Drugs and the Nervous System

Pharmacodynamics of a Drug
• How the drug affects the tissues of the body.

Psychoactive drugs affect communication within the nervous system.

Categorization of Drug Effects.
• Desired (Therapeutic) Effects
• Side-Effects
  • Toxic Effects
    • Acute Toxicity versus Chronic Toxicity
    • Behavioral Toxicity versus Physiological Toxicity
Dose Response Curve - Shows how the effect of a drug changes over different doses.

Important Features of Dose Response Curves
• Different drug effects can have different dose response curves.

Important Features of Dose Response Curves
• Most drugs have a minimal and maximal effective dose.
Important Features of Dose Response Curves

• Potency - drugs with larger effects at the same dose are more potent.

![Dose Response Curve Diagram]

Important Features of Dose Response Curves

• Efficacy - drugs that have higher maximal effects have higher efficacy.

![Dose Response Curve Diagram]

2 Important Dose Response Measures

• ED50 - Median Effective Dose.
• LD50 - Median Lethal Dose

![Dose Response Curve Diagram]
Therapeutic Index (TI) - Indicator of drug safety.
- LD50/ED50

The higher the therapeutic index, the safer the drug.
- Safest drugs have TIs of > 100.
- Dangerous drugs have TIs of < 10.

Therapeutic Index using LD50/ED50 isn’t always useful.
- There are negative outcomes besides death.
- Therapeutic Window is a more useful measure.
Psychoactive drugs exert their effects on the nervous system.

Divisions of the nervous system:
- Central Nervous System (CNS)
- Peripheral Nervous System (PNS)

Overview of Mammalian Brain Organization
**Hindbrain (brainstem)**
- Medulla
  - Controls important bodily functions (Respiration, HR).
  - Contains area postrema.
  - Exchanges sensory and motor (muscle) information with spinal cord.

Overview of Mammalian Brain Organization
**Hindbrain continued...**
- Cerebellum
  - Responsible for coordinated muscle movements.
  - Responsible for "motor learning".
  - Sedative-hypnotics can cause "reversible-lesion".
  - Information enters and exits via the pons.
Overview of Mammalian Brain Organization

**Midbrain**
- Reticular formation important for alertness.
- Substantia nigra important for initiating voluntary movement.
- Periaqueductal gray provides pain control.

**Forebrain**
- Thalamus exchanges information between cerebral cortex and deeper structures.
- Hypothalamus controls many hormonal and stress related functions.
  - Controls pituitary gland.

**Deep Cortical Structures**
- Hippocampus important for memory and navigation.
- Amygdala important for emotion.
- Striatum (Caudate nucleus, Putamen & Globus Pallidus) important for voluntary movement.
Overview of Mammalian Brain Organization
Forebrain continued
• Cerebral Cortex
  • Contains processing centers for producing movements and sensation.
  • Mediates higher cognition (language, perception, social control, personality, etc…).

Information enters and leaves the CNS via the Peripheral Nervous System (PNS).
• Cranial and Spinal Nerves.

Divisions of the PNS
• Somatic division controls voluntary movement.
• Autonomic division controls involuntary movement.

The autonomic nervous system is largely controlled by the hypothalamus.
2 ANS divisions:
• Sympathetic Nervous System arouses the body (4 Fs).
  • Stimulants are “sympathomimetic”
• Parasympathetic Nervous System – relaxes the body.
Cells of the nervous system.
- Neurons - Fundamental unit of the NS.
- Glial Cells - Support cells of the NS.

Parts of a Neuron
- Dendrites
- Cell Body (soma)
- Axon
- Myelin Sheath
- Nodes of Ranvier

The nervous system processes information.
- Information enters the body through the PNS…
- The CNS makes a decision…
- The PNS sends the result to the muscles of the body.
Neurons carry and transmit information in the nervous system.

- Information is received through dendrites.
- Information is sent through axons.

Transfer of information requires:

- Information flow within neurons.
- Information flow between neurons.

Transfer of information within neurons is electrical.

- The Action Potential
- Electric current - movement of electrons.
- Neurons use ions to move electrons.
  - Na⁺, K⁺, Cl⁻, Ca²⁺
Because:
- Electric current is the movement of electrical charges….

And:
- Ions are charged particles….

Moving ions around is the same as generating electric current.

Voltage
- Difference in electrical charge from one place to another.
- Neurons are polarized with respect to charge.
  - Inside voltage is about -65 mV relative to outside.
- Resting Membrane Potential

What causes the resting membrane potential?
- More negative charges inside the cell than outside.
- More positive charges outside the cell than inside.
Ionic concentrations.

- Inside the neuron:
  - Lots of K⁺.
  - Lots of Proteins

- Outside the neuron:
  - Lots of Na⁺
  - Lots of Cl⁻
  - Lots of Ca²⁺

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<thead>
<tr>
<th>Inside of Cell</th>
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<td>A⁻</td>
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- Ions move across membranes through channels created by proteins.
- Each channel is shaped to allow only a certain ion to pass.

- During the “resting state” the channels are normally closed.
  - Membrane is impermeable to ions.
  - Certain events can cause the channels to open.
Forces driving ions when channels open:
• Diffusion

Forces driving ions when channels open:
• Electrostatic Pressure
  • Positive ions are driven into the cell.
  • Negative ions are driven out of the cell.

Net Ionic movement is determined by the combination of these two factors.
• If the membrane suddenly becomes permeable:
  K+ will move out.
  Na+ will move in.
1. **Resting State: Membrane voltage -65 mV**
   - Voltage-gated Na+ and K+ channels closed.

2. **Stimulation raises cell voltage to AP threshold.**
   - Voltage-gated Na+ channels open.
   - Na+ enters cell.
   - Internal voltage rises to +30 mV at activated node.
3. About a millisecond later:
- Voltage-gated Na+ channels close.
- Voltage-gated K+ channels open.
- K+ exits the cell.
- Internal voltage falls to -80 mV.

4. About a millisecond later:
- Voltage-gated K+ channels close.
- Na+ ions activate the next node.

5. ...and the process is repeated until the voltage spike reaches the end of the axon.
Some psychoactive drugs affect the action potential.
• Topical anesthetics block voltage-gated sodium channels.
• Ethanol affects membrane permeability.
• Lithium substitutes for Na⁺ or K⁺.

Transfer of information between neurons is chemical.
• Synapse - Junction between two neurons.
• Synaptic Transmission

[Diagram of Synaptic Transmission]
Neurotransmitters (NTs) are chemical messengers used by neurons.

- Many different varieties of NTs.
- NTs are stored in vesicles in the presynaptic neuron.

Summary of “classical” synaptic transmission.

1: Action potential reaches end of the axon (axon terminal).

2: Voltage increase activates voltage-gated calcium channels in terminal.

- Calcium enters cell.
3: NT vesicles fuse with presynaptic membrane.
   • NT released into synaptic cleft.

4: NT diffuses across the cleft and binds to postsynaptic receptors.
   • NT can bind to only a certain type of receptor.
     • Lock and Key analogy.

5: Postsynaptic receptor opens an ion channel in postsynaptic membrane.
   • Chemically-Gated Channels.
**Excitatory** NTs open channels that cause *increases* in membrane voltage.

- Excitatory Post Synaptic Potentials (EPSPs)

**Inhibitory** NTs open channels that cause *decreases* in membrane voltage.

- Inhibitory Post Synaptic Potentials (IPSPs)

6: If the voltage of the postsynaptic cell rises to the AP threshold, the postsynaptic cell fires an AP.

- The message is sent down the axon.
The postsynaptic cell adds up all the EPSPs and IPSPs to “decide” whether to fire an AP.

- Spatial Summation

What is the “language” of the nervous system?

- Frequency Coding - Action potential frequency is used to transmit information.
  - Example: Mechanoreceptors

Regulation of synaptic transmission.

- Each NT system has many receptor subtypes.
- Two categories of NT receptors.
  - *Ionotropic* receptors mediate fast and transient (classical) synaptic transmission.
    - Effects occur in less than a ms.
    - Effects last a few 100 ms or less.
  - *Metabotropic* receptors mediate slow and enduring synaptic transmission.
    - Effects occur in 100s of ms.
    - Effects last for seconds, minutes, or longer.
Metabotropic receptors affect activity indirectly.

- Neurotransmitter (neuromodulator) binding results in activation of a G-protein.
- Proteins in the membrane that bind guanosine triphosphate (GTP)
- G-proteins then affect ion channels, enzymes.
- Alters excitability and/or genetic expression.

**Autoreceptors are metabotropic receptors found on the presynaptic membrane.**

- Autoreceptors are bound by the same NT released by the presynaptic neuron.
- G-protein activation causes a reduction in presynaptic Ca++ influx at depolarization.
- Net result is decrease in NT release.

Changes in receptor density can play a role in postsynaptic regulation of synaptic transmission.

- Accomplished via a metabotropic receptor or use-dependent changes.
- Too much receptor binding can lead to receptor downregulation.
Changes in receptor density continued…

• Too little receptor binding can lead to receptor upregulation.

Psychoactive drugs can affect virtually all stages of synaptic transmission.

Neurotransmitter Synthesis
• Occurs within the secreting neuron.
• Requires precursors.

Psychoactive drugs can alter NT synthesis by:
• Serving as precursors.
  • Example: L-DOPA
• Directly affecting NT synthesis.
  • Example: PCPA
• Altering NT storage.
  • Example: Reserpine
**NT release**
- NT vesicles fuse with the presynaptic membrane.
- Psychoactive drugs can alter NT release.
  - Example: Amphetamine

**NT Binding to the Receptor**
- NT binding results in a postsynaptic effect.
- Psychoactive drugs can alter this...

**Drugs can increase transmission at the receptor.**
- By binding to a receptor and eliciting the same effect as a NT.
  - Example: Nicotine
... or by binding to the same receptor and *increasing* the effect of the NT.
  • Example: Valium

In either case, the drug is a receptor *agonist*.

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**Drugs can *decrease* transmission at the receptor.**
  • By binding to the same receptor *without* exerting an effect inside the cell.
  • Lock and Key Analogy
  • Prevents normal NT from binding.
  • Example: Haldol

These drugs are receptor *antagonists*.

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**Termination of NT action.**
  • NT Reuptake - Presynaptic cell reabsorbs NT.
  • NT Degradation - Enzymes in cleft destroy NT.

• Psychoactive drugs can interfere with these processes.
  • Examples: Prozac, Cholinesterase inhibitors.
4 basic categories of neurotransmitters.

• Amino Acids
• Monoamines
• Acetylcholine
• Peptides

Amino Acid NTs mediate most ionotropic transmission.

• Glutamate
  • Principle excitatory NT in the brain.
  ![Glutamate](image)
• GABA (Gamma-Aminobutyric Acid)
  • Principle inhibitory NT in the brain.
  • Agonists generally act as behavioral sedatives.
  ![Gamma-aminobutyric Acid(GABA)](image)

Dopamine, norepinephrine, and serotonin are monoamines.

• Possess a single amine (NH$_2$) group.
• The monoamines can be further subdivided into the catecholamines...
  • Dopamine and Norepinephrine
  • Serotonin.
  • Serotonin.
The catecholamines share the same metabolic pathway.

- Synthesis starts with Tyrosine.
- Catecholamine availability is finely regulated:
  - Tyrosine hydroxylase activity increased by internal Ca++ and inhibited by intracellular catecholamine.
  - Monoamines degraded within the terminal by monoamine oxidase.
  - MAO inhibitors as drugs.
- Clearance by reuptake pumps.

Most Dopamine (DA) is produced by two important midbrain structures.

- DA produced by Substantia nigra involved in voluntary movement.
- Implicated in Parkinson’s disease.
- DA produced by ventral tegmental area (VTA) involved in motivation, addiction, and higher cognition.

Most norepinephrine (NE) in the brain is produced by the midbrain cells of the locus coeruleus.

- These noradrenergic neurons project to most major areas of the brain.
NE involved in arousal, attention and emotion.
- Locus coeruleus part of reticular activating system.
- NE release by ANS causes arousal.
  - Stimulants.
  - Some antidepressants affect NE.

Serotonin (5-hydroxytryptamine; 5-HT) is produced by a different synthesis pathway than the catecholamines.

Most 5-HT in the brain is produced by the brainstem Raphe Nuclei.
- 5-HT involved in:
  - Pain perception.
  - Arousal/Sleep.
  - Emotion.

Serotonin has the most diverse population of receptors.
- 7 different families (5-HT₁ - 5HT₇),
  - Up to 15 distinct subtypes.
Acetylcholine (Ach) in the brain mostly originates in 2 areas.
- Basal Forebrain
  - Implicated in Alzheimer’s Disease.
- Brainstem near the pons and midbrain junction.
  - Regulates the thalamus and medulla.

Acetylcholine is also found in the PNS.
- In the neuromuscular Junction.
  - Altering ACh transmission can cause paralysis.
    - Botulinum toxin
    - Nerve gas.
      - Acetylcholine esterase inhibitors.
  - In the autonomic nervous system.

Two subtypes of ACh receptors.
- Muscarinic receptors are activated by muscarine.
  - Metabotropic receptor.
  - Found in the brain and ANS.
- Nicotinic receptors are activated by nicotine.
  - Ionotropic receptor.
  - Found in the brain, ANS, and NMJ.

NT effect depends on the receptor.
- Muscarinic receptors in the parasympathetic NS directly slow the heart.
- Nicotinic receptors in the sympathetic NS indirectly speed up the heart.
There are many types of peptide NTs.
• Peptides are short chains of amino acids.
• Neuroactive peptides are produced in the soma...
  ...packaged into secretory granules
  ...and then transported to the terminal.

Endorphins are peptide NTs.
• Endorphins (enkephalins) are opioid-like
  neurotransmitters that produce natural analgesia.
• Exogenous opioids produce analgesia.
• 3 opioid receptor subtypes: mu, kappa, and delta.