

- At rest, the cell is almost exclusively permeable to K+
- K+ leaves the cell continuously, but never reaches **concentration** equilibrium (same conc. on both sides) because…
- An **electrical** potential develops due to separation of + and – charges which is EQUAL and OPPOSITE to the concentration force.
- Balance is at ~-70mV, near the Equilibrium potential for K+
- Because cell is a little permeable to Na+ (which enters), Vm is a little less negative than if K+ was the only ion that moved

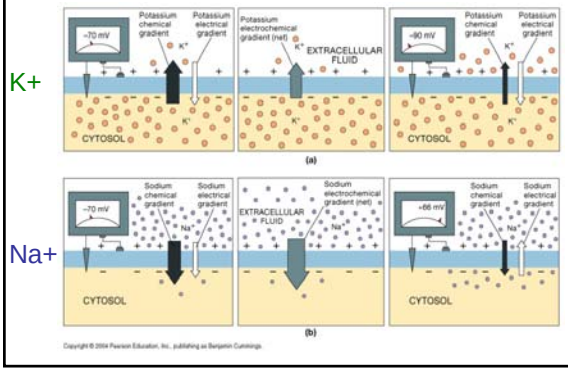
Interesting note

- The amount of potassium ions that must leave the cell in order to leave behind a negative charge is negligible.
- Hard to believe, but true

Electrochemical gradient at rest

- For K+:
  - Concentration force points **out** (wants to leave)
  - Electrical force points **in**
  - **Close to balanced at rest**
- For Na+
  - Concentration force points **in**
  - Electrical force points **in** (as it would for any positive ion)
  - FAR from balanced at rest (HUGE tendency for sodium to come IN)

Electrochemical gradients



Active Forces Across the Membrane

- *Sodium–potassium ATPase* (exchange pump):
  - powered by ATP, carries 3 Na^+ out and 2 K^+ in
  - Creates the concentration gradients that allow the resting potential to develop

Ion movements in neurons

- Ions can only move through the membrane using channels
- There are different kinds of channels
  - Passive or non-gated channels
  - Active or gated channels

Passive channels

- **Always** open
- The reason that neurons are more permeable to K+ than to Na+ at rest is there are far more passive, non-gated K+ channels in the membrane than there are passive Na+ channels

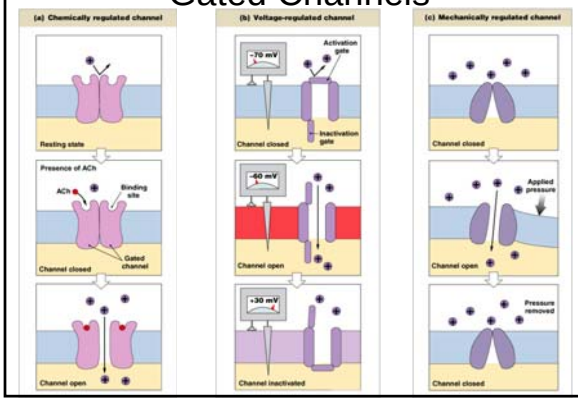
Gated channels

Types:

- Chemically regulated (receptors)
- Voltage regulated
- Mechanically regulated (rare)

Have we seen examples of these channels in other tissue?

Gated Channels



If the gated channels are opened..

- What happens to the membrane potential?
- At a synapse, what type of channels are likely to be activated **first**, chemically regulated or voltage dependent?

Changes in Membrane Potential

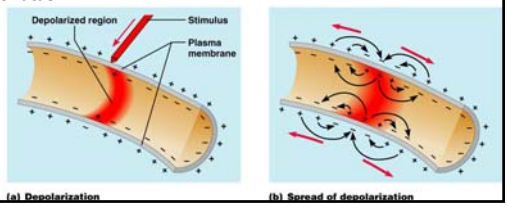
- Transmembrane potential rises or falls:
  - in response to temporary changes in membrane permeability resulting from **opening or closing** gated membrane channels
  - Remember it is ion movement that causes electrical signals
- Types of signals – graded potentials and action potentials

Graded Potentials → Action Potentials

- Graded Potentials, caused by chemically gated channels, often start off the activity in a neuron, which then gets passed on down the cell via electrically gated channels
- Graded potentials occur at a synapse caused by neurotransmitters, then lead to action potentials

Graded potential

- "Graded" because it can have several different values
- A change in the transmembrane potential that **does not travel far** from the area of stimulation because it decreases as it goes (decremental)
- Also called local potentials
- Opening gated **sodium channels** produces graded potentials



Changes in Membrane Potential

- Changes are caused by three events
  - Depolarization – the inside of the membrane becomes less negative (shifts towards 0mV)
  - Repolarization – the membrane returns to its resting membrane potential
  - Hyperpolarization – the inside of the membrane becomes more negative than the resting potential

Changes in Membrane Potential

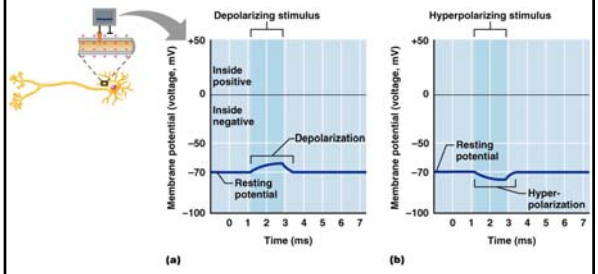
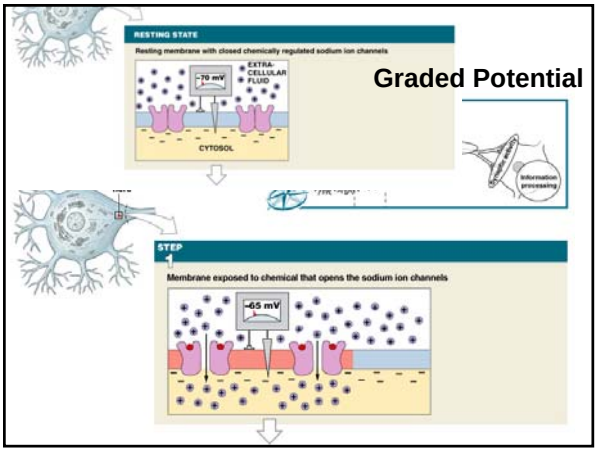


Figure 11.9



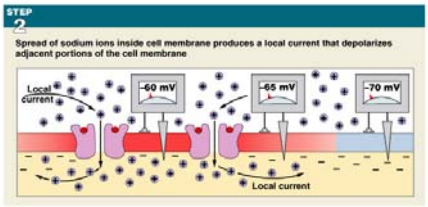
Graded Potentials: Step 1

- Resting membrane exposed to chemical stimulus (often a neurotransmitter in a synapse)
- Chemically gated sodium channel opens
- Sodium ions enter the cell
- Membrane potential rises (becomes less negative) = Depolarization

Graded Potentials: Step 2

- Movement of Na+ through channel produces local current
- This depolarizes nearby regions of cell membrane (graded potential)
- Change in potential is **proportional** to the **stimulus** (this is very different than action potentials)

Graded potentials can lead to action potentials



Action Potentials

- Propagated changes in the transmembrane potential that spread through a neuron from the axon hillock to the synaptic terminals and result in release of neurotransmitters
- Key Features:
  - Change in membrane potential
  - Travels length of axon in one direction
  - **Always the same regardless of stimulus**
  - Function: Link activity at cell body and dendrites with synaptic activity at terminals

Initiating Action Potential

- Initial stimulus:
  - a graded depolarization must reach the axon hillock and be large enough (10 to 15 mV) to change membrane potential from -70 mV (resting) to threshold (about -60 to -55 mV)
  - Threshold = voltage that, if it is attained at the axon hillock, will always* cause an action potential
    - It is the point at which **voltage-gated sodium channels** open
    - Hillock is the critical decision point because it has the highest concentration of voltage gated sodium channels

All-or-None Principle

- If a stimulus exceeds threshold :
  - the action potential is the same no matter how large the stimulus
- It is decidedly NOT proportional to the stimulus; as long as you get there, it's all the same
- Action potential is either triggered, or not
- Gun analogy

Keys to the AP

- Electrochemical gradient for Na+ is **really big pointing in** (both concentration and electrical forces are pulling Na+ in)
- When threshold is reached, voltage-gated Na+ channels open, allowing Na+ to "rush" in

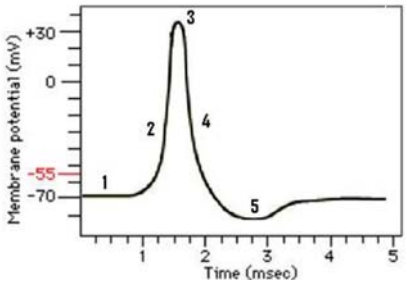
Keys to the AP

- In a **positive feedback mechanism**, Na+ coming in through *chemically gated* channels (graded potential) depolarize the membrane causing *voltage gated* Na+ channels to open.
- Voltage-gated Na+ channels allow more Na+ in, this depolarizes the membrane more, opens more voltage-gated Na+ channels, etc.
- Na+ in→depolarization→opens Na+ channels

Keys to the AP

- At about +30 mV, Na+ channels close, ending the depolarization
- Now voltage gated K+ channels open (in addition to the passive K+ channels that are always open) to help return the voltage to its resting value of -70mV
- These cause the potential to overshoot -70 and go a little more negative.
- When they close, Vm returns to -70mV

Action Potential

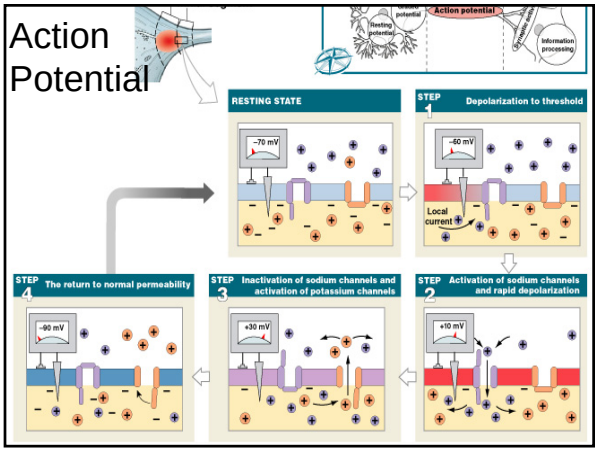


What do you think is happening at each numbered point? DISCUSS

Movie

- Action potential

Action Potential

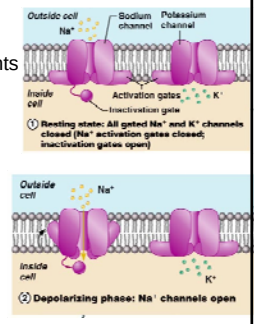


4 Steps in the Generation of Action Potentials

At rest, Na^+ and K^+ channels are closed

Leakage accounts for all movements of Na^+ and K

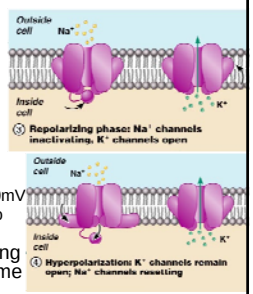
1. Depolarization to threshold
2. Activation of Na^+ channels:
   - Activation gated open
   - rapid depolarization
   - Na^+ ions rush into cytoplasm
   - inner membrane changes from negative to positive



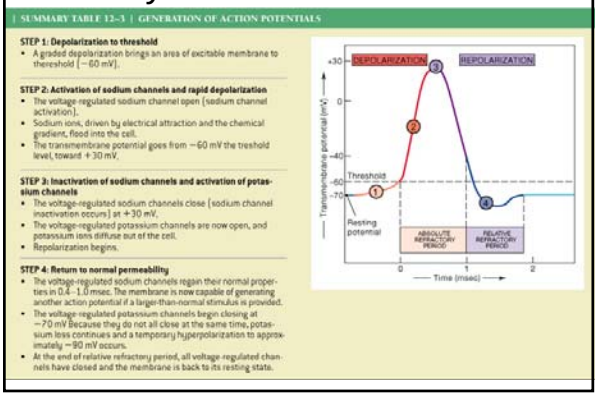
4 Steps in the Generation of Action Potentials

3. At peak (+30 mV):
   - -- Na+ inactivation gates close (Na^+ channel inactivation)
   - K^+ channels open, repolarization begins
4. Return to normal permeability:
   - K^+ channels *begin* to close when membrane reaches normal resting potential (-70 mV)
   - K^+ channels *finish* closing when membrane is hyperpolarized to -80mV
   - transmembrane potential returns to resting level

- **Ionic** redistribution back to resting conditions is restored by over time by the sodium-potassium pump (neurons need ATP to function)

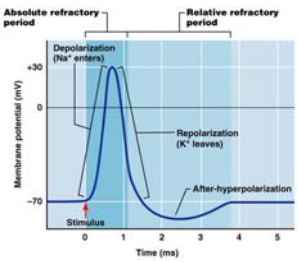


Summary – Action Potentials



The Refractory Period

- The time period from beginning of action potential until the return to resting state
- During this period, membrane will not respond normally to additional stimuli
- Causes the action potential to be unidirectional (absolute)



2 Divisions of the Refractory Period

1. Absolute refractory period:
   - sodium channels open or inactivated
   - no action potential possible
2. Relative refractory period:
   - membrane potential almost normal
   - very large stimulus can initiate action potential

Propagation (Conduction) of Action Potentials

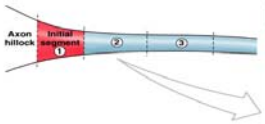
- Propagation:
  - moves action potentials generated in axon hillock along entire length of axon
  - This occurs in a series of repeated actions, not by passive flow
- Rate of impulse propagation is determined by:
  - Axon diameter – the larger the diameter, the faster the impulse (less resistance in large axons)
  - Presence of a myelin sheath – myelination dramatically increases impulse speed

2 Methods of Propagating Action Potentials

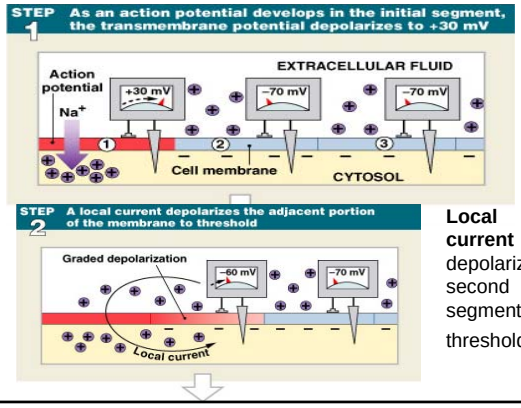
1. Continuous propagation:
   - unmyelinated axons
2. Saltatory propagation:
   - myelinated axons

Continuous Propagation

- Of action potentials along an unmyelinated axon
- Affects 1 segment of axon at a time
- Each segment experiences AP

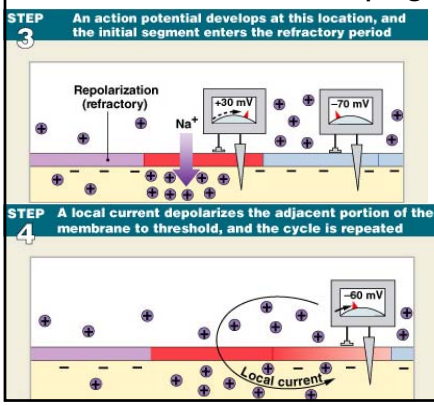


Continuous Propagation



Local current depolarizes second segment to threshold

Continuous Propagation



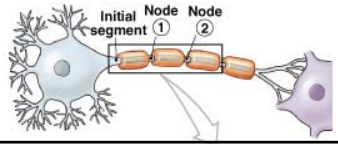
-Second segment develops action potential
-First segment enters refractory period
-Local current depolarizes next segment
-Cycle repeats
-Action potential travels in 1 direction at 1 m/sec

Why can APs only travel in one direction?

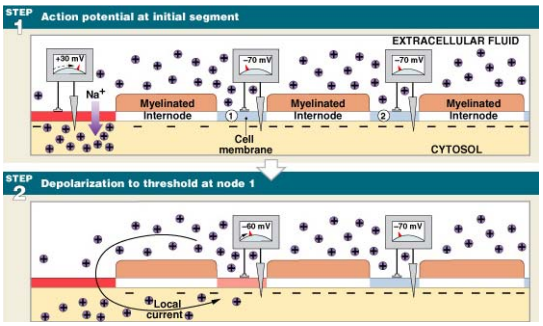
- What if you started one right in the middle of the axon (say, by injecting a bunch of Na+)?

Saltatory Propagation

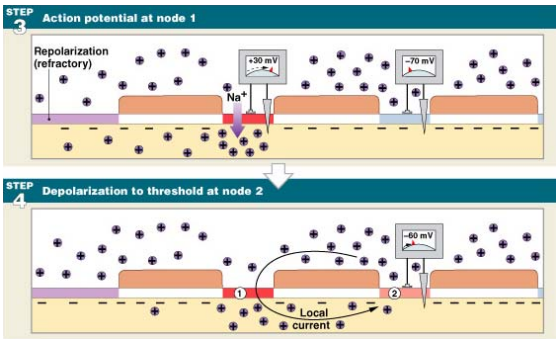
- **Faster** (why?) and uses **less energy** (why?) than continuous propagation
- Myelin insulates axon, prevents continuous propagation
- Local current "jumps" from node to node
- Depolarization occurs onlv at nodes



Saltatory Propagation



Saltatory Propagation



Multiple Sclerosis (MS)

- An autoimmune disease that mainly affects young adults
- Symptoms: visual disturbances, weakness, loss of muscular control, and urinary incontinence
- Nerve fibers are severed and myelin sheaths in the CNS become nonfunctional scleroses
- Shunting and short-circuiting of nerve impulses occurs

KEY CONCEPT

- "Information" travels within the nervous system as propagated electrical signals (action potentials)
- The most important information (vision, balance, motor commands) is carried by large-diameter myelinated axons

Movie

- Synapse activity
- Action potentials:
  - are transmitted from presynaptic neuron to postsynaptic neuron (or other postsynaptic cell) across a synapse

2 Types of Synapses

1. Electrical synapses:
   - direct physical contact between cells
2. Chemical synapses:
   - signal transmitted across a gap by chemical neurotransmitters

Synapse types

- Electrical Synapses
  - locked together at gap junctions
  - Allow ions to pass between cells
  - Produce continuous local current and action potential propagation
- Chemical synapses
  - found in most synapses between neurons and all synapses between neurons and other cells
  - Synaptic delay = time needed to release NT, bine to receptors, open channels (0.3-5.0 ms)

Chemical Synapses

- The most common type of synapse (think about why this might be)
- Response of the postsynaptic cell is **dependent on the neurotransmitter AND** the **type of receptor** found in the cell membrane of the postsynaptic cell

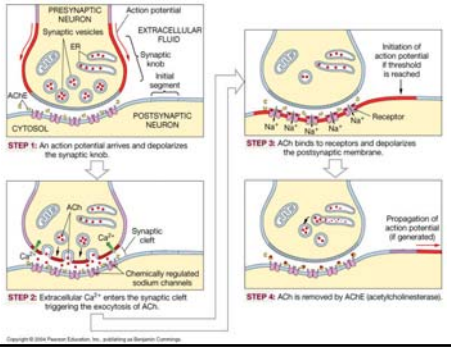
An example

- ACh causes a depolarization in the membrane of skeletal muscles and in the heart, ACh causes a transient hyperpolarization
- The response to ACh depends on the receptor in the membrane of the post-synaptic cell

Acetylcholine

- Synapses that release ACh are called **cholinergic** synapses
- Released at
  - All neuromuscular junctions involving skeletal muscles
  - Synapses in the CNS
  - Neuron-neuron synapses in the PNS
  - All neuromuscular and neuroglandular junctions in the Parasympathetic Nervous System (division of the autonomic NS)

Review what happens at a cholinergic synapse



General Synapse

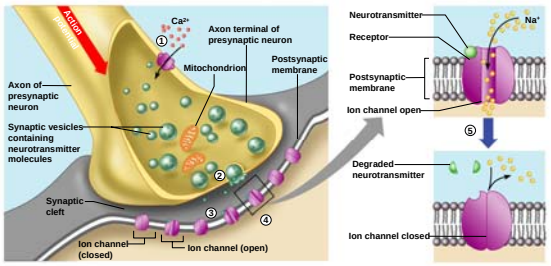


Figure 11.18

Stopping the Message

- Removal of neurotransmitters occurs when they:
  - Are degraded by enzymes (like AChE)
  - Are reabsorbed by astrocytes or the presynaptic terminals (reuptake)
  - Diffuse from the synaptic cleft

Acetylcholine (ACh)

- Two types of receptors that bind Ach
  - Nicotinic (the ones in muscles)
    - Fast acting
  - Muscarinic
    - Slower, modulatory

Small Molecule Neurotransmitters: Amines

- Amino acid derivatives (similar to amino acids)
- All have indirect, modulatory effects
  - Dopamine - rewarding, pleasurable
  - Norepinephrine (and epinephrine) found in the brain and Autonomic Nervous System
  - Serotonin – low levels implicated in depression
    - SSRIs

Small Molecule Neurotransmitters: Amino Acids

- Glutamate
  - Most important excitatory neurotransmitter in brain
  - Important in learning and memory
- Glycine
  - Produces postsynaptic inhibition
  - Poison strychnine blocks glycine receptors, results in fatal convulsions
- GABA (gamma amino butyric acid)
  - Most important inhibtory neurotransmitter
  - Many general anesthetics work by increasing GABA activity

Neurotransmitters: Neuropeptides

Many mediate pain and analgesia

- Substance P
  - Important in pain signaling
- Opioids
  - Endorphins, enkephalins - pain control
  - Opiates (morphine) bind to the same receptors

Functional Classification of Neurotransmitters

- Two classifications: excitatory and inhibitory
  - Excitatory neurotransmitters cause depolarizations (e.g., glutamate)
  - Inhibitory neurotransmitters cause hyperpolarizations (e.g., GABA and glycine)
- Some neurotransmitters have both excitatory and inhibitory effects
  - Determined by the receptor type of the postsynaptic neuron
  - Example: acetylcholine
    - Excitatory at neuromuscular junctions with skeletal muscle
    - Inhibitory in cardiac muscle

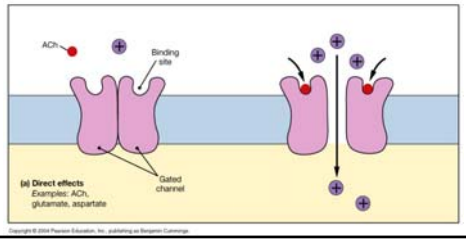
Neurotransmitters activate other cells by three main mechanisms

- Direct effects (e.g. ACh)
- Indirect via G proteins (e.g. serotonin)
- Indirect via intracellular enzymes

Remember: several neurotransmitters can have wither direct or indirect effects, depending on what receptors are present at a synapse

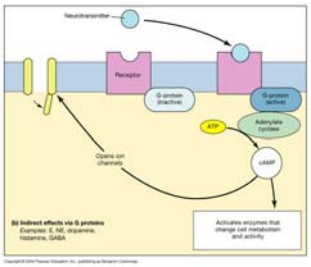
Direct

- NT binds to receptor, receptor itself is a channel that opens (or closes)
- Rapid, short-lived effects



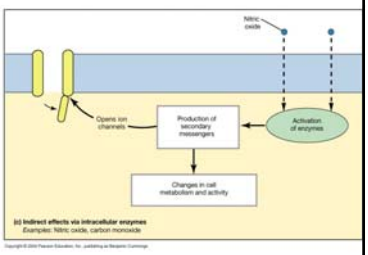
Indirect via G proteins

- NT binds to receptor, activates a G protein, which then has several effects:
  - Open or close ion channels
  - Activate kinase enzymes
  - Phosphorylate channel proteins
  - **Activate genes and induce protein synthesis**
- Also called 2nd messenger systems
- Slower, more modulatory effects

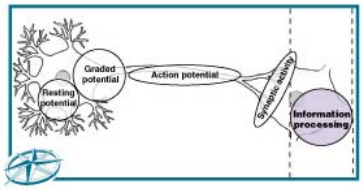


Indirect via intracellular proteins

- Gases don't need an extracellular receptor. Why not?
- Enzymes activated inside cell
- Also involves 2nd messenger systems
- Modulatory, like G proteins



Information Processing



Synapses

- WTF?
- Why do neurons go right up next to each other and then stop, leaving a little space?
- Wouldn't it just be better if they were all connected by gap junctions? Why is a system with many discrete cells better than cells being just little parts of a huge aggregation?

Information Processing

- At the simplest level (individual neurons):
  - many dendrites receive neurotransmitter messages simultaneously
  - some excitatory, some inhibitory
  - net effect on axon hillock determines if action potential is produced

2 Types of Postsynaptic Potentials

1. Excitatory postsynaptic potential (EPSP):
   - graded depolarization of postsynaptic membrane (postsynaptic membranes do not generate action potentials – why not?)
2. Inhibitory postsynaptic potential (IPSP):
   - graded hyperpolarization of postsynaptic membrane

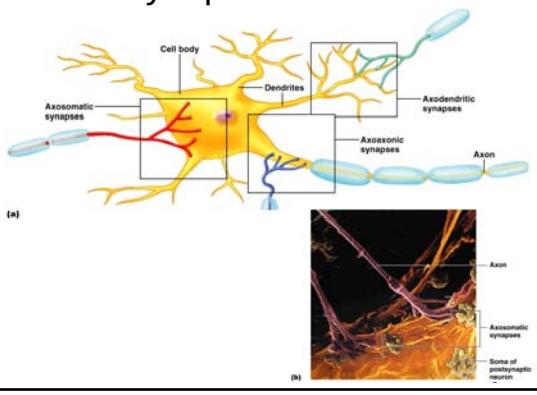
Inhibition

- A neuron that receives many IPSPs:
  - is inhibited from producing an action potential
  - because the stimulation needed to reach threshold is increased

Summation

- To trigger an action potential:
  - 1 EPSP is not enough
  - EPSPs (and IPSPs) combine through summation:
    - temporal summation
    - spatial summation

Synapse Location



Coding for Stimulus Intensity

- All action potentials are alike and are independent of stimulus intensity
- Frequency of action potentials depends on degree of depolarization above threshold
  - Strong stimuli can generate an action potential more often than weaker stimuli
- The CNS determines stimulus intensity by the frequency of impulse transmission

Stimulus Strength and AP

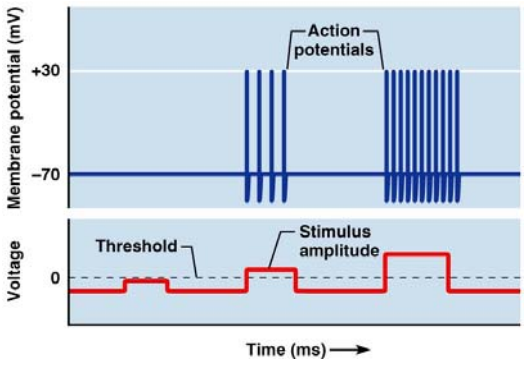
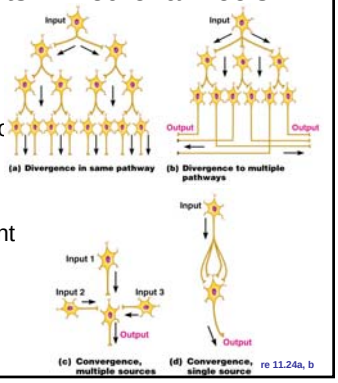


Figure 11.14

Types of Circuits in Neuronal Pools

- Divergent – one incoming fiber stimulates ever increasing number c fibers, often amplifying circuits
- Convergent – opposite of divergent circuits, resulting in either strong stimulation or inhibition



re 11.24a, b

Types of Circuits

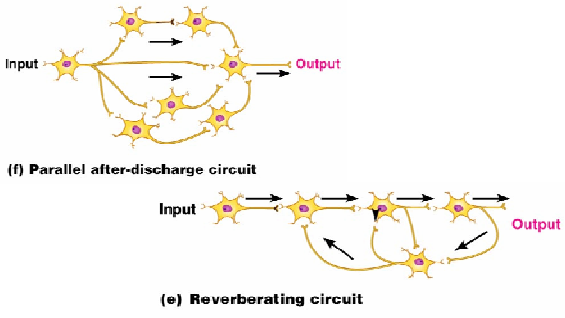


Figure 11.24c, d

Summary: Principles of Information Processing

SUMMARY TABLE 12–7 | INFORMATION PROCESSING

- The neurotransmitters released at a synapse may have either excitatory or inhibitory effects. The effect on the axon's initial segment reflects a summation of the stimuli that arrive at any moment. The frequency of generation of action potentials is an indication of the degree of sustained depolarization at the axon hillock.
- Neuromodulators can alter either the rate of neurotransmitter release or the response of a postsynaptic neuron to specific neurotransmitters.
- Neurons may be facilitated or inhibited by extracellular chemicals other than neurotransmitters or neuromodulators.
- The response of a postsynaptic neuron to the activation of a presynaptic neuron can be altered by (1) the presence of neuromodulators or other chemicals that cause facilitation or inhibition at the synapse, (2) activity under way at other synapses affecting the postsynaptic cell, and (3) modification of the rate of neurotransmitter release through presynaptic facilitation or presynaptic inhibition. Information is relayed in the form of action potentials. In general, the degree of sensory stimulation or the strength of the motor response is proportional to the frequency of action potentials.