Lecture 7

How do Drugs and Hormones affect the Brain and Behavior

Drugs

- Chemicals that have physiological effects
- Includes from herbal teas to drugs of abuse such as heroine or cocaine

History

Drugs in Early Times

- Earliest experiences with psychoactive drugs came from tasting naturally growing plants

Drugs in the 19th Century

- Psychoactive drugs widely used, principally in the form of patent medicines
- By the end of the century the risks of drug dependence began to be recognized

Classification of Psychoactive Drugs

- Drugs are classified by its most pronounced behavioral or psychoactive effect
    - Antianxiety Agents and Sedative Hypnotics
    - Antipsychotic Agents

    - Antidepressants/Mood Stabilizers
    - Opioid Analgesics
    - Psychotropics

Antianxiety Agents and Sedative Hypnotics

- At low doses, they depress inhibitory parts of the brain, leading to disinhibition or relaxation and talkativeness
- As the dose is increased, the neural functions become depressed, leading to uncoordinated movements and unconsciousness
- Includes
    - Alcohol
    - Barbiturates
    - Benzodiazepines (Valium)
    - Ketamine (Special K)

Antipsychotic Agents

- Psychosis: Behavioral disorders
    - e.g., Schizophrenia (1 in 100 people)
- Antipsychotics:
    - Can calm psychotic patients
    - e.g., Haloperidol (Block D2 receptors)

Antidepressants and Mood Stabilizers

Major depression

- Mood disorder characterized by
    - Prolonged feelings of worthlessness and guilt

    - Disruption of normal eating habits
    - Sleep disturbances
    - General slowing of behavior
    - Frequent thoughts of suicide
- Common: ~6% of adult population
- Twice as common in women as in men
- Most Antidepressants increase serotonin and norepinephrine systems

Bipolar disorder

- Mood disorder characterized by
    - Period of depression alternating with normal period and periods of intense excitation
- Mood stabilizers mute the intensity of one pole of the disorder, making the other pole less likely to occur
- Mechanisms are not well understood
    - Lithium may stimulate neuronal repair
    - Valproate may stimulate GABA activity

Opioid Analgesics

- Analgesic (pain killers) drugs that produce a relaxed dream-like state and can lead to sleep
- A.K.A. **Narcotics**
- They are different from depressants because there is no reckless abandon, slurred speech or staggering. They act on different parts of the brain
- Includes

    - Morphine
    - Codeine
    - Methadone
    - Heroin

Psychotropic Drugs (Behavioral Stimulants)

- Produce wakefulness and a sense of energy and well-being
- The most powerful one can lead to manic state of excitement combined with paranoia and hallucinations
- Includes
    - Cocaine
    - Amphetamines
    - Caffeine

Psychotropic Drugs (Hallucinogens)

- Produce altered perceptions, including unusual visual sensations and quite often changes in the perception of one's body
- Includes
    - Mescaline
    - LSD
    - PCP

Nicotine

- Mild stimulant
- Some relaxant properties

Marijuana

- Relaxant but different from all other categories
- At high doses it can produce hallucinations
- Endocannabinoid Receptors (CB1) are distributed widely in the brain

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Pharmacokinetics

- While the chemical structure of a drugs determines its action, several other factors are also very important
- E.g., The dose of the drug administered is important, but what really matters is how much of the drug remains in the blood free to bind targets (**bioavailability**)
- **Pharmacokinetics**: The study of the factors affecting bioavailability

Routes of drug administration

- Affects when the drug will reach its target and how much of it will get there
    - Oral administration
    - Intravenous Administration (IV injection)
    - Intramuscular Administration (IM injection)
    - Intraperitoneal Administration (IP injection)
    - Subcutaneous Administration (SC injection)
    - Inhalation drugs

- Topic Administration
- Special injection methods (intracranial, epidural, etc)

All drugs will be distributed by the circulatory system

- Ingested drugs will have to go to
    1. Stomach (Acid, enzymes)
    2. Intestine (pH=7.3, enzymes)
    3. Liver (detoxifier)
- Only after that they will enter the circulatory system

Distribution of drugs is fairly generalized through capillaries

- Once drugs are in the blood they will start “leaking” through capillary holes into all tissues
- The chemical nature of the drug is irrelevant at this point
- Thus, areas with more blood will have more drug (heart, brain, kidneys, liver)

Blood Brain Barrier (BBB)

- Selective barriers
- Consists of capillaries that are bound **very** tight so things can’t get through
- Capillaries are surrounded by glial cells that make it harder for things to go through
- Lipid soluble substances can still go through
- There are special carriers for the rest

The Placenta

- Connects the fetus with the mother's uterine wall
- Brings nutrients and gases to the fetus
- Removes wastes
- Lipid soluble substances will diffuse easily through the placenta
- Water soluble ones will have a harder time

Drugs cross the Placenta affecting the fetus

- Alcohol
    - Fetal alcohol syndrome
    - Decreased birth weight
    - Adverse cognitive outcomes
    - Poorer linguistic abilities
    - Deficits in attention and memory
- Cocaine
    - Decreased neonatal head circumference
    - Birth weight
    - Prematurity
    - Growth retardation
    - Fetal loss
    - Decreased adaptability to stress
    - Impaired attention
- Marijuana
    - Decreased birth weight and length
    - Deleterious cognitive and attention effects in some preschool

and early school-age samples

- Nicotine
    - Physical, cognitive and behavioral effects in offspring
- Heroin
    - Neonatal abstinence syndrome
- Cocaine
    - Intrathecal morphine associated with fetal bradycardia
- Caffeine
    - Prospective cohort: low birth weight, small head circumference

Drug Elimination/Half-Life

- Drugs are eliminated from the body by several mechanisms
- These include metabolism and excretion of drugs and its metabolites
- **Half-Life**: The amount of time required to remove 50% of the drug from blood

Biotransformation of Drugs

- Most drugs are altered by the body's enzymes before they are excreted
- These changes take place in many organs, including
    - Liver (most important)
    - Stomach
    - Kidney
    - Brain
    - Intestine

- Blood plasma

The Liver

- Plays a major role in drug transformation
- Contains large amounts of enzymes that can metabolize a wide variety of compounds
- These are called **microsomal enzymes**
- One of the most important microsomal enzymes is the **cytochrome p450** enzyme family
- There are 30+ different enzymes and they oxidize a wide variety of drugs

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Pharmacology of Synaptic Transmission

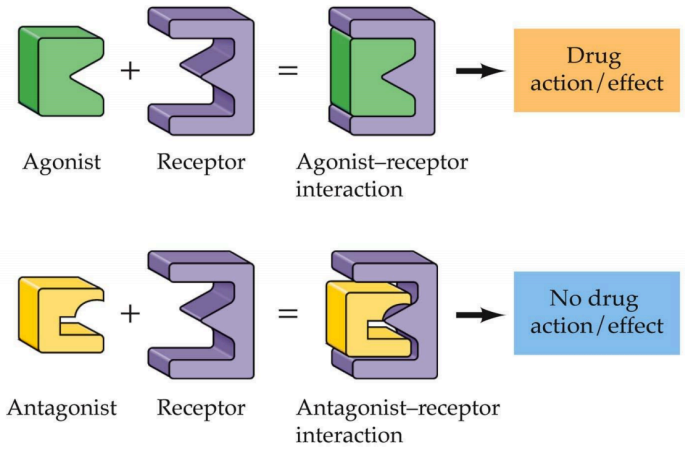
How do drugs exert their effects?

- This is done by altering synaptic transmission
- It can change the
    - Levels of neurotransmitters made
    - Amount of neurotransmitters available in the synapse
    - Sensitivity of the receptors
    - Availability of receptors (e.g., by blocking them)

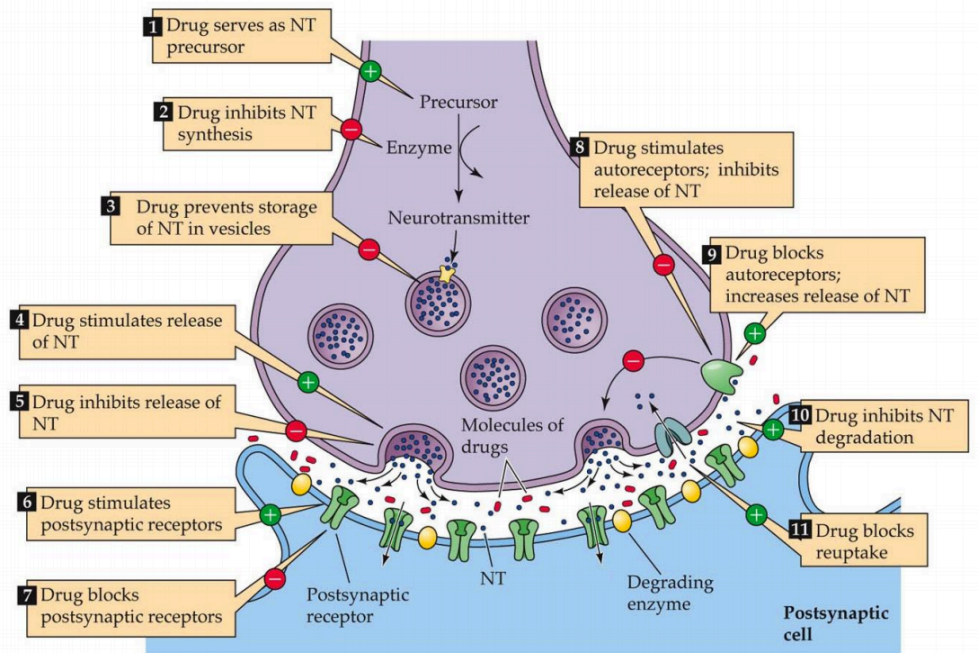
- Effects can be either acute or chronic
- Terminology
    - **Agonist**: Substance that **ENHANCES** the function of a synapse
    - **Antagonist:**: Substance that **BLOCKS/DECREASES** the function of a synapse

Characteristics of Receptor-Ligand Interactions

- Very specific
- The better they match the ligand binding site, the better and stronger the interactin



How do Drugs exert their effects?



Depression and SSRIs

- Depression is usually diagnosed through behavioral assessment of subjects (sleep patterns, mood, changes in feeding behavior)
- The most prescribed treatment is pharmacological
    - E.g., Serotonin-reuptake inhibitors

Antidepressants

Monoamine Oxidase (MAO) Inhibitors**

- Block the enzyme MAO from degrading neurotransmitters such as dopamine, noradrenaline, and serotonin

Tricyclic Antidepressants

- First-generation antidepressants with a chemical structure characterized by three rings that block serotonin reuptake transporter proteins

Second-Generation Antidepressants

- Action similar to first-generation antidepressants
- More selective in action on the serotonin reuptake proteins
- A.K.A. Atypical antidepressants

Selective Serotonin Reuptake Inhibitors (SRRIs)

- Block the reuptake of serotonin into the presynaptic terminal

Antidepressants: Questions remain

- Although antidepressants affect synapses very quickly, their antidepressive actions take weeks to develop
- Prozac, an SSRI, enhances neurogenesis in the hippocampus
- ~20% of patients with depression fail to respond to antidepressants, suggesting that depression can likely have many causes

Alcohol and Depressant Drugs

- Many of them act on the GABA ionotropic receptor, which is a GABA gated ion channel
- When open, the channel allows chloride to come into the cell, which makes it harder to fire an action potential
- These drugs increase the amount of chloride coming in
- Because they do not act on the same sites of the receptor, they potentiate each other
- Therefore it is dangerous to consume them together
- In addition, many of the drugs that affect GABAergic signaling are metabolized by the same enzymes, which leads to **cross-tolerance**

Amphetamine and Cocaine

- They increase dopaminergic signaling by overlapping mechanisms