PSYCHOPHARMACOLOGY

Drugs and Neurotransmitters
Chapter 4
Some Basics About Molecules
Atoms are the Basic Building Blocks of Matter

Outer shell electrons
Vacant places in the outer shell available for bonding
(Carbon can make four bonds)
Bonds Occur When Atoms Share Electrons

"Tinker Toy" Atoms

- \( \text{H}^- \) one bond
- \( \text{C}^- \) four bonds
- \( \text{N}^- \) three bonds (usually)
- \( \text{O}^- \) two bonds

Some Tinker Toy Molecules
- Water: \( \text{H-O-H} \)
- Ammonia: \( \text{H-N-H} \)
- Methane: \( \text{H-C-H} \)

Molecular Building Blocks
- Hydroxy-: \( \text{H-O-} \)
- Amino-: \( \text{N-H} \)
- Methyl-: \( \text{H-C-} \)

Some Organic Molecules
- Methane: \( \text{H-C-H} \)
- Ethane: \( \text{H-C-H} \)
- Propane: \( \text{H-C-C-H} \)
- Butane: \( \text{H-C-C-C-H} \)
- Pentane: \( \text{H-C-C-C-C-H} \)
- Hexane: \( \text{H-C-C-C-C-C-H} \)
- Pentene: \( \text{H-C=C-C-C-H} \)
- Cyclohexane: \( \text{H-C-C-C-C-C-H} \)
- Benzene: \( \text{H-C=C-C=C-H} \)
Polar bonds: sometimes one atom pulls harder on the electrons than the other

\(-\)O - H\(^{+}\)

Ionic bonds: sometimes one atom captures the electrons entirely

Cl\(^-\) Na\(^+\)

Covalent bonds: sometimes the atoms share the electrons more or less equally

H - C
the water molecule is not straight

the oxygen pulls on the shared electrons harder than the hydrogens do

water is a polar molecule

nonpolar things do not do well in a polar environment (oil and water don't mix!)
Radicals

* a.k.a., functional groups
* molecules with unpaired electrons
* in “Tinker Toy Atoms”, these are shown by unused “sticks”

(No, not that kind of radical!)
Free Radicals (An Aside)

Free radicals can be formed in the body in many ways. They can damage and even kill cells, including brain cells.
Carbon-Carbon bonds

* all life on earth is carbon-based
* life is made from molecules that have long carbon chains and carbon rings
* carbon-carbon bonds are non-polar
* C-H bonds are also (largely) nonpolar, so hydrocarbons show no external electrical properties
Carbon-Carbon-Hydrogen

“Tinker Toys”

arachidonic acid - an unsaturated fatty acid

palmitic acid - a saturated fatty acid

Note the hydrocarbon tails.
Carbon Rings

benzene rings

phenyl–
Now you can look at diagrams like these without wanting to chew your leg off to get away!

Some Commonly Used Psychoactive Drugs

- Aspirin
- Caffeine
- Nicotine
- Morphine
What do you notice about these molecules?

1) They are all very similar in chemical structure.

2) Some of them occur naturally in the brain, and some of them are placed there from external sources.

3) Some of them are quite polar and, therefore, will not cross the blood-brain barrier.
Membrane Structure

the lipid bilayer with embedded and attached proteins
Membrane Structure (just a bit more)

How does something get through a membrane?

1) through a channel
2) by active transport
3) by dissolving in the membrane and diffusing through

the moral: if you want to get a drug into your brain, it had better be able to dissolve in fat
* polar things do not dissolve in fat
* -OH and -NH₂ make molecules polar
* -C-C- and -CH₃ make molecules nonpolar
* the molecule on the left crosses the blood-brain barrier; the molecule on the right does not
Enzymes are protein molecules that act as organic catalysts.

example: MAO or monoamine oxidase

(Note: this sequence can also run in the opposite direction.)

(Further note: you do not need to know the names of enzymes, unless I say otherwise.)
The Role of Enzymes in Neurotransmitter Biosynthesis

- Tyrosine - the precursor from the diet
- Tyrosine hydroxylase
- Dopa (or L-DOPA) - the intermediate
- Dopa decarboxylase
- Dopamine - the end product
The Role of Enzymes in Drug Metabolism

Acetaldehyde is probably largely responsible for the hangover the following morning.

Acetaldehyde is broken down to acetic acid and water by acetaldehyde dehydrogenase.
The Role of Enzymes in Drug Metabolism

* Some people have unusually high alcohol dehydrogenase activity. When they drink, their bodies are flooded with acetaldehyde, which causes "alcohol flush."

* Many of those people also have low aldehyde dehydrogenase activity, which makes them prone to very bad hangovers.

* There is also a drug that blocks the enzyme aldehyde dehydrogenase - Antabuse.

* One possible drug action
The Role of Enzymes in Drug Metabolism

* What if you drink the "wrong kind" of alcohol?

Isopropanol

Rule: Anything that comes in a container like this is probably something you do NOT want a whole lot of in your body!

"Hello NAC. Can you make me the first stop on your truck today? I'm out of acetone and I've glued myself to the floor."
* symptoms of acetone poisoning
  * nausea, vomiting
  * abdominal pain
  * fruity odor on breath
  * sweet taste in mouth
  * acting as if drunk
  * difficulty breathing
  * drowsiness, stupor, coma
The Role of Enzymes in Drug Metabolism

* What if you drink the “wrong kind” of alcohol, part two?

Kinda gives a whole new meaning to the expression “getting pickled”!

(Note: this is not the same “embalming fluid” that joints are sometimes “soaked” in.)
Some Definitions

**psychopharmacology** The study of the effects of drugs on the nervous system and on behavior.

**drug effect** The changes a drug produces in an animal’s physiological processes and behavior.

**sites of action** The locations at which molecules of drugs interact with molecules located on or in cells of the body, thus affecting some biochemical processes of these cells.

**drug actions** - the physiological changes caused by the drug (what the drug does at the synapse; the mechanism by which the drug works)

**drug effects** - the “behavior” changes (including sweating, heavy breathing, dilation of the pupils, EEG changes, etc.) caused by the drug

e.g., “at dopamine synapses”
Pharmacokinetics

* To get to the brain, the drug must be taken up and transported in the blood.

* It must also cross the blood-brain barrier.

* If depot binding occurs in the blood or fat tissue, this may dramatically alter the time course of distribution.
Pharmacokinetics

Note: Ph = phenyl ring structure
Pharmacokinetics

intravenous (IV) injection  Injection of a substance directly into a vein.

intraperitoneal (IP) injection (*in tra pair i toe nee ul*) Injection of a substance into the peritoneal cavity—the space that surrounds the stomach, intestines, liver, and other abdominal organs.

intramuscular (IM) injection  Injection of a substance into a muscle.

subcutaneous (SC) injection  Injection of a substance into the space beneath the skin.

oral administration  Administration of a substance into the mouth, so that it is swallowed.

routes of drug administration
Pharmacokinetics

The concentration of cocaine in blood plasma after intravenous injection, inhalation, sniffing, and oral administration.

Adapted from Feldman, Meyer, and Quenzer, 1997; after Jones, 1990.
Pharmacokinetics

A dose-response curve. Increasingly stronger doses of the drug produce increasingly larger effects until the maximum effect is reached. After that point, increments in the dose do not produce any increments in the drug’s effect. However, the risk of adverse side effects increases.

Dose of drug

Effect of drug

low

high

low

After this point, increasing the dose does not produce a stronger effect.
**Pharmacokinetics**

Dose-response curves for the analgesic effect of morphine and for the drug's adverse side effects, its depressant effect on respiration. A drug's margin of safety is reflected by the difference between the dose-response curve for its therapeutic effects and that for its adverse side effects.

therapeutic index

\[ TI = \frac{LD_{50}}{ED_{50}} \]

barbiturates have a low therapeutic index

benzodiazepines have a much higher therapeutic index
Pharmacokinetics

Tolerance and Sensitization

Initially, the drug produces an intense high and may also cause emotional depression as the drug wears off. The user may conclude that the drug is harmless. With repeated use, a craving and a tolerance develop simultaneously. Over time, the addict ends up chasing a high by taking increased amounts of the drug more frequently to compensate for increased depression. When the supply is gone, the addict has an intense craving along with severe depression that may reach suicidal level.
Agonists and Antagonists

**antagonist** A drug that opposes or inhibits the effects of a particular neurotransmitter on the postsynaptic cell.

**agonist** A drug that facilitates the effects of a particular neurotransmitter on the postsynaptic cell.

- antihistamines
- beta blockers
- antipsychotics
- nicotine
- cocaine
- morphine
Review of How the Synapse Works

Seven Steps in Neurotransmitter Action

1) biosynthesis
2) storage
3) “clean up” by MAO
4) exocytosis
5) self-regulation via autoreceptors
6) activation of postsynaptic receptor
7) inactivation by reuptake or enzymes
Drugs and Synapses

A summary of the ways in which drugs can affect the synaptic transmission (AGO = agonist; ANT = antagonist; NT = neurotransmitter). Drugs that act as agonists are marked in blue; drugs that act as antagonists are marked in red.

1. Drug serves as precursor AGO (e.g., L-DOPA—dopamine)
2. Drug inactivates synthetic enzyme; inhibits synthesis of NT ANT (e.g., PCPA—serotonin)
3. Drug prevents storage of NT in vesicles ANT (e.g., reserpine—monoamines)
4. Drug stimulates release of NT AGO (e.g., black widow spider venom—ACh)
5. Drug inhibits release of NT 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 NT ANT (e.g., apomorphine—dopamine)
9. Drug blocks autoreceptors; increases synthesis/release of NT AGO (e.g., idazoxan—norepinephrine)
10. Drug blocks reuptake AGO (e.g., cocaine—dopamine)
11. Drug inactivates acetylcholinesterase AGO (e.g., physostigmine—ACh)