SLOs 7.1 – 7.2

- Describe the different types of neurons and supporting cells, and identify their functions.
- Identify the myelin sheath and describe how it is formed in the CNS and PNS.
- Describe the nature and significance of the BBB.
- Explain step by step how an AP is created and reproduced.
- Describe the characteristics of APs and explain how they are conducted by unmyelinated and myelinated axons.
- Explain the refractory period and its significance.
SLOs 7.3 – 7.7

- Describe the structure and function of electrical and chemical synapses
- Identify the nature of EPSPs and IPSPs
- Explain how ligand-gated channels produce synaptic potentials, using the **nicotinic ACh receptor** as an example.
- Explain how G-protein-coupled channels produce synaptic potentials, using the **muscarinic ACh receptor** as an example.
- Describe the action and significance of **ACh-esterase**
- Compare EPSPs and APs; identify where each is produced and explain how APs can be stimulated by EPSPs
- Identify the monoamine NTs and explain how they are inactivated at the synapse
- Identify 2 neural pathways in the brain that use dopamine as a NT, and explain their significance
- Describe action and significance of GABA and glycine
- Explain nature of spatial and temporal summation at the synapse
Anatomy Review: Organization of NS

Compare to Fig 7.3
## Terminology Pertaining to the Nervous System

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central nervous system (CNS)</td>
<td>Brain and spinal cord</td>
</tr>
<tr>
<td>Peripheral nervous system (PNS)</td>
<td>Nerves, ganglia, and nerve plexuses (outside of the CNS)</td>
</tr>
<tr>
<td>Association neuron (interneuron)</td>
<td>Multipolar neuron located entirely within the CNS</td>
</tr>
<tr>
<td>Sensory neuron (afferent neuron)</td>
<td>Neuron that transmits impulses from a sensory receptor into the CNS</td>
</tr>
<tr>
<td>Motor neuron (efferent neuron)</td>
<td>Neuron that transmits impulses from the CNS to an effector organ; for example, a muscle</td>
</tr>
<tr>
<td>Nerve</td>
<td>Cablelike collection of many axons in the PNS; may be “mixed” (contain both sensory and motor fibers)</td>
</tr>
<tr>
<td>Somatic motor nerve</td>
<td>Nerve that stimulates contraction of skeletal muscles</td>
</tr>
<tr>
<td>Autonomic motor nerve</td>
<td>Nerve that stimulates contraction (or inhibits contraction) of smooth muscle and cardiac muscle and that stimulates glandular secretion</td>
</tr>
<tr>
<td>Ganglion</td>
<td>Grouping of neuron cell bodies located outside the CNS</td>
</tr>
<tr>
<td>Nucleus</td>
<td>Grouping of neuron cell bodies within the CNS</td>
</tr>
<tr>
<td>Tract</td>
<td>Grouping of axons that interconnect regions of the CNS</td>
</tr>
</tbody>
</table>
Neurons and Supporting Cells

Nerve cell = __________________
  – Functional unit of nervous system
  – Excitable ⇒ can generate & carry electrical signals

Support cells = __________________

Neuron classification either structural or functional (?)

Distinguish between neuron and nerve
General structure and function of neurons

• Neurons vary in size and shape, but they all have:
  – A cell body that contains the nucleus and other organelles
    • cluster in groups called nuclei in the CNS and ganglia in the PNS
  – Dendrites: receive impulses and conducts a graded impulse toward the cell body
  – Axon: conducts action potentials away from the cell body
Axonal Transport

What is it?
Why is it necessary?

Slow axonal transport (0.2 - 8 mm/day)
Transport of enzymes etc. that are not quickly consumed

Fast axonal transport (up to 400 mm/day)
Utilizes kinesins & dynactins. They walk along

Used for active transport of vesicles up and down axons
Axonal Transport

Also: Mechanism of infection by herpes virus, rabies virus, tetanus toxin
Neuroglial Cells

*In CNS:*
1. ________________
2. ________________
3. ________________ (modified ________________)
4. ________________

*In PNS:*
5. ________________
6. Satellite cells
Neurilemma and Myelin Sheath

All axons in PNS are surrounded by a sheath of Schwann cells: ________________
Axon Collaterals

Single CNS neuron can synapse with many other neurons (30,000-60,000)
**Regeneration of a Cut Neuron**

*In PNS:*

Severed part of axon degenerates.

Regeneration tube formed by Schwann cells.

- Release of growth factors
  ➞ axon sprouts within regeneration tube

- New axon connects to undamaged axon or effector

*Fig 7.9*
CNS Regeneration

Adult CNS axons do not readily regenerate. Oligodendrocytes produce *Nogo* protein to inhibit axon regeneration.

Hot research topic in field of spinal cord injury and otherwise restoring lost CNS function.

**Neurotrophins** promote neuronal growth in the fetal brain: Nerve growth factor (**NGF**)

In adults, neurotrophins play a role in activity-dependent learning and memory.
Astrocytes

Most abundant glial cell

Processes with end-feet associate with blood capillaries and axon terminals

Influence interactions between neurons and between neurons and blood

**Astrocyte Functions:**
1. Take up K\(^+\) from ECF
2. Take up glucose from blood for use by neurons
3. Form the BBB - significance of BBB?

....and many more functions
Electrical Activity in Axons

Changes in resting membrane potential are the basis for electrical signaling.

Only ______ and ______ cells are excitable (= able to propagate electrical signals).

Excitability (= irritability): Ability to produce and conduct electrical signal.

Factors influencing membrane potential.
**Terminology**

- **RMP** = _______
- **Changes in Ion Permeability** lead to change in membrane potential

**Stimulus**

- Depolarization
- Repolarization
- Hyperpolarization

**Fig 7-11**

- Membrane potential difference ($V_m$)
- Depolarization
- Repolarization
- Hyperpolarization

**Graph**

- $V_m$ decreases
- $V_m$ increases

**Time (msec)**
Membrane Potential Review

*Nernst equation* describes equilibrium potential for single ions

*Goldman-Hodgkin-Katz (GHK) equation* considers contribution of all permeable ions to membrane potential

Resting membrane potential of cell is based on combined contributions of conc. gradients and membrane permeability for Na\(^+\), K\(^+\) (*and* Cl\(^-\*)
Ion Movement across Cell Membrane Creates Electrical Signal

• Change in RPM due to changes in ion permeability

• Requires ion channels
  – Leakage channels
  – Gated channels:
    • Voltage gated
    • Mechanically gated
    • Chemically gated

• Very few ions need to move for big change in membrane potential \( \Rightarrow \) membrane potential changes but ion conc. stays the “same”
Two Basic Types of Electrical Signals

Graded potentials

- variable strength
- travel over short distances only

Action potentials

- constant strength
- travel rapidly over longer distances
- initiated by strong graded potential
Four Basic Components of Signal Movement Through Neuron

1. Input signal (Graded Potential)

2. Integration of input signal at trigger zone

3. Conduction signal to distal part of neuron (= Action Potential)

4. Output signal (usually neurotransmitter)
Ion Gating in Axons

Ions channels in neurons:

– Non-gated channels
  • $K^+$ Leakage Channels

– Gated channels
  • $Na^+$ voltage-gated channels
  • $K^+$ voltage-gated channels

Fig 7.12
Action Potentials (APs)

- **Threshold** membrane potential: −55mV
- Positive feedback loop!
- During **depolarization** membrane potential reaches +30mV

![Diagram of Action Potentials (APs)](image_url)

**Fig 7.13**
Summary of Ion Movement across Cell Membrane During AP

Sudden increase in Na$^+$ permeability

Na$^+$ enters cell down ______________ gradient (pos. feedback loop for $\sim 0.5$ msec)

Influx causes depolarization of membrane potential: This is the electrical signal

What stops + feedback loop?

Fig 7.14
**Na⁺ Channels in Axon Have 2 Gates**

**Activation gate and Inactivation gate**

Na⁺ entry based on pos. feedback loop
⇒ needs intervention to stop

Inactivation gates close in delayed response to depolarization
⇒ stops escalating pos. feedback loop
Model of Activation and Inactivation Gates

(a) At the resting membrane potential, the activation gate closes the channel.

(b) Depolarizing stimulus arrives at the channel.

(c) With activation gate open, Na⁺ enters the cell.

(d) Inactivation gate closes and Na⁺ entry stops.

(e) During repolarization caused by K⁺ leaving the cell, the two gates reset to their original positions.
1. Rising: ___________________
   \((\text{Na}^+ \text{ permeability})\)

2. Falling: ___________________
   \((\text{K}^+ \text{ permeability})\)

3. “Undershoot” or ____________

Role of \(\text{Na}^+ / \text{K}^+\) pumps in all this?
**AP Review:**

- Location of AP?

- Represent movement of ____ and ____ across membrane

- Are all identical: **All-or-None Law.** Independent on stimulus strength. Amplitude always ______

- Once **threshold** has been reached, **AP** will happen

- Travel over long/short distances

- Do not loose strength as they travel
Coding for Stimulus Intensity

A stronger stimulus

- will make APs occur more frequently: (frequency modulated)
- may activate more neurons in a nerve: Recruitment.

![Diagram showing action potentials and stimulus intensity](image)
Refractory Periods

• APs can only increase in frequency to a certain point due to **refractory period**.

  • **Absolute refractory period**: \( Na^+ \) channels inactive – Inactivation gates closed!

  • **Relative refractory period**: \( K^+ \) channels still open, stronger than normal stimulus required

• Outcome: Each AP remains a separate all-or-none event
Absolute & Relative Refractory Periods

No movement of Na\(^+\) possible

**Absolute refractory period**
During the absolute refractory period, no stimulus can trigger another action potential.

**Relative refractory period**
During the relative refractory period, only a larger-than-normal stimulus can initiate a new action potential.

Na\(^+\) channels reset to resting state; K\(^+\) channels still open \(\Rightarrow\) > normal stimulus necessary
Main Purpose of Refractory Periods

1. Limit signal transmission rate (no summation!)

2. Assure one way transmission!

Forward current excites, backward current does NOT re-excite!
Conduction of Nerve Impulses

AP at one location serves as the depolarization stimulus for the next region of the axon.

APs are recreated down the entire length of the axon at every patch of membrane.

Conduction rate in unmyelinated axons slow because so many (identical) APs generated.

Conduction in a myelinated neuron: Na⁺ ion channels concentrated at nodes → Saltatory conduction.
Conduction in a Myelinated Neuron

AP conduction speed determined by:

- **Diameter** of axon
- **Degree of myelination**
Saltatory Transduction

Demyelination diseases (E.g. ?)
Clinical Application:

• **MS** (p. 168)

• **Local anesthetics** (p. 175)
7.3 The Synapse

**Def:** Functional connection between a neuron and the cell it is signaling

- *In CNS signal goes to* ______________________________
- *In PNS* ___________ or effector cell: ____________, or ____________

Presynaptic and postsynaptic neurons

axodendritic, axosomatic, and axoaxonic synapses.
**Electrical Synapse vs. Chemical Synapse**

- **In cardiac & smooth muscle; between glial cells & some CNS neurons**
- **Gap junctions**
- **Stimulation causes phosphorylation or dephosphorylation of connexin proteins to open or close channels**

- **Release of NT from axon terminals**
- **The synaptic cleft very small (necessary for successful ________)**
- **Presynaptic and postsynaptic cells held together by cell adhesion molecules (CAMs)**
Chemical Synapses

Majority of synapses

**Neurotransmitters** carry info from cell to cell

Axon terminals have mitochondria & synaptic vesicles containing neurotransmitter

*Compare to Fig 7-22*
Events at the Synapse: Release of NT

AP reaches axon terminal

Voltage-gated Ca\(^{2+}\) channels open

Ca\(^{2+}\) entry and binding to protein

Exocytosis of neurotransmitter containing vesicles
Actions of NTs

1. **NT** (ligand) binds to postsynaptic receptor

2. Ligand-gated ion channels open or close \(\Rightarrow\) **RMP changes** depending on which ion channel is opened or closed

3. Postsynaptic potential may be depolarizing

\[= \quad \text{___________}\]

or

hyperpolarizing

\[= \quad \text{___________}\]

Which is it?
EPSPs vs. IPSPs

Opening Na\(^+\) or Ca\(^{2+}\) channels
⇒ What happens with RMP?
⇒ __________

Opening K\(^+\) or Cl\(^-\) channels
⇒ What happens with RMP?
⇒ __________
Subthreshold potential vs. Suprathreshold potential

1. 
2. 

Fig 8-7 b) & c)
Integration of Neural Info Transfer

Postsynaptic Responses can lead to either EPSP or IPSP

Any one synapse can only be either excitatory or inhibitory

Multiple graded potentials are integrated at ______________ to evaluate necessity of AP
1. A graded potential above threshold reaches the trigger zone.

2. Voltage-gated Na⁺ channels open and Na⁺ enters the axon.

3. Positive charge flows into adjacent sections of the axon by local current flow.

4. Local current flow from the active region causes new sections of the membrane to depolarize.

5. The refractory period prevents backward conduction. Loss of K⁺ from the cytoplasm repolarizes the membrane.
Summary of Neurotransmitter Action

Presynaptic neuron:
- Action potentials conducted by axon
- Axon terminals
  - Open voltage-gated Ca\(^{2+}\) channels
  - Release of excitatory neurotransmitter

Postsynaptic neuron:
- Dendrites and cell bodies
  - Opens chemically (ligand) gated channels
  - Inward diffusion of Na\(^{+}\) causes depolarization (EPSP)
  - Localized, decremental conduction of EPSP
- Axon initial segment
  - Opens voltage-gated Na\(^{+}\) and then K\(^{+}\) channels
- Axon
  - Conduction of action potential
7.4 Acetylcholine (ACh) as a NT

Excitatory in CNS, ganglia, and at neuromuscular junction of somatic motor neurons due to **nicotinic ACh receptors**.

Excitatory or inhibitory at neuro-effector junctions of autonomic motor neurons due to **muscarinic ACh receptors**.
Two Types of Acetylcholine Receptors:

1) Nicotinic cholinergic receptors

Ligand gated channels

In autonomic ganglia, somatic NS, and some parts of CNS

- **Nicotine** = ____________

- Directly opens monovalent Na\(^+\) / K\(^+\) channels: \(\Rightarrow ?\)

- **Curare** inactivates this receptor \(\Rightarrow = \) ________________

*(see Table 7-5)*
2) Muscarinic cholinergic receptor

Muscarine = _________

Found in neuro-effector junctions of parasympathetic branch (smooth and cardiac muscles and glands), and some parts of CNS

Atropine = antagonist *(used for?)*
Agonists and Antagonist of ANS

Direct Antagonists

- Atropin → ?
- Curare → ?
Interruption of Neuromuscular Transmission

• Tetrodotoxin found in Puffer fish. 1200 times more poisonous than cyanide.
Drugs that Affect the Neural Control of Skeletal Muscles

<table>
<thead>
<tr>
<th>Drug</th>
<th>Origin</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Botulinum toxin</td>
<td>Produced by Clostridium botulinum (bacteria)</td>
<td>Inhibits release of acetylcholine (ACh)</td>
</tr>
<tr>
<td>Curare</td>
<td>Resin from a South American tree</td>
<td>Prevents interaction of ACh with its nicotinic receptor proteins</td>
</tr>
<tr>
<td>α-Bungarotoxin</td>
<td>Venom of Bungarus snakes</td>
<td>Binds to ACh receptor proteins and prevents ACh from binding</td>
</tr>
<tr>
<td>Saxitoxin</td>
<td>Red tide (Gonyaulax) algae</td>
<td>Blocks voltage-gated Na⁺ channels</td>
</tr>
<tr>
<td>Tetrodotoxin</td>
<td>Pufferfish</td>
<td>Blocks voltage-gated Na⁺ channels</td>
</tr>
<tr>
<td>Nerve gas</td>
<td>Artificial</td>
<td>Inhibits acetylcholinesterase in postsynaptic membrane</td>
</tr>
<tr>
<td>Neostigmine</td>
<td>Nigerian bean</td>
<td>Inhibits acetylcholinesterase in postsynaptic membrane</td>
</tr>
<tr>
<td>Strychnine</td>
<td>Seeds of an Asian tree</td>
<td>Prevents IPSPs in spinal cord that inhibit contraction of antagonistic muscles</td>
</tr>
</tbody>
</table>
Muscarinic ACh Receptors are G-protein Mediated

Compare to Fig 7.27

heart

______polarization

Dig tract

______polarization
Termination of NT Activity:

Removal of neurotransmitter from the synaptic cleft.
1. Enzymatic degradation
2. Re-uptake
3. Diffuse out of synaptic cleft, picked up by astrocytes
7.5 Monoamines as NTs

• Monoamines are derived from amino acids.

• Tyrosine: Catecholamines, such as dopamine, norepinephrine, and epinephrine

• Tryptophan: Serotonin (SSRIs!)

• Histidine: Histamine, NT as well as other regulatory functions

• None of the receptors are direct ion channels

• All use second messenger system. Most common? ________

• Inactivation through reuptake and degradation: MAO = __________________________
Monoamine Action and Inactivation

1. Monoamine produced and stored in synaptic vesicles
2. Action potentials open gated Ca$^{2+}$ channels, leading to release of neurotransmitter
3. Neurotransmitters enter synaptic cleft
4. Reuptake of most neurotransmitter from synaptic cleft
5. Inactivation of most neurotransmitter by MAO
Norepinephrine Action

Exact action depends on exact type of **adrenergic receptor**

G protein linked, with various 2\textsuperscript{nd} messenger mechanisms

*Example:*

1. Norepinephrine binds to its receptor
2. G-protein subunits dissociate
3. Adenylate cyclase activated
4. cAMP activates protein kinase, which opens ion channels

\[ \text{Fig 7-30} \]
Serotonin as a NT

Used by neurons in middle region of brain stem

- Implicated in
  - Mood
  - Behavior
  - Appetite
  - Circulation, etc.

- LSD and other hallucinogenic drugs may be agonists

- Many receptors allow for diversity of function

- Different drugs target specific serotonin receptors

  \[\Rightarrow\] various SSRIs used to treat _______________

  (Prozac, Paxil, Zoloft)
Dopamine as a NT

Dopaminergic neurons highly concentrated in two main areas of midbrain:

- **Nigrostriatal** – motor control
- **Mesolimbic** – emotional control
- **Associated diseases?**
NE as a NT

- Used in CNS and PNS
- Sympathetic neuro-effector junction (smooth muscles, cardiac muscles, and glands)
- CNS neurons associated with arousal
- Amphetamines stimulate NE pathways in brain
7.6 Other NTs: Inhibitory NTs

• Glycine and GABA

• Produce IPSPs. How possible?

• For regulation of skeletal muscle movement. Allows antagonistic muscle groups to relax while others are contracting. Also relaxation of diaphragm

• Strychnine blocks glycine receptors ⇒ death by asphyxiation.

• Huntington disease ⇒ Progressive degeneration of GABA-neurons in cerebellum
1. Channel closed until receptor binds to GABA

2. GABA receptor binds to GABA, Cl⁻ channel opens

3. Diffusion of Cl⁻ into cell causes hyperpolarization (IPSP)
7.7 Synaptic Integration

Neural Pathways May Involve Many Neurons

Divergence vs. Convergence

- **Divergence**
  - A mechanism for spreading stimulation to multiple neurons or neuronal pools in the CNS

- **Convergence**
  - A mechanism for providing input to a single neuron from multiple sources

Axons have collateral branches
Summation of EPSPs and IPSPs at axon hillock: Multiple graded potentials are integrated to evaluate necessity of AP

Spatial Summation: stimuli from different locations are added up

Temporal Summation due to sequential stimuli due to successive waves of NT release is added up
Spatial Summation

Fig 7-33
Postsynaptic Inhibition

• Postsynaptic inhibition due to hyperpolarization of postsynaptic neuron.

• How possible?

• In spinal cord mainly due to release of ______________

• in brain __________

Fig 7-34
Clinical Investigation: Red Tide Warning

Health warning for shellfish from Half Moon Bay, Monterey Bay. SF Gate, August 21

Next crab season remains murky. Half Moon Bay Review, August 17

State sets up information link for algal blooms. Central Valley Business Times, August 17