Chapter 12

Synapses and Neurotransmitters
Synapses

- a nerve signal can go no further when it reaches the end of the axon
  - action potential must trigger the release of a neurotransmitter
  - stimulates a new wave of electrical activity in the next cell across the synapse

- synapse between two neurons
  - 1st neuron in the signal path is the presynaptic neuron
    - releases neurotransmitter
  - 2nd neuron is postsynaptic neuron
    - responds to neurotransmitter
Synapses

- **presynaptic neuron**
  - may synapse with
    - Dendrite
    - Soma
    - Axon of postsynaptic neuron
  - form different types of synapses
    - Axodendritic synapses
    - Axosomatic synapses
    - Axoaxonic synapses

- neuron can have an enormous number of synapses
  - **spinal motor neuron** covered by about 10,000 synaptic knobs from other neurons
    - 8000 ending on its dendrites
    - 2000 ending on its soma

- **cerebellum** of brain, one neuron can have as many as 100,000 synapses
Synaptic Relationships Between Neurons

(a) Axodendritic synapse

(b) Axosomatic synapse

Axoaxonic synapse
The Discovery of Neurotransmitters (1 of 2)

• **The synaptic cleft**
  – gap between neurons was discovered by Ramón y Cajal through histological observations
  – Challenged the notion of a “pure” electrical nervous system

• **Otto Loewi**, in 1921, demonstrated that neurons communicate by releasing chemicals – the *chemical synapses*
  – he flooded exposed hearts of two frogs with saline
  – stimulated vagus nerve of the first frog and the heart slowed
  – removed saline from that frog and found it slowed heart of second frog
  – named it *Vagusstoffe* (“vagus substance”)
    • later renamed *acetylcholine*, the first known neurotransmitter
Discovery of Neurotransmitters (2 of 2)

- **electrical synapses** do exist
  - some neurons, neuroglia, and cardiac and single-unit smooth muscle
  - **gap junctions** join adjacent cells
    - ions diffuse through the gap junctions from one cell to the next
  - **advantage** of quick transmission
    - no delay for release and binding of neurotransmitter
    - cardiac and smooth muscle and some neurons
  - **disadvantage** is they cannot integrate information and make decisions
    - **ability reserved for chemical synapses** in which neurons communicate by releasing neurotransmitters
Synaptic Knobs

Axon of presynaptic neuron

Synaptic knob

Soma of postsynaptic neuron
Structure of a Chemical Synapse

- **synaptic knob** of **presynaptic neuron** contains **synaptic vesicles** containing **neurotransmitter**
  - many docked on release sites of the plasma membrane
    - ready to release neurotransmitter on demand
  - a reserve pool of synaptic vesicles located further away from membrane

- **postsynaptic neuron** membrane contains **proteins**
  - Some function as **receptors**
  - Some function as **ligand-regulated ion gates**
Structure of a Chemical Synapse

- presynaptic neurons have synaptic vesicles with neurotransmitter and postsynaptic have receptors and ligand-regulated ion channels
Neurotransmitters and Related Messengers

- more than 100 neurotransmitters have been identified

- fall into four major categories according to chemical composition
  - acetylcholine
    - in a class by itself
    - formed from acetic acid and choline
  - amino acid neurotransmitters
    - include glycine, glutamate, aspartate, and γ-aminobutyric acid (GABA)
  - monoamines
    - synthesized from amino acids by removal of the –COOH group
    - retaining the –NH₂ (amino) group
    - major monoamines are:
      - the catecholamines = epinephrine, norepinephrine, dopamine
      - histamine and serotonin
  - neuropeptides
Categories of Neurotransmitters

### Acetylcholine
\[
\text{H}_2\text{C} - \text{N}^+ - \text{CH}_2 - \text{CH}_2 - \text{O} - \text{C} - \text{CH}_3
\]

### Monoamines
- **Catecholamines**
  - **Epinephrine**
  - **Norepinephrine**
  - **Dopamine**
- **Serotonin**
- **Histamine**

### Amino acids
- **GABA**
- **Glycine**
- **Aspartic acid**
- **Glutamic acid**

### Neuropeptides
- **Enkephalin**
- **χ-endorphin**
- **Cholecystokinin**
- **Substance P**
Neuropeptides

- chains of 2 to 40 amino acids
  - beta-endorphin and substance P
- act at lower concentrations than other neurotransmitters
- longer lasting effects
- stored in axon terminal as larger secretory granules (called dense-core vesicles)
- some function as hormones or neuromodulators
- some also released from digestive tract
  - gut-brain peptides cause food cravings
Function of Neurotransmitters at Synapse

• they are synthesized by the presynaptic neuron

• they are released in response to stimulation

• they bind to specific receptors on the postsynaptic cell

• they alter the physiology of that cell
Effects of Neurotransmitters

- a given neurotransmitter does not have the same effect everywhere in the body
- multiple receptor types exist for a particular neurotransmitter
  - 14 receptor types for serotonin
- receptor governs the effect the neurotransmitter has on the target cell
- Note: the same molecule may function as a hormone, a neurotransmitter, or a neuromodulator!
Synaptic Transmission

• **neurotransmitters** are diverse in their action
  – some excitatory
  – some inhibitory
  – some the effect depends on what kind of receptor the postsynaptic cell has
  – some open ligand-regulated ion gates
  – some act through second-messenger systems

• **synaptic delay** – time from the arrival of a signal at the axon terminal of a presynaptic cell to the beginning of an action potential in the postsynaptic cell
  – 0.5 msec for all the complex sequence of events to occur

• three kinds of synapses with different modes of action
  – excitatory cholinergic synapse
  – inhibitory GABA-ergic synapse
  – excitatory adrenergic synapse
Excitatory Cholinergic Synapse

- **cholinergic synapse** – employs acetylcholine (ACh) as its neurotransmitter
  - ACh excites some (most!) postsynaptic cells
    - skeletal muscle
  - inhibits others

- **describing excitatory action**
  - nerve signal approaching the synapse, opens the voltage-regulated calcium gates in synaptic knob
  - Ca^{2+} enters the knob
  - triggers exocytosis of synaptic vesicles releasing ACh
  - empty vesicles drop back into the cytoplasm to be refilled with ACh
  - reserve pool of synaptic vesicles move to the active sites and release their ACh
  - ACh diffuses across the synaptic cleft
  - binds to ligand-regulated gates on the postsynaptic neuron
  - gates open
  - allowing Na^{+} to enter cell and K^{+} to leave
    - pass in opposite directions through same gate
  - as Na^{+} enters the cell it spreads out along the inside of the plasma membrane and depolarizes it producing a local potential called the postsynaptic potential
  - if it is strong enough and persistent enough
  - it opens voltage-regulated ion gates in the trigger zone
  - causing the postsynaptic neuron to fire
Excitatory Cholinergic Synapse
Inhibitory GABA-ergic Synapse

- GABA-ergic synapse employs γ-aminobutyric acid as its neurotransmitter.
- Nerve signal triggers release of GABA into synaptic cleft.
- GABA receptors are chloride channels.
- $\text{Cl}^-$ enters cell and makes the inside more negative than the resting membrane potential.
- Postsynaptic neuron is inhibited.
- Less likely to fire.
Excitatory Adrenergic Synapse

• **adrenergic synapse**
  – employs the neurotransmitter **norepinephrine** (NE) also called noradrenaline

• **Receptor for adrenergic synapses**
  – not an ion gate
  – a transmembrane protein associated with a **G protein**

• NE and other monoamines, and neuropeptides acts through **second messenger systems** such as **cyclic AMP** (cAMP)
Action of Adrenergic Transmembrane Receptor and G Protein

- unstimulated NE receptor is bound to a G protein
  - binding of NE to the receptor causes the G protein to dissociate from it
  - G protein binds to adenylate cyclase
    - activates this enzyme
  - induces the conversion of ATP to cyclic AMP
    - cyclic AMP can induce several alternative effects in the cell
      - causes the production of an internal chemical that binds to a ligand-regulated ion gate from inside of the membrane, opening the gate and depolarizing the cell
      - can activate preexisting cytoplasmic enzymes that lead to diverse metabolic changes
      - can induce genetic transcription, so that the cell produces new cytoplasmic enzymes that can lead to diverse metabolic effects
- slower to respond than cholinergic and GABA-ergic synapses
- has advantage of enzyme amplification – single molecule of NE can produce vast numbers of product molecules in the cell
Excitatory Adrenergic Synapse

- Postsynaptic neuron

- Presynaptic neuron

Neurotransmitter receptor

- Norepinephrine

- G protein

- Adenylate cyclase

- cAMP

- ATP

- Ligand-regulated gates opened

- Na+

- Postsynaptic potential

1. Enzyme activation
2. Multiple possible effects
3. Metabolic changes
4. Genetic transcription
5. Enzyme synthesis
6. Postsynaptic potential
Cessation of the Signal

- mechanisms to **turn off stimulation** to keep postsynaptic neuron from firing indefinitely
  - neurotransmitter molecule binds to its receptor for only 1 msec or so
    - then dissociates from it
  - if presynaptic cell continues to release neurotransmitter
    - one molecule is quickly replaced by another and the neuron is restimulated

- **stop adding neurotransmitter** and **get rid of that which is already there**
  - stop signals in the presynaptic nerve fiber
  - getting rid of neurotransmitter by:
    - **diffusion**
      - neurotransmitter escapes the synapse into the nearby ECF
      - astrocytes in CNS absorb it and return it to neurons
    - **reuptake**
      - synaptic knob reabsorbs amino acids and monoamines by endocytosis
      - break neurotransmitters down with monoamine oxidase (MAO) enzyme
      - some antidepressant drugs work by inhibiting MAO
    - **degradation in the synaptic cleft**
      - enzyme **acetylcholinesterase** (AChE) in synaptic cleft degrades ACh into acetate and choline
      - choline reabsorbed by synaptic knob
Neuromodulators

- hormones, neuropeptides, and other messengers that modify synaptic transmission
  - may stimulate a neuron to install more receptors in the postsynaptic membrane adjusting its sensitivity to the neurotransmitter
  - may alter the rate of neurotransmitter synthesis, release, reuptake, or breakdown

- enkephalins & endorphins – a neuromodulator family
  - small peptides that inhibit spinal interneurons from transmitting pain signals to the brain

- nitric oxide (NO) – simpler neuromodulator
  - a lightweight gas release by the postsynaptic neurons in some areas of the brain concerned with learning and memory
  - diffuses into the presynaptic neuron
  - stimulates it to release more neurotransmitter
  - one neuron’s way of telling the other to ‘give me more’
  - some chemical communication that goes backward across the synapse
Neural Integration

• **neural integration** – the ability of your neurons to process information, store and recall it, and make decisions
  - synaptic delay slows the transmission of nerve signals
  - more synapses in a neural pathway, the longer it takes for information to get from its origin to its destination
    • synapses are not due to limitation of nerve fiber length
    • gap junctions allow some cells to communicate more rapidly than chemical synapses

• So why do we have synapses?
Postsynaptic Potentials - EPSP

• **neural integration** is based on the **postsynaptic potentials produced by neurotransmitters**

• typical neuron has a resting membrane potential of -70 mV and threshold of about -55 mV

• **excitatory postsynaptic potentials (EPSP)**
  – any voltage change in the direction of threshold that makes a neuron more likely to fire
    • usually results from Na⁺ flowing into the cell cancelling some of the negative charge on the inside of the membrane
  – glutamate and aspartate are excitatory brain neurotransmitters that produce EPSPs
Postsynaptic Potentials - IPSP

- inhibitory postsynaptic potentials (IPSP)
  - any voltage change away from threshold that makes a neuron less likely to fire
    - neurotransmitter hyperpolarizes the postsynaptic cell and makes it more negative than the RMP making it less likely to fire
    - produced by neurotransmitters that open ligand-regulated chloride gates
      - causing inflow of CI- making the cytosol more negative
  - glycine and GABA produce IPSPs and are inhibitory
  - acetylcholine (ACh) and norepinephrine are excitatory to some cells and inhibitory to others
    - depending on the type of receptors on the target cell
    - ACh excites skeletal muscle, but inhibits cardiac muscle due to the different type of receptors
Postsynaptic Potentials

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Summation, Facilitation, and Inhibition

- one neuron can receive input from thousands of other neurons
- some incoming nerve fibers may produce EPSPs while others produce IPSPs
- neuron’s response depends on whether the net input is excitatory or inhibitory
- **summation** – the process of adding up postsynaptic potentials and responding to their net effect
  - occurs in the trigger zone
- the balance between EPSPs and IPSPs enables the nervous system to make decisions
- **temporal summation** – occurs when a single synapse generates EPSPs so quickly that each is generated before the previous one fades
  - allows EPSPs to add up over time to a threshold voltage that triggers an action potential
- **spatial summation** – occurs when EPSPs from several different synapses add up to threshold at an axon hillock.
  - several synapses admit enough Na⁺ to reach threshold
  - presynaptic neurons cooperate to induce the postsynaptic neuron to fire
Temporal and Spatial Summation

(a) Temporal summation

1. Intense stimulation by one presynaptic neuron

2. EPSPs spread from one synapse to trigger zone

3. Postsynaptic neuron fires

(b) Spatial summation

1. Simultaneous stimulation by several presynaptic neurons

2. EPSPs spread from several synapses to trigger zone

3. Postsynaptic neuron fires
Summation of EPSPs

- EPSPs
- Threshold
- Action potential
- Resting membrane potential
- Stimuli

Time

mV

+40
+20
0
-20
-40
-60
-80
neurons routinely work in groups to modify each other’s action

- **facilitation** – a process in which one neuron enhances the effect of another one
  - combined effort of several neurons facilitates firing of postsynaptic neuron

- **presynaptic inhibition** – process in which one presynaptic neuron suppresses another one
  - the opposite of facilitation
  - reduces or halts unwanted synaptic transmission
  - neuron I releases inhibitory GABA
    - prevents voltage-gated calcium channels from opening in synaptic knob and presynaptic neuron releases less or no neurotransmitter