Terms you should know: synapse, neuromuscular junction (NMJ), pre-synaptic, post-synaptic, synaptic cleft, acetylcholine (ACh), acetylcholine receptor, curare, ligand-dependent, acetylcholinesterase (AChase), EPSP, IPSP, gamma-amino butyric acid (GABA), steady-state potential (reversal potential), catecholamine, ionotropic, metabotropic, second messenger, G-protein, transmitter inactivation, spatial summation, temporal summation.

I. The flexibility of the nervous system is based on signals passing between neurons, a process called synaptic transmission.
   A. Along an axon, the intensity of a signal is coded in the frequency of action potentials. (When many neurons respond to the same input, intensity can also be encoded in the number of neurons activated.)
   B. The flexibility of the nervous system arises because most pathways through the system include several neurons, and the properties of a signal are modified at each of the synaptic junctions between the neurons.

II. Signal transmission between neurons is usually chemically mediated, and unlike action potentials, synaptic signals are graded in amplitude.
   A. Transmission occurs at points of contact called synapses. The best-studied synapse is the vertebrate neuromuscular junction (NMJ), between the axon terminal of a motor neuron and a skeletal muscle (Fig. 3.1).
      1. Structures
         a. Pre-synaptic terminal.
         b. Post-synaptic membrane (also called “junctional folds” at the NMJ).

      ![](image.png)
      **Fig. 3.1.** Left: Nerve terminating on frog muscle fibers. Right: Schematic of a neuromuscular junction.

      2. Summary of function (Fig. 3.2):
         a. Molecules of neurotransmitter are released by depolarization of the presynaptic terminal.
         b. Neurotransmitter molecules diffuse across the synaptic cleft and interact with receptor molecules on the postsynaptic membrane.
         c. This binding produces a change in conductance to one or more ions Ions, which flow through the open channels, causing a change in $V_m$ in the postsynaptic cell.
         d. At the NMJ, the $V_m$ depolarizes the muscle membrane enough to initiate an action potential.
Fig. 3.2. Left: an electron micrograph of vesicles being released at a NMJ. Right: Schematic of the steps in vesicle release.

B. Details of the electrical and chemical events in synaptic transmission at the NMJ.
(Other synapses are similar, but the transmitter, the nature of the receptor molecules, and the effect on the post-synaptic neuron varies among synapses.)

1. At the presynaptic terminal:
   a. Action potential opens Ca\(^{++}\) channels. (Certain Ca\(^{++}\) channel blockers specifically prevent this channel opening.)
   b. Vesicles containing the neurotransmitter fuse with the plasma membrane.
   c. Transmitter--**acetylcholine (ACh)**--is released into the synaptic cleft and diffuses in the cleft.

2. At the postsynaptic membrane:
   a. ACh binds to receptor molecules in the postsynaptic membrane.
      (Curare, a competitive inhibitor, binds to the receptors and blocks ACh binding.)
   b. An ion channel that is part of the receptor protein complex opens (they are called **ionotropic** receptors) producing an excitatory postsynaptic potential (**EPSP**).
   c. These receptors are opened **only** by this chemical signal, so it is **ligand-dependent** (not voltage-dependent).
   d. When this conductance opens, ions will move if they are permitted through the channel **and** there is a driving force on them: \(I_x = G_x (V_m - E_x)\)
   e. The NMJ channels aren't very selective; they allow both Na\(^+\) and K\(^+\) to flow, so:
      \[
      I_{total} = I_{Na} + I_K = G_{Na} (V_m - E_{Na}) + G_{K} (V_m - E_{K})
      \]
      Note: synaptic channels have a much larger conductance than leak channels, so they determine the membrane potential.
   f. ACh is rapidly broken down in the synaptic cleft by **acetylcholinesterase (AChase)**.
      (Mustard gas and organophosphate insecticides block AChase, prolonging synaptic potentials.)
g. The PSP is terminated when so few ACh molecules are bound to receptors that the postsynaptic membrane approaches the conductance at the resting potential.

3. PSP’s can be either **excitatory** (depolarizing) or **inhibitory** (usually, but not always, hyperpolarizing); they are called **EPSPs** and **IPSPs** (Fig. 3.3).

a. Some transmitters, like ACh and glutamate, are usually excitatory.

b. Other transmitters, like **gamma-amino-butyric acid (GABA)** and glycine, are usually inhibitory.

c. **NOTICE:** In the end, whether a PSP is excitatory or inhibitory—or will cause a change in V_m at all—is determined by the same forces as for the resting potential:

   i. which channels are open;
   
   ii. the direction that ions flow in response to the forces acting on them \( I_X = G_X (V_m - E_X) \); and
   
   iii. the charge on the ions.

d. For **EPSPs**, the **steady-state potential** (aka **reversal potential**) lies above the threshold for the action potential, so the membrane potential depolarizes when ions flow (Fig. 3.4A).

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**Fig. 3.3**

Some PSPs cause hyperpolarization:

Others cause depolarization:

Notice the amplitude of PSPs compared with action potentials.

**Fig. 3.4**

**Fig. 3.4A.** Reversal potentials for the EPSP at a NMJ.

**Fig. 3.4B.** Ionic currents responsible for the reversal potential.
e. The reversal potential is the sum of opposing currents; for example, the EPSP at the NMJ depends upon Na\(^+\) and K\(^+\) currents (Fig. 3.4B).

f. Similarly, an IPSP also has a reversal potential:

![Graph showing reversal potentials for EPSP and IPSP](image)

**Fig. 3.5.** This example of an IPSP shows that its reversal potential (around -90 mV) causes a hyperpolarization from the resting potential (-68 mV) and an even larger hyperpolarization when the membrane potential is near the threshold potential (-50 mV).

![Graph showing EPSP and threshold potential](image)

**Fig. 3.6.** An EPSP is depolarizing and can bring the membrane potential above threshold.

i. For excitatory EPSPs, the $E_{EPSP}$ is always more positive than $V_{threshold}$, so an EPSP always makes the neuron more likely to produce an action potential (Fig. 3.6).

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### Lecture 3. **Synaptic Transmission**

- **e.** The reversal potential is the sum of opposing currents; for example, the EPSP at the NMJ depends upon Na\(^+\) and K\(^+\) currents (Fig. 3.4B).
- **f.** Similarly, an IPSP also has a reversal potential:

![Graph showing reversal potentials for EPSP and IPSP](image)

**Fig. 3.5.** This example of an IPSP shows that its reversal potential (around -90 mV) causes a hyperpolarization from the resting potential (-68 mV) and an even larger hyperpolarization when the membrane potential is near the threshold potential (-50 mV).

![Graph showing EPSP and threshold potential](image)

**Fig. 3.6.** An EPSP is depolarizing and can bring the membrane potential above threshold.
ii. For **IPSPs**, the reversal potential lies below the threshold for the action potential (**Fig. 3.7**), so the membrane potential cannot depolarize beyond the $E_{\text{IPSP}}$, and no action potential can be generated.

**Fig. 3.7.** Usually, an IPSP is *hyperpolarizing* because the reversal potential ($E_{\text{IPSP1}}$) is more negative than the resting potential.

**Fig. 3.8.** In some cases, however, an IPSP is *depolarizing*, but can never bring the membrane potential to threshold because its reversal potential ($E_{\text{IPSP2}}$) is below the threshold potential ($V_{\text{threshold}}$), so the membrane potential is kept from reaching threshold.
C. Postsynaptic mechanisms are of two types (Fig. 3.9).

1. **Ionotropic** (fast, direct): receptor and the channel are the same protein complex (e.g., the NMJ).
2. **Metabotropic** (slow, indirect): the receptor is separate from the channel.

![Diagram of postsynaptic mechanisms](image)

**Fig. 3.9.** Types of postsynaptic receptor mechanisms (Fig. 8-23 from Silverthorn, 6th edition).

- a. Metabotropic receptors always activate a **second messenger**, often a **G-protein**, associated with the receptor; it diffuses internally and binds to the ionic channel.
- b. The opening and closing of the channel is slow: it may take seconds to turn on and can last for minutes.
c. The second messenger usually activates a cascade of enzymes systems, and may even activate gene transcription.
   i. This cascade amplifies the effects of the transmitter.
   ii. The cascade also often changes the internal metabolism of the neuron.

D. **Mechanisms of transmitter inactivation.**
1. Re-uptake: specialized transporters move transmitter into the presynaptic terminal (and glial cells).
2. Enzymes: breaks down the transmitter molecules; can be on postsynaptic membranes, in the gap, or even in the presynaptic cytoplasm.
3. Overflow: diffuse out of the terminals into the interstitial fluid or bloodstream.

**Fig. 3.10.** Inactivation of neurotransmitters. The 3 major mechanisms for terminating the actions of transmitters: (1) re-uptake, (2) breakdown; and (3) overflow.

E. Many of the most effective drugs for treating emotional disorders (e.g., depression, schizophrenia) interfere with transmitter inactivation, thereby prolonging the lifetime of the transmitter molecules.

F. Many drugs of abuse (e.g., heroin, cocaine) either mimic the effects of natural transmitters or block their re-uptake.

G. Several types of molecules other than acetylcholine have been identified as neurotransmitters, including:
   a. Modified amino acids (catecholamines), including GABA, serotonin, epinephrine, norepinephrine, and dopamine.
   b. Some unmodified amino acids, such as glutamic acid, aspartic acid, and glycine.
   c. Several small to medium-sized peptides.
   d. All of these--plus many more (e.g., ATP, NO)--are found in the central nervous system.
Table 3.1. Typical small neurotransmitters, their structures and functions.

<table>
<thead>
<tr>
<th>Neurotransmitter</th>
<th>Typical effects</th>
<th>Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetylcholine (Ach)</td>
<td>Fast excitation; slow inhibition</td>
<td><img src="image" alt="Acetylcholine structure" /></td>
</tr>
<tr>
<td>Glycine (Gly)</td>
<td>Fast inhibition</td>
<td><img src="image" alt="Glycine structure" /></td>
</tr>
<tr>
<td>γ-aminobutyric acid (GABA)</td>
<td>Fast inhibition; slow inhibition</td>
<td><img src="image" alt="γ-aminobutyric acid structure" /></td>
</tr>
<tr>
<td>Glutamate (Glu)</td>
<td>Fast excitation; slow change in postsynaptic metabolism</td>
<td><img src="image" alt="Glutamate structure" /></td>
</tr>
<tr>
<td>Norepinephrine (Nor-epi)</td>
<td>Slow excitation; slow inhibition</td>
<td><img src="image" alt="Norepinephrine structure" /></td>
</tr>
<tr>
<td>Dopamine</td>
<td>Differs with location but causes slow postsynaptic effects</td>
<td><img src="image" alt="Dopamine structure" /></td>
</tr>
<tr>
<td>Serotonin (5-HT = 5-hydroxytryptamine)</td>
<td>Slow excitation or slow inhibition</td>
<td><img src="image" alt="Serotonin structure" /></td>
</tr>
<tr>
<td>Nitrogen oxide (NO)</td>
<td>Synaptic modulation</td>
<td><img src="image" alt="Nitrogen oxide structure" /></td>
</tr>
<tr>
<td>Adenosine triphosphate (ATP)</td>
<td>Both fast and slow synaptic transmission</td>
<td><img src="image" alt="Adenosine triphosphate structure" /></td>
</tr>
<tr>
<td>Histamine</td>
<td>Slow modulation</td>
<td><img src="image" alt="Histamine structure" /></td>
</tr>
</tbody>
</table>

Notice: the effect of a neurotransmitter depends upon the response of the target (postsynaptic) cell, not on the chemical nature of the transmitter.
E. Usually more than one (presynaptic) neuron synapses onto any particular (postsynaptic) neuron, which can produce **summation** of the synaptic potentials.

![Diagram of synaptic transmission](image)

**Fig. 3.11.** The consequences of spatial and temporal summation.

1. **EPSPs depolarize the postsynaptic cell; IPSPs can either depolarize or hyperpolarize the cell, always making it less likely that the cell will produce action potentials.**

2. **Spatial summation:** input from more than one presynaptic neuron at nearly the same time.

3. **Temporal summation:** input from a single presynaptic neuron at a high rate (i.e., short intervals).

4. **EPSPs from just one neuron rarely initiate action potentials in another neuron.** As a result, the nervous system has great flexibility in how signals travel through neuronal networks.

### Table 3.2. SUMMARY: Comparisons of action potentials, EPSPs and IPSPs

<table>
<thead>
<tr>
<th></th>
<th>Action potentials</th>
<th>EPSPs (at NMJ)</th>
<th>IPSPs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effect of depolarization:</td>
<td>Initiates APs</td>
<td>Decreases $V_{EPSP}$</td>
<td>It's complicated...</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No effect on $G_{EPSP}$</td>
<td>No effect on $G_{IPSP}$</td>
</tr>
<tr>
<td>Neurotransmitter effect:</td>
<td>No effect</td>
<td>$ACh$ increases $G_{ions}$</td>
<td>Transmitter increases $G_{ions}$</td>
</tr>
<tr>
<td>Response regenerative or graded?</td>
<td>Regenerative</td>
<td>Graded with amount of $ACh$</td>
<td>Graded with amount of transmitter</td>
</tr>
<tr>
<td>Ions involved:</td>
<td>$Na^+$, $K^+$ and sometimes $Ca^{++}$</td>
<td>$Na^+$, $K^+$</td>
<td>$K^+$ and/or $Cl^-$</td>
</tr>
<tr>
<td>Ions move through same or separate channels?</td>
<td>Separate</td>
<td>Same</td>
<td>Separate</td>
</tr>
<tr>
<td>Effect of TTX:</td>
<td>Blocked</td>
<td>Action potentials</td>
<td>Action potentials</td>
</tr>
<tr>
<td>Effect of TEA:</td>
<td>Prolonged</td>
<td>No effect</td>
<td>No effect</td>
</tr>
<tr>
<td>Effect of curare:</td>
<td>No effect</td>
<td>Blocked</td>
<td>No effect</td>
</tr>
</tbody>
</table>

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**Table 3.2.** SUMMARY: Comparisons of action potentials, EPSPs and IPSPs.