Behavioral Neuroscience Notes

PSYC 360

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Behavioral Neuroscience Lecture Notes

CHAPTER 7

PSYCHOPHARMACOLOGY

7.1 Overview – Unit 3

- Neurotransmitters and Neuromodulators
  - Psychopharmacology
  - Disorders
  - Pain

7.1.1 Psychopharmacology in Detail

- The scientific study of the effects of drugs on the nervous system and behavior.
- Psychopharmacology is the study of how drugs affect the mind and behavior.
  - Psychotherapeutic drugs
  - Better understanding of how things normally work.

Principles of Drug Action

- *Selective Action* – Drugs are selective in their action on the nervous system.
  - *Sites of Action* – The location at which a drug interacts with the body to produce its effects.
  - Side effects are often due to the drug acting on sites other than the intended target.
    - Thus, side effects are relative to what our preferred site of action is.
  - *Example*: Opioids primarily affect the opioid receptor system.
- Drugs don't CREATE effects, they *modulate* ongoing cellular activity.
  - That is, they affect behavior by affecting neural transmission in some way.
  - *Agonist* – A drug that mimics or enhances the **effects of a neurotransmitter**.
    - Facilitates post synaptic effects.
    - *Example*: Morphine mimics endorphins, which are natural painkillers.
  - *Antagonist* – A drug that blocks or inhibits the effects of a neurotransmitter.
    - Inhibits post synaptic effects.
    - *Example*: Naloxone blocks the effects of opioids, reversing their effects.
  - Agonistic effects can become antagonistic if the drug is taken in excess.
    - *Example*: I make a neuron fire a neurotransmitter, but I also block the reuptake of that neurotransmitter.

Basic Process

- *Precursor* – A substance from which another substance is formed. AKA, the ingredients used to make a neurotransmitter.
- $$\text{Precursor} \xrightarrow{\text{Synthetic Enzyme}} \text{NT} \xrightarrow{\text{Metabolic Enzyme}} \text{Inactive Metabolite}$$
  - *Synthesis* – The process of creating a neurotransmitter from its precursors.
  - Sometimes, we break down the precursor to build the neurotransmitter.

7.1.2 Other Ways of Agonist and Antagonist

- Block Ca^{2+} channels from opening (antagonist)
- *Mimetic* – Mimics the action of a neurotransmitter.
  - *Direct Agonist* – Binds to the same receptor as the neurotransmitter and mimics its effects.
  - *Indirect Agonist* – Binds to a different site on the receptor and enhances the effects of the neurotransmitter.
- Blocking agent
  - Competitive
    - *Direct Antagonist* – Binds to the same receptor as the neurotransmitter and blocks its effects.
  - Non-competitive
    - *Indirect Antagonist* – Binds to a different site on the receptor and blocks the effects of the neurotransmitter.
  - *Inverse Agonist* – Binds to the same receptor as the neurotransmitter and produces the opposite effect.
- *Depolarizing* or *Desensitizing Agent* – A drug that causes the AP to stay in a depolarized state; refusing to let the neuron go through another AP, and it stays in the absolute refractory period. (Antagonist)
- Interfere with vesicles (leaky or transporter proteins). (Antagonist)
- Interfere with docking proteins. (Antagonist)
- Selectively deactivate autoreceptors. (Agonist)
- Selectively activate autoreceptors. (Antagonist)

7.2 What Do These Chemicals Between Neurons Do?

- Transmit information.
  - Glutamate
  - GABA
  - Glycine
- Modulate information.
  - Every other neurotransmitter.

7.3 Classes of Neurotransmitters (Revisited from Lab)

- Amino Acids
  - Glutamate, GABA, Glycine
    - *Glutamate* – Synthesized from precursor glutamine by an enzyme called *glutaminase*. It is the most common excitatory neurotransmitter in the brain.
      - Related closely with the *NMDA* receptor, which is a type of glutamate receptor that is important for synaptic plasticity and memory formation.
      - One drug that binds to this site, *Phencyclidine (PCP)* (direct antagonist), is a drug that blocks the NMDA receptor and causes hallucinations and dissociation. Another drug that is thought to bind here, *Ketamine* (direct antagonist), is a dissociative anesthetic that is used in surgery and is also being studied as a treatment for depression.
      - **Reuptake and Deactivation**
        - Reuptake is done by the *excitatory amino acid transporters (EAATs)*. These are important because it reduces the change of excitotoxicity, which is believed to be involved in damage to the brain in stroke and amyotrophic later sclerosis (ALS, Lou Gehrig's disease).
    - *GABA* – Synthesized from precursor glutamate by an enzyme called *glutamic acid decarboxylase (GAD)*. It is the most common inhibitory neurotransmitter in the brain.
- *Amines* (monoamines) – Derived from amino acids
  - Catecholamines
    - Contain catechol and derived from the amino acid tyrosine.
    - *Tyrosine* – Precursor for the catecholamines.
    - Dopamine (DA), Norepinephrine (NE), Epinephrine (Adrenaline)
    - Dopaminergic, Adrenergic, and Noradrenergic systems.
  - *Indolamines*

- *Serotonin* (5-HT)
- *Melatonin*

- Peptides (AKA: Neuropeptides)
  - Endogenous Opioids
- Acetylcholine (ACh)
- Lipids
  - *Anadamide* (Sanskrit for "bliss") – Endogenous cannabinoid.
  - These appear to be synthesized on demand; produced and released as needed and not stored in synaptic vesicles.
  - Anadamide is deactivated by the enzyme *fatty acid amide hydrolase (FAAH)*.
- **Two Other Classes**
  - Nucleosides
    - Adenosine
  - Soluble Gases
    - *Nitric Oxide (NO)* – Required for an erection.

7.4 Acetylcholine (ACh)

- First neurotransmitter discovered.
  - Otto von Loewy – Discovered ACh in 1921.
    - This guy took a frog heart and put it in saline. Then, he took simulated the parasympathetic part of the vagus nerve, and saw that the heart slowed down.
    - He then took the saline and put it in a different frog heart, and saw that the heart slowed down again.
    - "Vagusstoff" (ACh) – The chemical that was released from the vagus nerve that slowed the heart down.
    - Cholinergic – Referring to ACh.
- ***Some* Functions**
  - **Function in the ANS:**
    - Sympathetic
      - Spinal nerve leaves the cord and synapses in the paravertebral ganglion (ACh)
      - Then makes neuromuscular junction with smooth muscles and glands (NE)
        - *Neuromusclar Junction* – The synapse between a motor neuron and a muscle fiber.

        - *Paravertebral Ganglion* – A ganglion located next to the spinal cord.
        - Except sweat glands (ACh)
      - *Sympathetic Chain* – A chain of ganglia that runs parallel to the spinal cord. This is the reason for when you get anxious, ALL of your body gets anxious.
    - Parasympathetic
      - Spinal nerve leaves the cord and synapse in the parasympathetic ganglion (ACh)
      - Then makes neuromuscular junction with smooth muscles and glands (ACh)
    - The only NT in the parasympathetic branch.
    - NT of the preganglionic sympathetic branch.
  - **Function in the Somatic NS**
    - Excites the neuromusclar junction (ACh)
    - So, ACh is important for getting motor messages out to all kinds of muscles and glands.
  - **Function in the CNS**
    - ACh is important in:
      - Learning and alertness (*Basal Forebrain*)—activates the cortex and facilitates learning.
        - *Nucleus Basalis* – Projects to the cortex
        - *Medial Septal Nucleus* and *Nucleus of Diagonal Band* – Projects to the hippocampus through the fornix.
      - Memory (*medial septal nucleus*)—modulate the hippocampus
      - REM sleep generation (*Pedunculopontine nucleus (PPT)* and *Laterodorsal Tegmental Nucleus (LDT)*)—projects to the pons and thalamus.
      - Reward system.
- **Synthesis and Metabolism**
- **Drugs and Disorders**

7.4.1 ACh Synthesis and Metabolism

- **Synthesis**
  - In a nutshell: A breakdown of lipids leads to Choline, which is the precursor for ACh. Acetate is the anion in vinegar (Acetic acid). Then, this is combined with Acetate to make ACh.
  - In more detail:
    - CoA attaches to an acetate ion (*Acetylcoenzyme A (acetyl-CoA)*).

    - Then, *choline acetyltransferase (ChAT)* transfers the acetate from the acetyl-CoA to the choline molecule.
    - Mnemonic: **ChAT**: From right to left: Transfers acetate to choline.

- **Metabolism**
    - ACh is broken down by the enzyme *acetylcholinesterase (AChE)* into acetate and choline. Nice and simple!
    - The choline is taken back up by active transport and reused, and the acetate is broken down and eliminated.

7.4.2 Two Types of Cholinergic Receptors

- Nicotinic Receptors
    - Agonist at low doses, but antagonist at high doses.
    - Iontropic.
    - Found at the Neuromusclar Function in the PNS.
    - *Curare* (direct antagonist) – A drug that blocks nicotinic receptors, causing paralysis.
        - Competitive blocking agent
        - Paralysis, surgery
- Muscarinic Receptors
    - Comes from a hallucinogenic mushroom (Amanita muscaria).
        - **Don't confuse with Serotonin's Mescaline: Cactus; nor Psilocybin: Mushroom.**
    - Vikings (probably took this drug before raiding) and Koryaks (Nordic people who used this mushroom in religious practices).
    - Metabotropic receptors.
    - Predominates in the CNS (although, both types are found in the CNS).
    - *Atropine* (direct antagonist) – A drug that blocks muscarinic receptors, causing pupil dilation and increased heart rate.
        - Competitive blocking agent
        - Belladonna alkaloids (deadly nightshade)

7.5 MORE Drugs and Toxins Affecting ACh

- *Botulinum Toxin* – A waste product of *Clostridium botulinum*, which are bacteria who grows without oxygen.

- Interferes with Ca^{2+} influx channels, preventing the release of ACh.
- Because Botox causes paralysis, it can interfere with emotional *expression* because it paralyzes muscles like the orbicularis oculi.
- Additionally, since we know that expression influences experience, when we paralyze these muscles, then the emotional *experience* is also negatively affected.
- **Does Botox Decrease Emotional Experiences?**
  - Population: Women who want wrinkles gone.
  - One IV: two levels: Botox or restylane (dermal filler).
  - Method: Everyone had wrinkle reduction. AND, Everyone watches some emotion evoking movies.
  - Results: Botox group had less emotional experience than the restylane group.
  - **Is this a good thing?**
    - Another study takes a sample of depressed people and gives them either Botox or a placebo.
    - Results: 15% of placebo had a decrease in depression, while 52% of the Botox group had a decrease in depression.
- Botox can also be used to treat migraines, cerebral palsy, and hyperhidrosis (excessive sweating).

- *Black Widow Spider Venom* – A neurotoxin that causes the release of ACh at the neuromuscular junction, causing continual release of ACh and paralysis.
- *Cobra and Krait Venom* – A neurotoxin that blocks the binding of ACh to nicotinic receptors, causing paralysis.
- *AchE Blockers* – Comes into contact with the enzyme that breaks down ACh, causing an increase in ACh in the synaptic cleft.
  - Irreversible
    - Insecticides (Parathion)
    - Nerve gas: DFP (Diisopropylfluorophosphate (don't need to know the whole name)) and Sarin.
      - Readily crosses the blood-brain barrier so PNS and CNS are affected.
      - Antidote?
        - *Atropine* – A drug that blocks muscarinic receptors, preventing the effects of excess ACh.
        - *Pralidoxime* – A drug that reactivates AChE, allowing it to break down ACh again.
  - Reversible
    - *Neostgmine* (**Prostigmin**) and *Physostigmine* (**Antilirum**) – Drugs that inhibit AChE, increasing the amount of ACh in the synaptic cleft.
      - Doesn't cross the blood-brain barrier, so it only affects the PNS.

- Used to treat *myasthenia gravis* (a disease that causes muscle weakness and fatigue).
  - Autoimmune disease that attacks nicotinic receptors at the neuromuscular junction.
- *Donepezil* (**Aricept**) and *rivastigmine* (**Exelon**) – These drugs do the same thing as the above drugs, but they cross the blood-brain barrier and are used to treat Alzheimer's disease and Parkinson's disease (only the cognitive part).

7.6 New Drug for Schizophrenia

- We'll talk about dopamine drugs later in this unit.
- This new drug now:
  - *Xanomelne and trospium chloride* (**Cobenfy**) – A drug that blocks the muscarinic receptors in the CNS, but not in the PNS.
  - Dopamine but also Ach!

7.7 Catecholamines

- Dopamine (DA)
- Norepinephrine (NE)
- Epinephrine (Adrenaline)

7.7.1 Dopamine (DA)

- Synthesis and Metabolism
- Function
- Drugs and Disorders

Dopamine Synthesis

- Tyrosine was first discovered from cheese (tyrosine = cheese).
  - Tyrosine is the precursor for DA, NE, and Epi.
  - *Tyrosine Hydroxylase* – The rate-limiting enzyme in the synthesis of catecholamines.
    - Converts tyrosine to L-DOPA.
    - L-DOPA is the precursor for DA, NE, and Epi.
  - L-DOPA is converted to DA by the enzyme *DOPA decarboxylase*.

Dopamine Metabolism

- DA is broken down by the enzyme *Monoamine Oxidase (MAO)* into *Dihydroxyphenylacetric acid (DOPAC)*.
- Then, *Catechol-O-methyltransferase (COMT)* converts DOPAC into *Homovanillic acid (HVA)*.
- Also, starting from DA, we can use COMT to convert it to 3-methoxytyramine (3-MT), then with MAO, we can convert it to HVA.

DA Function

- **Movement/Motor systems**
  - *Nigrostriatal System* – Starts in the substantia nigra and ends in the striatum (caudate nucleus and putamen).
  - Here's the route: We start at the striatum, which then sends an inhibitory GABA signal to the substantia nigra, who sends a reciprocal inhibitory DOPA signal back to the striatum nerve that sends an inhibitory GABA signal to the globus pallidus. Then, the globus pallidus excites the thalamus, who then excites the primary motor cortex, who then excites movement.
    - Note that if the inhibitory signal to the substantia nigra is limited, then the signal that the striatum sends to the globus pallidus is much stronger, which leads to a weaker signal to the thalamus, and thus to movements.
  - Parkinson's Disease symptoms:
    - Weakness,
    - Tremor at rest,
    - Muscle rigidity,
    - Problems with balance,
    - Abnormal gait,
    - Trouble learning
  - Treatment
    - *Reserpine* (**Raudixin**) for ↓ **BP** (Not in use anymore because it caused Parkinson's-like symptoms)
      - 1960's
        - Blocks monoamine transporters
          - Developed Parkinson's symptoms
          - Can't fill vesicles and DA is lowered
      - Then, discovered Substantia Nigra was pale.
    - L-DOPA can be a direct treatment for Parkinson's as well.
    - *MPTP* – Neurotoxin for DA cells in the Nigrostriatal System (which is not endogenous).

- **History of MPTP – or why you shouldn't use illicit drugs**
  - 1982 – young California heroin users
  - Had used what they THOUGHT was synthetic heroin
    - *MPPP* – Opioid analgesic drug
      - Not used clinically
      - Illegally manufactured for recreational drug use
    - INSTEAD it was MPTP (oh no!)
      - They instantly developed Parkinson's-like symptoms
      - Bad for them, but good for us because we can study it.
        - Led to animal model development and possible treatment ideas.
  - We don't know why Parkinson's patient's cells are dying, but maybe something similar.
  - MPTP is converted to the chemical *MPP+* by the enzyme MAO (which is what breaks down DA), which is what damaged the cells.
    - Question: Could MAO-I improve Parkinson's?
    - Yes!
    - *Deprenyl*, also called *selegiline* (**Eldepryl**, **Jumex**) – A drug that inhibits MAO, can slow down progression of the disease.
- New treatment
  - Molecule keeps proteins from misfolding
  - *Lewy Bodies* – Misfolded proteins that are found in the brains of people with Parkinson's.
    - These are toxic to DA cells
- *Huntington's Chorea* – A genetic disorder that leads to uncontrolled movements and cognitive decline.
  - Too little GABA from the Striatum to the Substantia Nigra causes an increase in dopamine back to the Striatum which, in turn, lessens the signal to the Globus Palidus, which increases overall movements.
  - *Tetrabenazine* (**Xenazine**) – Drug that inhibits the DA vesicle transporters.
  - *Pallidotomy* – A surgery that affects the Globus Pallidus to inhibit movement.
- *Choreoathetotic Movements* – too much movement
  - *Athetosis* – Slow continually writing movements
  - *Choreic* (to dance) – Rapid, purposeless, involvuntary movements

- **Behavioral Arousal and Attention**
  - Narcolepsy
    - *Methylphenidate* (**Ritalin**) – A drug that increases DA and NE in the brain, used to treat ADHD, but can also be used for narcolepsy.

- *Hypocretine* – A neuropeptide that is involved in the regulation of sleep and wakefulness.
  - Created by the lateral hypothalamus.
  - Hypocretine: *Hypo* for *hypo*thalamus, *cretine* for *secretin* (a hormone).
  - *Orexin* – Another name for hypocretine; makes you want to eat.
- From hypocretine, researchers developed an antagonist for the orexin receptor, which is used to treat insomnia. This drug is called *Suvorexant* (**Belsomra**).
- **Treatment**
  - *TAK-994* – OX2R (Orexin-2 receptor) Agonist
  - *Hcrt-1* – Intranasal hypocretine-1 (orexin-1) agonist
  - Hypocretine Cell Transplant
  - Gene Therapy: *introduce* preprohypocretin gene into the brain to make more hypocretine.
  - Opiates (exogenous) can increase the number of hypocretin-producing cells in the brain.
  - Indirect role for opiate agonists in treating narcolepsy.

- ADHD
  - Uses Methylphenidate for selective attention.
- *Mesocortical System*
  - From ventral tegmental nucleus to prefrontal cortex, limbic CORTEX, hippocampus, all frontal lobes, and association areas of parietal and temporal lobes in primates.
  - Short-term memories, planning, and problem-solving are all associated with this system.

- **Reinforcement and Reward**
  - *Mesolimbic System (MLS)* – Responsible for reward and reinforcement.
    - From vental tegmental nucleus to limbic system
      - Amygdala, hippocampus, and nucleus accumbens.
      - Opioids cause the release of dopamine at the nucleus accumbens, which is the pleasure center of the brain.
  - James Olds & Peter Milner (1954)
    - They asked: "Does electrical stimulation of the reticular formation facilitate learning?"
    - James Olds visits a conference and listens to Neal Miller, who says electrical stimulation is aversive, so it should be avoided.
    - One lone rat was put in a box with a lever, and when the rat pressed the lever, it would get a shock to the reticular formation. He ended up pressing the level 700 times per hour.

- More studies of this
  - Skinner box
    - Rats press 2000 times per hour for a shock to the MLS.
    - Monkeys press 8000 times per hour for a shock to the MLS.
    - Starving animals will choose the MLS over food 80% of the time.
    - They also press the button for these conditions too:
      - Thirsty,
      - Getting shocked (at their feet),
      - Mother instincts.
- Delgado (1969) – For people who were getting their brain stimulated for seizures, this researcher also asked them about what they thought of the stimulation. They all thought that it was pleasurable.

Part II

Behavioral Neuroscience Lab Notes

CHAPTER 8

LAB 3: SLEEP LAB

NEW NOTES FOR 04/10/25

8.1 What Do We Know About Sleep?

- Sleep is an active process.
- Sleepiness and alertness are controlled in part by a biological clock.
- Things can go wrong
  - There are whole books that discuss sleep disorders.
- *Suprachiasmatic nucleus (SCN)* is the master clock of the body.
  - The SCN is located in the hypothalamus and is responsible for regulating circadian rhythms.
  - Note the name of the SCN, it is *above* the *chiasm* of the optic nerve.
- *International Classification of Sleep Disorders (ICSD)* – A system for classifying sleep disorders.
- Three kinds of rhythms:
  - *Ultradian* rhythms: cycles shorter than 24 hours (e.g., heart rate, respiration).
  - *Circadian* rhythms: cycles of about 24 hours (e.g., sleep-wake cycle, body temperature).
    - Our circadian rhythm is an endogenous clock that is influenced by exogenous factors.
    - *Free-running* is when the circadian rhythm is not influenced by external cues (e.g., light, temperature).
    - It is about 24.2 hours in humans.
  - *Infradian* rhythms: cycles longer than 24 hours (e.g., menstrual cycle, seasonal changes).
- *Zeitgeber* is a stimulus that helps to regulate the biological clock (e.g., light, temperature).
- Human clocks run long when left free running. Rats are short.

8.2 What is Sleep?

- For regular people, sleep is behaviorally defined as a state of reduced movement, species specific posture, reduced response to stimuli, and reversibility.
- For sleep researchers, they take a more physiological definition of sleep.
  - *Polysomnography (PSG)* is a method of recording various physiological signals during sleep, including:
    - **Electroencephalography (EEG):** measures electrical activity in the brain.
    - **Electromyogram (EMG):** measures muscle activity.
    - **Electrooculogram (EOG):** measures eye movements.
    - Rechtschaffen and Kales (1968) defined sleep stages based on EEG patterns.
    - In 2007, the American Academy of Sleep Medicine (AASM) updated the sleep stage criteria.

Name	Frequency	Amplitude	Description	State
Beta β	12 – 50 Hz (variable)	Lower and Variable	Desynchronous	Awake and Paying Attention
Alpha α	8 – 12 Hz	50 Microvolts	Synchronous	Relaxed Wakefulness (eye closed, not fully attending, and usually largest occipitally)
Theta θ	3.5 – 7.5 Hz	Low in voltage Microvolts	Synchronous	Drowsy, Light Sleep (Stage 1)
Delta δ	1 – 3.5 Hz	20 – 200 Microvolts	Synchronous	Deep Sleep (Stages 3 and 4)

Table 8.1: Summary of EEG Wave Characteristics

8.3 Two States of Consciousness

8.3.1 Being Awake

- Physiological definition of wakefulness:
  - Supposed to be awake for $\frac{2}{3}^{\text{rd}}$ of the day.

- $< 5\%$ of the day is spent in REM sleep.
- Predominantly alpha and beta waves in the brain when drowsy.
- Muscle activity – high muscle tone when awake.
  - Lose muscle tone when you are sleeping.
    - EMG is high when awake
- Variability in the eye movement

8.3.2 Being Asleep

- Delta waves and theta waves predominantly.
- EMG is low
- Slow rolling eye movements everytime you fall asleep.
- *Hypnic Jerk* – a sudden muscle contraction that occurs when falling asleep.
- *NREM Sleep* – non-rapid eye movement sleep, which is divided into three stages:
  - *N1* – light sleep, theta waves, low EMG, and slow rolling eye movements (5-10% of the night).
    - Transition between wakefulness and sleep.
    - Hypnic jerks can occur in this stage.
    - Muscle tone is reduced, but not completely lost.
  - *N2* – light sleep, theta waves, sleep spindles, K-complexes, low EMG, and slow rolling eye movements (45-55% of the night).
    - Sleep spindles and K-complexes are characteristic of this stage.
    - Muscle tone is further reduced compared to N1.
  - *N3* – deep sleep, delta waves (3-8%), low EMG, and slow rolling eye movements (10-15% of the night).
    - Characterized by high-amplitude delta waves.
    - Muscle tone is at its lowest in this stage.
- *REM Sleep* – rapid eye movement sleep.
  - Aserinsky (1952): Discovered 70% in infants, 20-25% for healthy adults
  - Characteristics:
    - EEG – Low voltage, random, fast with sawtooth waves.
    - Fast activity, low amplitude, and desynchronous.
    - EMG – atonia (loss of muscle tone).
    - Paradoxical sleep: brain is active, but body is paralyzed.
    - Intercostal muscles are paralyzed, but not the diaphragm (obviously).
    - EOG – Bursts of rapid eye movements