Psychopharmacology

Chapter 4

Majority of illustrations in this presentation are from Biological Psychology, 6th edition (G. Linear Publications).

Psychopharmacology

1. Pharmacology comes from a classical Greek word pharmakon, meaning poison in modern Greek it means drug. Logus of course means study.
2. Psychopharmacology is an interdisciplinary field combining psychology with pharmacology and dealing largely with psychotropic drugs, neurohormones, and neurotransmitters (NTs).

Drugs

The term drug has many meanings:
   a. Medication to treat a disease.
   b. A chemical that can be abused.
   c. An exogenous chemical that significantly alters the function of certain bodily cells when taken in relatively low doses (chemical that is NOT required for normal cellular functioning).
Neurotransmitters

Likewise neurotransmitters can mean:

a. Special endogenous chemicals (NTs) released in the brain or glands.
b. When these chemicals are exogenously induced as drugs they alter brain and behavior.
c. Are neurotransmitters.
d. Where NTs have widespread effect, drugs have localized effect in the brain.

Criteria for NTs

1. Substance must exist in the presynaptic terminals.
2. Enzymes for synthesis are present in the terminals or cell body.
3. Nerve impulse (action potential) releases significant amounts of the substance.
4. Substance binds to receptors on the postsynaptic cell.

Criteria for NTs

5. Experimental application of the substance produces changes in the postsynaptic cell.
Kinds of NTs

- **Neurotransmitter**
  - Amines
    - Monoamines
      - Acetylcholine
      - Catecholamines
        - Norepinephrine
        - Epinephrine
        - Serotonin
      - Histamine
    - Monoamines
      - GABA
      - Glycin
      - Glutamate
  - Amino Acids
  - Neuropeptides
  - Peptide Hormones
  - Gases

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- **Neurotransmitter**
  - Amines
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  - Depression
  - Substance P
    - Cholecystokinin (CCK)
    - Hypothalamic Releasing Hormones
    - Vasopressin

  - Nitric Oxide (NO)
    - Carbon Monoxide (CO)

Neurotransmitters can bind to **ionotropic** and **metabotropic** receptors in a variety of ways opening or closing them like keys.
Agonists

Agonists are chemicals that mimic NT behavior. These can bind to receptors and cause similar effects produced by NTs.

Antagonists

Agonists are chemicals that work opposite to NTs. These can bind to receptors blocking or deactivating them.

Acetylcholine

1. Acetylcholine (ACh) was first identified by Henry Dale in 1914 and was confirmed as a by Otto Loewi, (1938) through a dream (1921) as a neurotransmitter, he called vagusstoff (from vagus nerve).
2. Otto Loewi’s determination of vagusstoff was made in the cardiac muscle of the frog. And supported the idea of this chemical release at the synaptic cleft.

3. This vagusstoff or acetylcholine was not only found in PNS but also CNS of many organisms including humans.

4. Acetylcholine is used in ANS (autonomic ganglia) and the only neurotransmitter used in the motor division of the somatic nervous system.

5. Acetylcholine was extensively studied at the neuromuscular junction (NMJ).

6. Acetylcholine neurons are found in **dorsolateral pons, medial septum, & basal forebrain**. Its release in brain results in facilitatory effects. And this NT is involved with learning and memory in the CNS.
**Myasthenia Gravis**

Depletion of ACh in the PNS leads to a number of muscular problems, like *Myasthenia Gravis* in which the patient suffers from dropping eyelid. When ACh is increased the condition is ameliorated.

> When an intravenous injection of edrophonium chloride or neostigmine is given it reverses eye dropping, by breaking down Acetylcholinesterase (AChE) and increasing ACh.

**Alzheimer’s Disease**

1. Reduction of ACh in the CNS is implicated in Alzheimer’s disease affecting memory and other functions.
2. In this disease Choline acetyltransferase (ChAT) an enzyme is less active and does not assist in ACh synthesis in the terminal vesicles.
3. Drugs or enzymes that boost ACh improve Alzheimer patients.

**ACh Receptors**

1. ACh ionotropic receptor consists of five subunits. And can be bound by agonists like nicotine and muscarine
2. These are fast acting ligand-gated receptors and open channels for Na+ ions.
3. Most ACh receptors are found in NMJ autonomic ganglia and some in CNS.
ACh and Agonists

A number of ACh agonists and antagonists have been studied in detail. Among these agonists nicotine (tobacco) and muscarine (mushrooms) mimic ACh-like responses.

Nicotine Effects

1. Nicotine is a stimulant and increases blood pressure, secretion of hydrochloric acid in the stomach and motor activity of the bowels.
2. It binds to ACh receptors, and opens up Na⁺ channels increasing activity in the muscles through PNS.

Muscarinic Effects

1. There are five different kinds of of ACh metabotropic (muscarinic) receptors (M1-5) and are thus slower than nACh receptors.
2. These are found in heart, smooth muscle and CNS.
Nicotine & Muscarine Antagonists

1. Curare (d-tubocurarine) block nACh receptors thus act like antagonists.
2. Atropine and scopolamine are muscarine antagonists.

ACh Inactivation & Facilitation

1. ACh can be inactivated by blocking Choline reuptake mechanism by Hemicholium.
2. ACh release is also blocked by botulinum toxin (Botox). Botox blocks ACh release, muscle contractions and wrinkles.
3. ACh release is facilitated by black widow spider venom (muscle spasms) and Neostigmine. They both interfere with AChE activity.

Monoamines

Catecholamines consist of dopamine (DA), norepinephrine (NE), and epinephrine (EPI), and indolamines include serotonin (5-HT) and melatonin they all share chemical structure.
1. Over one million neurons in the brain contain DA, this number is extremely small, however DA plays a major role in severe disorders like schizophrenia and Parkinson’s disease.

2. Dopamine neurons contain several types of DA receptors (DA1-5).

3. Drugs can affect DA receptors differently. Affinity of antipsychotic drug haloperidol is twice to DA2 than DA1, thus relieves schizophrenic symptoms.

4. In the brain there are two systems that regulate DA activity. One is mesostriatal system which projects from the substantia nigra to the caudate nucleus and putamen, and is implicated in Parkinson’s disease.

5. A disease marked with resting tremors to complete paralysis. The condition ameliorated with L-dopa.

6. The second system is called the mesolimbic system that projects from ventral tegmental area to the limbic system. Over activity of this pathway is implicated in schizophrenia.
Norepinephrine

1. The locus coeruleus (LC) gives rise to NE fiber system that connects to spinal cord, cerebellum, brain stem, thalamus, amygdala, and basal cerebrum.
2. Norepinephrine is synthesized from dopamine within vesicles and is secreted from varicosities of LC along fibers.

3. Norepinephrine will increase from LC during stress and will alter cognitive function engaging prefrontal cortex to increase motivation.
4. Animal models of LC destruction and reduction in NE suggests its important role in Alzheimer's disease.
5. Norepinephrine release from LC is related to REM sleep.

Serotonin

1. Serotonin (5-HT) cells are mostly located in the gut (98%) with only 2% in the brain.
2. Serotonin cell bodies are located in brainstem raphe nuclei and project to cortex.
3. Serotonin regulates moods, anxiety and arousal.
4. Serotonin and NE are implicated in bipolar and other mood disorders.
Glutamate

1. Glutamate (and aspartate) are two excitatory neurotransmitters in the brain.

2. Glutamate binds to many ionotropic receptors like α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), N-methyl-o-aspartate (NMDA), kinate and a few metabotropic receptors.

3. Glutamate can cause excitotoxicity killing neurons. Astrocytes clear glutamate from the cleft to save neurons.

4. Interest in glutamate, was greatly increased due its implication in memory and long-term potentiating (LTP).

Glutamate Action

5. Glutamate (ligand) binds to NMDA receptors when depolarization is below 35 mv. This makes NMDA receptors ligand-gated and voltage sensitive. Increase in intracellular Ca²⁺ increase Na⁺ flux.
1. Unlike glutamate, GABA (and Glycine) is an inhibitory NT. There are three classes of GABA receptors (GABA_A, GABA_B, and GABA_C). GABA_A and GABA_C are ionotropic and GABA_B is metabotropic receptor.

2. Binding of GABA to its receptor opens up channel to let Cl⁻ ions to enter the neuron causing hyperpolarization.

3. It is GABA that blocks many excitatory responses in the brain resisting seizures. Drugs that block GABA can produce seizures.

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1. Opioid peptides (met-enkephalin, leu-enkephalin, β-endorphin and dynorphin) mimic opiate drugs like morphine.

2. Many other peptides (substance P, neotensin, cholecystokinin [CCK], neuropeptide Y, vasopressin, oxytosin) act like NTs and hormones.

3. Finally gases like nitric oxide (NO) and carbon monoxide (CO) act like NTs in neurons.
1. Neuropsychopharmacology is rapidly developing field of drugs related to altering behavior. Drugs are extracted from natural sources (plants etc.) or synthesized from artificial means (man-made).

2. Most of these drugs interact with specific receptors, unlike neurotransmitters that interact with all receptors.
Dose-response curve is a relationship between drug dose and observed effect. Low dosage is ineffectual and high dose lethal. Effective dosage (ED$_{50}$) is half maximal response.

Drug Testing

1. Dose-response curves can be used to assess different drugs. Effective dosage (ED$_{50}$) of Drug A is lower than drug B (Left Figure).
2. Drug A will bind more than drug B (Right Figure).

Drug Dose Range

Every drug at some dosage level becomes lethal. The wider the range a drug has between effective ED$_{50}$ and lethal dosage (LD$_{50}$), the safer the drug is. Drug represented by blue curves, is safer than one shown by yellow curves.
1. Repeated use of a drug leads to **tolerance**. **Metabolic tolerance** is a biochemical tolerance that increases the metabolites such that they become less effective. Liver generally eliminates such metabolites before tolerance occurs.

2. **Functional tolerance** leads to down-regulating receptors in the target neurons if an agonist continues to occupy neuronal environment.

### Other Drug Effects

1. **Cross Tolerance**: Tolerance to one drug that generalizes to other drugs.
2. **Sensitization**: Drug craving caused by changes in the brain and receptor up regulation.
3. **Withdrawal Symptoms**: Unpleasant cognitive sensation associated with drug cessation.

### Drug Administration

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<th>Route of administration</th>
<th>Examples and mechanisms</th>
<th>Typical speed of effects</th>
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<td><strong>INJECTION</strong></td>
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<td>Subcutaneous</td>
<td>Many drugs such as insulin, vaccines, etc.</td>
<td>Slow to medium</td>
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<td>Intramuscular</td>
<td>Many drugs such as insulin, vaccines, etc.</td>
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<td>Intravenous (peripheral)</td>
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Drugs Affecting Presynaptic Sites

1. Synthesis of transmitters is inhibited (enzymes) at the axon.
2. Axonal transport is impaired (microtubules) by Colchicine.
3. Action potentials are blocked by tetrodotoxin.

4. Reserpine inhibits uptake of transmitters into vesicles.
5. Ca** channel blockers (verapamil) inhibit NT release.
6. Modulation (caffeine) of transmitter release by presynaptic receptor.

7. Inactivation (amphetamine) of transmitter reuptake thus prolonging synaptic activity.
8. Blockade of transmitter degradation. MAOIs block enzymes that degrade NTs. Thus NT prolongs at the synapse.
Drugs Affecting Postsynaptic Sites

1. Inactivation of enzyme in the cleft to prolong transmitter activity.
2. Alteration (alcohol) of postsynaptic receptors (GABA) to increase inhibition.
3. Blockade (curare) of nAChrs.

Drugs Affecting Postsynaptic Sites

4. Activation (nicotine) activates ACh receptors.
5. Activation (lithium) of second messengers cyclic AMP.

Classes of Drugs (Analgesics)

1. Poppy flowers produce opium. Opium contains morphine, a powerful pain-killer (analgesic) and is addictive. Likewise heroin (artificial form of morphine) is also analgesic and addictive.
2. Hughes and Kosterlitz (1975) identified two peptides that bound to opioid receptors and called them enkephalins. Enkephalins like morphine relieved pain and were addictive.
Analgesics: Opiates

3. Other endogenous morphine (endorphins) and dynorphin were also discovered that were endogenous to the brain.
4. Pert and Snyder (1973) discovered opiate receptors in the limbic system, hypothalamus, locus coeruleus, and periaqueductal gray. Morphine bound to receptors in these regions.

Analgesics: Cannabinoids

1. The second class of analgesics is based on tetrahydrocannabinol (THC) main ingredient in marijuana and hashish extracted the cannabis plant.
2. In 1992 an endogenous cannabinoid ligand was discovered (anandamide).
3. Cannabinoid receptors are found in substantia nigra, hippocampus, cerebellum and the cortex.

Depressants

1. Throughout human history alcohol has been the easiest drug to concoct. It is a tension reducer.
2. Alcohol has a biphasic effect on the brain. An initial stimulating phase and longer depressant phase later on.
3. Prolonged usage of alcohol damages nerve cells. Purkinje cells (cerebellum), pyramidal neurons (hippocampus) show such damage. Thus motor and memory losses over the patient’s lifetime.
Depressants

4. Alcoholism and dietary deficiency (thiamine) leads to Korsakoff’s syndrome.
5. Low dosage of alcohol stimulate dopamine pathways (euphoria) and perhaps opiate receptors in numbing pain.
6. Alcohol’s depressive effect is because of its interaction with GABA<sub>2</sub> receptors which are involved with inhibition in the brain.

7. Abstinence from alcohol leads to brain recovery in gray matter (cortex) and reduction in lateral ventricular volume.

Anxiolytics

1. Anxiolytics (Anxiety and Greek lytics “able to loosen”) are drugs ameliorate disabling emotional distress, like fear and terror.
2. Benzodiazepines (Valium etc.) are anxiolytic and enhance GABA receptors activity to increase inhibition.
3. Hormone allopregnanolone suspected to be endogenous anxiolytic is increased by alcohol.
**Stimulants**

1. **Nicotine**: Found largely in tobacco stimulates nicotinic receptors at the neuromuscular junctions (NMJ). Also in the CNS.
2. **Cocaine**: Derived from coca leaves is used as a local anesthetic and also relieves depression. Increases dopamine in the synapse.
3. **Amphetamines**: Causes heightened alertness, and even euphoria and wards off boredom.

**Hallucinogens**

1. **Lysergic Acid Diethylamide (LSD)**:
   - Potent drug that causes hallucinations was discovered in 1938 by Hoffmann.
   - In the 1950s scientists thought that it would provide a model for psychosis.
   - Why LSD causes hallucinations is not understood?
   - Former users report *flashbacks* resembling hallucinations. Memory or plastic changes?

2. **Phencyclidine (PCP)**:
   - Also called *angel dust*, is a potent analgesic and anesthetic.
   - Dropped from use because of side effects (delirium, disorganized perception, hostility etc).
   - Toxic reactions (four Cs) combativeness, catatonia, convulsions (or coma), confusion.
   - May provide useful model of schizophrenia.
Hallucinogens

3. Peyote and Mushrooms:
   • Peyote seed and mushrooms can alter states of consciousness resembling hallucinations. Fewer side effects.
   • Eminent scientists advocated their use.

Recreational Drugs

All drugs used in recreational form have devastating effects on the brain. Drugs like Ecstasy, hallucinogenic amphetamine can reduce serotonin axons in the brain within a single dose.

Drug Abuse

Any comprehensive model of drug abuse should be able to answer the following questions.

1. What social and environmental factors lead the individual to start abusing the drug?
2. What factors make her continue?
3. What physiological factors makes a substance rewarding?
4. What is addiction in behavioral and physiological terms, and why it is so hard to quit?
Drug Models

1. The Moral Model: The abuser lacks morals and thus self-control. Train self-control (punishment?).
2. The Disease Model: Drug abuser is diseased thus needs the drug. Needs treatment rather than moral punishment.
3. The Physical Dependence Model: Drugs are continued because their cessation cause unpleasant withdrawal symptoms.

Individual Differences

Individuals differ in their susceptibility to be becoming drug addicts because of many factors.
1. Biological Factors: men are more likely to abuse drugs than women.
2. Family Situation: Family breakup, poor parental relationships, antisocial siblings lead to drug abuse.
Drug Abuse Prevention & Treatment

1. Detoxification: Drugs like benzodiazepines reduce early withdrawal symptoms of drug abusers.

2. Agonists: Agonists can wean the individual from drugs, e.g., methadone reduces heroin appetite.

3. Anticraving Medications: Drugs that reduce appetite for the abused substance, e.g., naltrexone reduces alcohol pleasure.

4. Immunizations: Trigger the immune system to produce antibodies that remove targeted drugs from circulation.