Monica
Class 5: The neurotransmitters (drugs); Chapter 4

Key terms

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

**Drug effect**: Changes observed in an animal's psychological process and behavior.

**Sites of action**: A location at which molecules of drugs interact with molecules located on or in cells of the body; affecting some biochemical process of these cells.

**Pharmacokinetics**: The process by which drugs are absorbed, distributed within the body, metabolized, and excreted.

**Routes of Administration**:
- **Intravenous Injection (IV)**: injection of a substance directly into a vein.
  - Fast
  - Precise
  - Direct access to brain
    (drug abuse, adrenaline)
- **Intraperitoneal (IP) injection**: injection of a substance into the peritoneal cavity - the space that surrounds the stomach, intestine, liver, and other abnormal organs.
  - Fast
  - Indirect access to brain
    (chemotherapy)
- **Intramuscular (IM) injection**: injection of a substance into a muscle.
  - Slower (capillaries)
  - Direct access to the brain.
    (vaccines, antibiotics)
- **Subcutaneous (SC) injection**: injection of a substance into the space beneath the skin.
  - Slow absorption (fat tissue)
  - Indirect access to brain
    (insuline)
- **Oral administration**: Administration of a substance into the mouth, so that is swallowed.
  - Easy
  - Delayed (has to go through stomach/ Intestines and live)
    (Aspirin)
- **Sublingual administration**: Administration of a substance by placing it beneath the tongue.
  - Easy (for humas)
  - Bypass digestive system
  - Capillaries of the tongue
    (steroids)
- **Intrarectal administration**: Administration of a substance into the rectrum.
  - Slow
  - Bypass the stomach
    (suppositories)
- **Inhalation**: Administration of a vaporous substance into the lungs.
  - Fast
  - Easy
Requires volatile substances
(nasal decongestant, drugs of abuse “MJ”, asthma)

- **Topical administration**: Administration of a substance directly onto the skin or mucous membrane.
  - Fast
  - Local (skin, mucous)
    - (nasal, eye drops, ear drops)

- **Intracerebral administration**: Administration of a substance directly into the brain.
  - Bypass the blood brain barrier
  - Local (specific brain area)
  - Mostly research

- **Intracerebroventricular (ICV) administration**: Administration of a substance into the cerebral ventricles.
  - Bypass Blood Brain Barrier
  - Global effect
  - Emergency
  - Inject in CFS

*FDA considers 111 routes of administration as valid. (epidural, transdermal)

**Kinetics of absorption:**
*An important factor that determines the rate at which a drug in the bloodstream reaches sites of action within the brain is lipid solubility.*

- Study of the effects on some specific brain areas.
- BBB (blood brain barrier) is a barrier for only water soluble molecules.
  - Molecules that are soluble in lipids pass through the cells that line the capillaries in the CNS; rapidly distributing themselves throughout the brain.
  - Lipid-soluble: heroin (rapid effect)
  - Water-soluble substances: morphine

  **Peak of Drug**: Rush phase
  ↓

  **Sustained phase**
  ↓

  **Inactivation or excretion**

- Many are deactivated by enzymes (found in the liver or sometimes blood)
- All are eventually excreted. (primarily by the kidney/urine)
Effectiveness: Dose response curve

- **Dose response curve**: A way to measure the effectiveness of a drug.
  “A graph of the magnitude of an effect of a drug as a function of the amount of drug administered”
- If the effect was proportional to the amount of drug: Linear curve
- *Most drugs*: **Non-linear** curve
- An increased dose does not produce effects but can produce side effects.

![Dose response curve](image)

**Margin of safety:**
- Drugs have multiple effects at different concentrations: **Side effects**
- * want large margin of safety

**Therapeutic Index:**
- **Therapeutic Index (TI)**: measure of a drugs margin of safety
  “The ratio between the dose that produces the desired effect in 50 percent of the animals and the dose that produces toxic effects in 50 percent of the animals”

Effectiveness: Affinity and Sites of Action

- **Affinity**: strength of binding; “Readyness with which two molecules join together”
  - Most drugs exert their effects by binding with other molecules located in the central nervous system—with presynaptic or postsynaptic receptors, with transporter molecules, or with enzymes involved in the production or deactivation of neurotransmitters.
  - High affinity will produce effects at low concentrations of the drug.
  - Low affinity will need high doses.
- **Morphine**: Analgesic
  - inhibits pain-perception neuron
- **Asprin**: Analgesic
  - suppresses chemical signal from damaged cell.

**Drug Misuse/Abuse**

Long term effects
- **Tolerance**: A decrease in the effectiveness of a drug that is administered repeatedly.
  - Need more drugs, compensatory mechanism (counteracting the effects of a drug)
  - E.G) decrease in affinity, decrease in receptor numbers.
• **Withdrawal symptoms**: The appearance of symptoms opposite to those produced by a drug when the drug is administered repeatedly and then suddenly no longer taken.
  - compensatory mechanism alone.
  - Opposite behavioral/emotional effect
  - E.G) Euphoria $\leftrightarrow$ Depression

- Effect **increase**:
  - **Sensitization**: an increase in the effectiveness of a drug that is administered repeatedly.
    - E.G) Antidepressants: need time to be effective

- Effect can be **psychological**:
  - **Placebo effect**: An inert substance that is given to an organism in lieu of a physiologically active drug; used experimentally to control for the effects of mere administration of a drug.
    - Mainly used in research
    - E.G) control for anxiety (humans)
    - E.G) control for the effect of drug administration (animals)

- Drug reinforcing effect depends on environment:
  - Nicotine and cues

**How do drugs work: AGONISTS, ANTAGONISTS**

- **Agonist**: same postsynaptic effects as a particular neurotransmitter (open and closes receptor)
- **Antagonist**: A drug that opposes or inhibits the effects of a particular neurotransmitter on the postsynaptic cell.
- **Direct agonist**: A drug that binds with and activates a receptor (opening).
- **Receptor blocker/ Direct antagonist**: A drug that binds with a receptor but does not activate it; prevents the natural ligand from binding with the receptor (Closing (blockers)).
- **Competitive binding**: competing for a spot on the ION channel.
- **Indirect antagonist**: A drug that attaches to a binding site on a receptor and interferes with the action of the receptor; does not interfere with the binding site for the principal ligand.
- **Indirect agonist**: A drug that attaches to a binding site on a receptor and facilitates the action of the receptor; does not interfere with the binding site for the principal ligand.
- **Non-competitive binding**: Binding of a drug to a site on a receptor; does not interfere with the binding site for the principal ligand.
Interfere with reuptake and degradation

- Reuptake
  - E.G: prevents reuptake (prevents recycling) (treating depression)
- Prevent enzymatic degradation
  - AChE

Neurotransmitters

- Goal of neurotransmitter release: postsynaptic potentials (EPSP/ IPSPs)
- Transmitter ID Card
  - synthesis and destruction
  - pathway of release
  - receptors
  - Disease + action of drug perception

The Main Families of Neurotransmitters:

- Amino acids:
  - Glutamate
  - GABA
  - Glycine
- Neuromodulators:
  - Acetylcholine (ACh)
  - Monoamines
    - Catecholamines
      - Dopamine
- Norepinephrine
- Epinephrine
  ■ Serotonin
  ■ Histamine
  o Neuropeptides
  o Other (lipids, nucleosides, soluble gases)

**AMINO ACIDS**

**Glutamate (Glu, Glutamic Acid):**

*most common*

Glutamate: An amino acid; the most important excitatory neurotransmitter in the brain

- **Synthesis:**
  o From proteins in food.

- **Found where?**:
  o Everywhere in the CNS.

- **Receptors:**
  o - Always Excitatory.
  o - Ionotropic for Na⁺ (AMPA, Kainate)
  o - Ionotropic for Na⁺ and Ca²⁺ (NMDA)
  o - Metabotropic glutamate receptor.

- **Psychopharmacology:**
  o - NMDA involved in learning and memory.
  o - AP5 blocks the glutamate binding site on NMDA receptors
  o - Alcohol blocks NMDA receptors.
  o - PCP (angel dust) blocks NMDA and blocks calcium entry in the cell. Hallucination and aggression. Also animal models for schizophrenia.
  o - Too much glutamate binding results in Excito-toxicity (cell-death)

**GABA:**

GABA: An amino acid; the most important inhibitory neurotransmitter in the brain.
- GABAₐₐₐ
- GABAₐₐₐₐ

- **Synthesis:**
  o From glutamate.

- **Found where?**:
  o Everywhere in the CNS.

- **Receptors:**
  o - Always inhibitory.
  o - Ionotropic for Cl⁻ (GABAₐ). 
  o - Metabotropic for K⁺ (GABAₐₐ). Exists presynaptically (Autoreceptor)

- **Psychopharmacology:**
  o - Controls spread of excitation (epilepsy, seizures)
○ Muscimol opens, and bicuculline blocks GABA₅.
○ Benzodiazepines (anxiolytics, sleep promoters, seizures reducers) open GABA₅ (ex: Valium= Diazepam, Librium)
○ GABA₅ is blocked by picrotoxin (convulsions)
○ Barbituates (low doses = anesthesia, higher dose = respiratory arrest, Low TI) open GABA₅
○ Gamma-HydroxyButyrate (GHB, ‘date rape drug’): GABA agonist.

**GLYCINE:**

Glycine: An amino acid; an important inhibitory neurotransmitter in the lower brain stem and spinal cord

- **Synthesis:**
  ○ Found in sugar cane.
  ○ Endogenous production unknown. Non essential (can be synthesized by the body, no need for external source)

- **Found Where?:**
  ○ Mainly: spinal cord.

- **Receptors:**
  ○ Always inhibitory
  ○ Ionotropic for Cl⁻

- **Psychopharmacology:**
  ○ Prevents excessive muscle contraction.
  ○ Tetanus: bacteria produces a chemical that blocks Glycin release.
  ○ Styrchnine blocks the Glycine receptor (convulsion and death. Used for animal control.)