Synaptic Transmission
Two key discoveries:

Sherrington (early 1900s): pre- and post-synaptic neurons are separated by a gap.

Loewi (1920s): synaptic transmission involves chemicals known as neurotransmitters (NTs) or neuromodulators.
Direct and Nondirect Synapses

Directed synapse: site of release and contact are in close proximity.

Nondirected synapse: site of release and contact are separated by some distance (e.g., hormones and neuromodulators).
## Synthesis, Packaging and Transport

<table>
<thead>
<tr>
<th></th>
<th>Small (4 types)</th>
<th>Large (1 type)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Synthesis</strong></td>
<td>in cytoplasm of terminal button</td>
<td>in cytoplasm of cell body</td>
</tr>
<tr>
<td><strong>Packaged</strong></td>
<td>Golgi complex</td>
<td>Golgi complex</td>
</tr>
<tr>
<td><strong>Transport</strong></td>
<td>no</td>
<td>by microtubules to the button (40 cm/day)</td>
</tr>
<tr>
<td><strong>Storage</strong></td>
<td>near pre-synaptic membrane</td>
<td>far from pre-synaptic membrane</td>
</tr>
</tbody>
</table>
Many neurons contain two neurotransmitters: most always, one small in small vesicles; and one large packaged in larger vesicles.
**Release of Neurotransmitter Molecules**

**Exocytosis**: the process of neurotransmitter release

**Process**: arrival of AP; Ca$^{2+}$ influx; vesicles fuse to membrane and release NT

**Small NT**: 1 AP = 1 vesicle

**Large NT**: temporal sum of APs = 1 vesicle

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Heuser et al., JCB, 1979
NT molecules produce signals in postsynaptic neurons by binding to receptors.

Receptors (proteins) are specific for a given NT.

Ligand: a molecule that binds to another. A NT is a ligand of its receptor.

There are multiple receptor subtypes for a given NT (usually in different brain areas).
Receptor Types

Ionotropic receptors: associated with ligand-activated ion channels
- Speed: fast (channel opens or closes quickly)
- Result: PSP
  (EPSP: Na⁺; IPSP: K⁺,Cl⁻)

Metabotropic receptors: associated with signal proteins and G proteins
- Speed: slow
- Result: longer-lasting, more varied
Metabotropic Receptors

- NT 1\textsuperscript{st} messenger binds

- G protein subunit breaks away and migrates

- Sometimes: ion channel opens or closes

- Usually: a 2\textsuperscript{nd} messenger is synthesized, which can have a variety of effects (e.g. enter nucleus, bind to DNA, alter gene expression).
Metabotropic receptors on pre-synaptic membrane; function is to maintain appropriate level of NT release
# Small vs Large Neurotransmitters

## Neurotransmitter molecules

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<tr>
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<th>Small (4 types)</th>
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<tr>
<td><strong>Synapse</strong></td>
<td>direct</td>
<td>nondirect</td>
</tr>
<tr>
<td><strong>Receptor</strong></td>
<td>ionotropic, metabolotropic that act directly on ion channels</td>
<td>metabolotropic that activate 2(^{nd}) messengers</td>
</tr>
<tr>
<td><strong>Function</strong></td>
<td>transmit rapid, brief PSPs</td>
<td>transmit slow, diffuse, long-lasting signals</td>
</tr>
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Reuptake and Enzymatic Degradation

- As long as NT is in the synapse, it is “active”; activity must somehow be turned off
- Reuptake (typical): scoop up and recycle NT
- Enzymatic degradation: NT is broken down by enzymes (for example, acetylcholine by acetylcholinesterase)
Seven Steps in Neurotransmitter Action

1. Neurotransmitter molecules are synthesized from precursors under the influence of enzymes.
2. Neurotransmitter molecules are stored in vesicles.
3. Neurotransmitter molecules that leak from their vesicles are destroyed by enzymes.
4. Action potentials cause vesicles to fuse with the presynaptic membrane and release their neurotransmitter molecules into the synapse.
5. Released neurotransmitter molecules bind with autoreceptors and inhibit subsequent neurotransmitter release.
6. Released neurotransmitter molecules bind to postsynaptic receptors.
7. Released neurotransmitter molecules are deactivated by either reuptake or enzymatic degradation.
Gap Junctions and Synaptic Transmission

Most synapses are chemical in nature, but some are electrical.

Gap junctions connect the cytoplasm of two adjacent cells.

Gap junctions exist between neurons, glia, and neurons and glia.

Tripartite synapse: astrocytes wrap around synapses and connect to both pre- and post-synaptic cells (coordination?)
# Classes of Neurotransmitters

## Small-Molecule Neurotransmitters

<table>
<thead>
<tr>
<th>Class</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amino acids</td>
<td>Glutamate, Aspartate, Glycine, GABA</td>
</tr>
<tr>
<td>Monoamines</td>
<td>Dopamine, Epinephrine, Norepinephrine</td>
</tr>
<tr>
<td>Indolamines</td>
<td>Serotonin</td>
</tr>
<tr>
<td>Acetylcholine</td>
<td>Acetylcholine</td>
</tr>
<tr>
<td>Soluble gases</td>
<td>Nitric oxide, Carbon monoxide</td>
</tr>
<tr>
<td>Endocannabinoids</td>
<td>Anandamide</td>
</tr>
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</table>

## Large-Molecule Neurotransmitters

<table>
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<th>Class</th>
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</thead>
<tbody>
<tr>
<td>Neuropeptides</td>
<td>Pituitary peptides, Hypothalamic peptides, Brain–gut peptides, Opioid peptides, Miscellaneous peptides</td>
</tr>
</tbody>
</table>
Amino acids: the molecular building blocks of proteins

Obtained from proteins we eat or synthesized (GABA from glutamate)

Found at fast-acting direct synapses

Glutamate: most prevalent excitatory neurotransmitter (AMPA and NMDA)

GABA: most prevalent inhibitory NT

Balance of arousal and quiescence
Monoamines

• Synthesized from single (mono) amino acids
  catecholamines: tyrosine
  indolamines: tryptophan
• Synapses tend to be nondirect (note: unusual for small NTs)
• Effects are variable
Acetylcholine

- Synthesized by adding an acetyl group to choline (in eggs and milk)
- Often fast-acting direct synapses
- Two types of receptors (nicotinic vs muscarinic), distributed differently in the nervous system
  - Nicotinic: ionotropic, activates muscle
  - Muscarinic: metabotropic, memory
Unconventional Small Neurotransmitters

<table>
<thead>
<tr>
<th>Unconventional neurotransmitters</th>
<th>Soluble gases</th>
<th>Nitric oxide Carbon monoxide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocannabinoids</td>
<td></td>
<td>Anandamide</td>
</tr>
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</table>

Soluble gases:
- exist only briefly
- easily pass through cell membranes
- involved in retrograde transmission (regulate activity of presynaptic cells)

Endocannabinoids:
- similar to THC (marijuana)
- exist only briefly
- inhibit release of NT
Neuropeptides

Large molecules
(3-40 amino acids)

Over 100 identified, loosely grouped

Released at nondirect synapses
Neurotransmitter Pharmacology

Agonists: increase or facilitate activity

Antagonists: decrease or inhibit activity

A drug may act to alter NT activity at any point in its “life cycle.”
Psychosis:
It was found that dopamine agonists - cocaine and amphetamines - produce a temporary disorder that resembles schizophrenia.

Dopamine antagonists are effective at reducing the symptoms of schizophrenia.