Carlson (7e)
PowerPoint Lecture Outline
Chapter 4: Psychopharmacology
Psychopharmacology

- **Psychopharmacology** is the study of the effects of drugs on the nervous system and on behavior.

- The term drug has many meanings:
  - Medication to treat a disease
  - A chemical that is likely to be abused
  - An "exogenous" chemical that significantly alters the function of certain bodily cells when taken in relatively low doses (chemical is not required for normal cellular functioning)
Pharmacokinetics

- Drug molecules interact with target sites to effect the nervous system
  - The drug must be absorbed into the bloodstream and then carried to the target site(s)
- **Pharmacokinetics** is the study of drug absorption, distribution within body, and drug elimination
  - **Absorption** depends on the route of administration
  - **Drug distribution** depends on how soluble the drug molecule is in fat (to pass through membranes) and on the extent to which the drug binds to blood proteins (albumin)
  - **Drug elimination** is accomplished by excretion into urine and/or by inactivation by enzymes in the liver
Drug Effectiveness

- Dose-response (DR) curve: Depicts the relation between drug dose and magnitude of drug effect
- Drugs can have more than one effect
- Drugs vary in effectiveness
  - Different sites of action
  - Different affinities for receptors
- The effectiveness of a drug is considered relative to its safety (therapeutic index)

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Routes of Drug Administration

- Routes of drug administration into the body
  - Intravenous (IV): into a vein (rapid absorption)
  - Intraperitoneal (IP): into the gut (used in lab animals)
  - Subcutaneous (SC): under the skin
  - Intramuscular (IM): into a muscle
  - Inhalation of the drug into the lungs
  - Topical: absorbed through the skin
  - Oral (PO): via the mouth
Tolerance and Sensitization

- Repeated administration of a drug can alter its subsequent effectiveness
  - **Tolerance**: Repeated drug administration results in diminished drug effect (or requires increased dosage to maintain constant effect)
    - Withdrawal effects are often the opposite of the drug effect and often accompanies tolerance
    - Tolerance can reflect decreased drug-receptor binding or reduced postsynaptic action of the drug
  - **Sensitization**: Repeated drug administration results in heightened drug effectiveness
Synaptic Transmission

- Transmitter substances are
  - Synthesized, stored, released, and terminated
  - Susceptible to drug manipulation

- Definitions:
  - Direct agonist: a drug that binds to and activates a receptor
  - Antagonist: a drug that binds to but does not activate a receptor
    - Indirect antagonists are drugs that attach to a binding site and interfere with the normal action of the receptor
Drug Action on Synaptic Transmission

1. Drug serves as precursor AGO (e.g., L-DOPA—dopamine)
2. Drug inactivates synthetic enzyme; inhibits synthesis of N.T ANT (e.g., PCPA—serotonin)
3. Drug prevents storage of N.T in vesicles ANT (e.g., reserpine—monoamines)
4. Drug stimulates release of N.T AGO (e.g., black widow spider venom—ACH)
5. Drug inhibits release of N.T ANT (e.g., botulinum toxin—ACH)
6. Drug stimulates postsynaptic receptors AGO (e.g., nicotine, muscarine—ACH)
7. Drug blocks postsynaptic receptors ANT (e.g., curare, atropine—ACH)
8. Drug stimulates autoreceptors; inhibits synthesis/release of N.T ANT (e.g., apomorphine—dopamine)
9. Drug blocks autoreceptors; increases synthesis/release of N.T AGO (e.g., clonidine—norepinephrine)
10. Drug blocks reuptake AGO (e.g., cocaine—dopamine)
11. Drug inactivates acetylcholinesterase AGO (e.g., physostigmine—ACH)

Agonist drugs are in red, Antagonists are in blue
Presynaptic Drug Actions

- Presynaptic autoreceptors regulate the amount of NT released from the axon terminal
  - Drugs that activate presynaptic autoreceptors reduce the amount of NT released, an antagonistic action
  - Drugs that inactivate presynaptic autoreceptors increase the amount of NT released, an agonistic action
- Presynaptic heteroreceptors are sensitive to NT released by another neuron, can be inhibitory or facilitatory
Neuromodulators

- Neurotransmitter binding to receptors produces either EPSPs or IPSPs
  - Glutamate produces EPSPs
  - GABA produces IPSPs
- Neuromodulators alter the action of systems of neurons that transmit information using either glutamate or GABA
Acetylcholine

- Acetylcholine (ACh) is the primary NT secreted by efferent CNS cells.
- In the periphery: ACh neurons are found in:
  - Autonomic ganglia (e.g. the heart)
  - The neuromuscular junction (activation of muscle movement)
- In brain: ACh neurons are found in:
  - Dorsolateral pons
  - Medial septum
  - Basal forebrain
  - ACh release in brain results in facilitatory effects
Synthesis of ACh

- ACh synthesis pathway:
  - Acetyl CoA + Choline $\rightarrow$ ACh
  - CoA arises from glucose metabolism
  - Synthesis is dependent on choline
  - ACh synthesis is blocked by NVP
Drug-ACh Interactions

- Choline is required for ACh synthesis
  - Hemicolium inhibits the reuptake of choline
- ACh release
  - Requires calcium ion entry
  - ACh release is blocked by botulinum toxin
  - ACh release is promoted by black widow spider venom
- ACh is degraded by AChE
  - Neostygmime interferes with AChE activity
Nictotinic receptors are found in skeletal muscle (ionotropic effect)
- Agonists: ACh, nicotine
- Antagonists: d-tubocurarine and curare

Muscarninic receptors are found in heart and smooth muscle (metabotropic effects)
- Agonists: ACh, muscarine
- Antagonists: Atropine and scopolamine
Termination of ACh Effect

- Recycled choline molecules
- Presynaptic membrane
- Choline transporter (can be inactivated by hemicholinium)
- Acetylcholine molecule
- Acetate ion
- Choline molecule
- Acetylcholinesterase (AChE)
- Action of AChE breaks apart acetylcholine molecule
Monoamine Neurotransmitters

- The **monoamine** transmitters share a common structure and form a family of neurotransmitters
  - **Catecholamines** include dopamine (DA), norepinephrine (NE), and epinephrine (EPI)
  - **Indolamines** include serotonin (5-HT)
- The cell bodies of monoamine neurons are located in the brainstem and give rise to axon terminals that are distributed widely throughout the brain
Catecholamine Synthesis

Tyrosine → Tyrosine hydroxylase → DOPA

L-DOPA → DOPA decarboxylase → Dopamine

Dopamine → Dopamine β-hydroxylase → Norepinephrine
Dopamine

- Dopamine is used by several neural systems
  - **Nigrostriatal** system projects from the substantia nigra to the caudate nucleus and putamen
  - **Mesolimbic** system projects from ventral tegmental area to the limbic system (including the nucleus accumbens, amygdala, and hippocampus)
  - **Mesocortical** system projects from the ventral tegmental area to the cortex

- Dopamine receptors are metabotropic
  - D1 receptors are postsynaptic, whereas D2 receptors are pre- and postsynaptic
Drug-Dopamine Interactions

- **AMPT** blocks tyrosine hydroxylase, preventing the conversion of tyrosine to l-DOPA
- **Reserpine** prevents the storage of dopamine within vesicles
- **Cocaine** blocks the reuptake of dopamine
- **Monoamine oxidase (MAO)** within the axon terminal degrades dopamine
  - **Deprenyl** blocks MAO-B to increase dopamine
Norepinephrine

- Norepinephrine is synthesized from dopamine within vesicles
- The locus coeruleus gives rise to NE fiber systems
  - NE is secreted from varicosities along fibers
- NE interacts with four receptor types in brain
  - $\alpha$-adrenergic (subtypes 1 and 2)
  - $\beta$-adrenergic (subtypes 1 and 2)
  - Adrenergic receptors are metabotropic
Seroitonin Synthesis

5-HT Precursor

Tryptophan

\[ \text{Tryptophan} \xrightarrow{Tryptophan\ hydroxylase} \]

5-hydroxytryptophan (5-HTP)

\[ \text{5-hydroxytryptophan (5-HTP)} \xrightarrow{5-HTP\ decarboxylase} \]

5-hydroxytryptamine (5-HT, or serotonin)

PCPA: inhibits TH

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Serotonin (5-HT) cells are mostly located in the gut (98%) with only 2% of serotonin cells in brain.

Serotonin cell bodies are located in brainstem raphe nuclei and project to cortex.

Serotonin systems:
- **D system** originates in the dorsal raphe nucleus but does not form synapses (5-HT as a neuromodulator).
- **M system** originates from the median raphe nucleus and these varicosities form synapses.
5-HT: Release and Termination

- Serotonin release:
  - 8-OHDPAT is an autoreceptor agonist that reduces 5-HT release
  - No selective release blocker
  - Fenfluramine is a 5-HT releasing drug

- Serotonin termination:
  - Reuptake is blocked by fluoxetine (elevates 5HT)
  - Degradation: MAO converts serotonin to 5-HIAA
Serotonin Receptors

- There are at least 9 types of 5-HT receptors
  - 5-HT$_1$: 1A, 1B, 1D, 1E, and 1F
  - 5-HT$_2$: 2A, 2B, and 2C
  - 5-HT$_3$
- 5-HT$_3$ receptors are ionotrophic, the remainder are metabotropic
- 5-HT$_{1B}$ and 5-HT$_{1D}$ are presynaptic autoreceptors
Glutamate

- **Glutamate** (glutamic acid) is an excitatory neurotransmitter
- **Glutamate interacts with four receptor types**
  - NMDA receptor: controls a CA$^{++}$ channel
    - Activation by glutamine requires glycine binding and displacement of magnesium ions
  - AMPA receptor: controls sodium channels
  - Kainate receptor: controls sodium channels
  - Metabotropic glutamate receptor
GABA

- **GABA** is synthesized from glutamic acid
- **GABA** induces IPSPs
- **GABA** acts via 2 receptors
  - $\text{GABA}_A$: ionotropic receptor (controls a chloride channel)
  - $\text{GABA}_A$ receptors contain 5 distinct binding sites
    - GABA site
    - Benzodiazepine site
    - Barbiturates
    - Steroid binding site
    - Picrotoxin binding site
  - $\text{GABA}_B$: metabotropic receptor (controls a $\text{K}^+$ channel)
Peptides

- Peptides consist of 2 or more amino acids (linked by peptide bonds)
- Peptides are synthesized in the soma and transported to axon terminal in vesicles
- Peptides are released from all parts of the terminal button and after release are enzymatically degraded (no reuptake)
- Peptides can be co-released with other NTs
  - Peptide can serve as neuromodulator
Lipids

- THC interacts with cannabinoid (CB) receptors in brain to produce analgesia and sedation
- There are two endogenous ligands for the CB receptors, each is derived from lipid precursors
  - Anandamide
  - 2-arachidonyl glycerol (2-AG)
- Anandamide interferes with 5-HT$_3$ receptors to reduce vomiting and nausea
Soluble Gases

- **Soluble gases** can diffuse widely to exert actions on distant cells.

- **Nitric oxide (NO)** is created within cells from the amino acid arginine.

  - NO exerts effects within intestinal muscles, dilates brain blood vessels, and contributes to the changes in blood vessels that produce penile erections.

  - NO activates an enzyme that produces cyclic GMP (a second messenger) within adjoining cells.