Psychology 210
Lecture 3
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Properties of Neurotransmitters
- Must be synthesized within the neuron
- Released in response to an action potential
- Can experimentally duplicate the action of a NT on a postsynaptic cell
- There is some mechanism that will stop the effects of the NT on the postsynaptic cell

Types of NTs
- Small-molecule transmitters
  - Amino acids
- Neuropeptides
  - Groups of amino acids

Small molecule NTs
- Acetylcholine (ACh)
- Catecholamines
- Indoleamines
- Amino Acid NTs
- ATP and byproducts

Chemical Messengers
- Neurotransmitters
  - Act on neurons locally
    - At one synapse
- Neuromodulators
  - Act on clusters of neurons
  - May not be in the immediate vicinity of where they were released
- Neurohormones
  - Act on neurons distant from their point of release
  - May enter blood flow

Cholinergic Neurons
- Use ACh as their major NT
- Acetylcholinesterase
  - Released into the synaptic cleft to break down extra ACh
- Found at neuromuscular junctions
- Also found in the brain in lower level structures
  - Believed to be involved in learning and memory
    - Alzheimer's Disease
Cholinergic Neurons

- Two main types
  - Nicotinic receptors
    - Reacts to both ACh and nicotine
  - Ionotropic
  - Muscarinic receptors
    - Reacts to both ACh and muscarine
    - Found in hallucinogenic mushrooms
    - Metabotropic

Action of NTs at synapse

- Can be either single step or multiple steps
  - Ionotropic: single step
  - NT binds to channels and opens them

Metabotropic receptors

- Multi-step process
- NT binds to receptor- triggers G protein to bind to ion channel and open it

Catecholamines and Indoleamines

- Catecholamines
  - Dopamine
  - Epinephrine
  - Norepinephrine
- Indoleamines
  - Serotonin
  - Melatonin

How to make catecholamines

- Tyrosine (an amine acid)
- Turns to L-Dopa
- Turns to Dopamine
- Turns to Norepinephrine
- Turns to Epinephrine
- They all have the same starting material
  - They’re just different steps in the process
  - Steps occur when enzymes are added to the molecules
Dopaminergic Neurons

- Use dopamine
- 3 main pathways
  - Substantia nigra-basal ganglia
  - Movement
  - Parkinson's disease
  - Midbrain-limbic system (hippocampus, amygdala, nucleus accumbens)
  - Feelings of reward
  - May play a role in addiction
  - Midbrain-frontal lobe
  - Higher level cognitive functions
  - Planning behavior

Norepinephrine and Epinephrine

- Act on noradrenergic and adrenergic receptors
- Named this because epinephrine used to be called adrenaline
- Both are NTs and hormones
- Norepinephrine
  - Important for attention and focus
  - Important in sympathetic nervous system
- Epinephrine
  - Important for short-term stress
  - Also important in sympathetic nervous system
- Side note: ACh is the NT for the parasympathetic nervous system

Catecholamines

- Many types of receptors
- At least 5 different dopaminergic receptors
- At least 4 different receptors that respond to both norepinephrine and epinephrine
- All are metabotropic

Indoleamines

- Trytophan – 5HTP – Serotonin – Melatonin
- Serotonin
  - Widespread throughout the brain, few in number
  - Most use metabotropic receptors
  - Important for sleep, mood, and appetite
- Melatonin
  - Secreted by the pineal gland
  - Acts on metabotropic receptors
  - Important for sleep wake cycles

Amino acid neurotransmitters

- Eight identified amino acid NTs
- Glutamate and GABA most important
- Glutamate is the most used excitatory NT in the CNS
- GABA is the most used inhibitory NT in the CNS
Glutamate

- An amino acid
- Synthesized from glutamine
- Works on both ionotropic and metabotropic receptors
- 3 major ionotropic receptors
  - NMDA
  - AMPA
  - Kainate

NMDA

- Both voltage dependent and glutamate dependent
- Usually located near AMPA receptors
- AMPA depolarizes the postsynaptic cell
  - Raises the voltage for the NMDA receptors
  - Magnesium responsible for blocking the NMDA receptors until high enough voltage
- NMDA allows both Ca$^{2+}$ and Na$^+$ to enter
  - Ca$^{2+}$ causes long term changes in the cell
  - Thought to be involved in long term memory

GABA

- Synthesized from glutamate
- Two different GABA receptors
  - One ionotropic, one metabotropic
- Works by allowing Cl$^-$ to enter the cell or allowing K$^+$ to leave the cell

ATP

- Involved in perception of pain
- Major byproduct of metabolism is also a NT
- Acts upon autonomic nervous system
  - Vas deferens, bladder, heart, gut
- Frequently coexists with other enzymes
- Also the body's major source of energy

Neuropeptides

- Chains of amino acids
- Over 40 different types of neuropeptides that are NTs
- Can be both hormones and NTs
- Reuptake from the synaptic cleft is quite slow
- Ex. Insulin
  - Involved in digestion and is also a NT

Drugs, Drugs, and More Drugs

- Agonists
  - Enhance the activity of the NT
- Antagonists
  - Reduce the activity of the NT
- Don't think of agonists and antagonists in terms of inhibition and excitation
- An agonist to GABA enhances the inhibition of the postsynaptic cell
Different Effects of Drugs

- **NT production**
  - Can reduce or enhance the amount of NT produced
  - Either reduces or enhances the action of that NT, respectively
  - If it interferes early enough, it could effect multiple NTs (i.e., the dopamine, norepinephrine, epinephrine sequence)
- **NT Storage**
  - Can reduce the amount of NT stored
  - Causes less NT to be available for release
- **NT Release**
  - Can promote or prevent exocytosis (NT release)
  - Agonists promote
  - Antagonists prevent

Examples: Effects on NT Production

- Increasing dairy intake leads to an increase in tryptophan levels
  - Leads to an increase in serotonin levels
- AMPT
  - Interferes with the activity of tyrosine hydroxylase
  - Leads to a decrease in the amount of dopamine, norepinephrine, and epinephrine

Examples: Effects on NT Storage

- Reserpine
  - Used to lower blood pressure
  - Interferes with the uptake of some NTs (serotonin) into synaptic vesicles
  - Has lead to depression
  - Rarely prescribed now

Examples: Effects on NT Release

- Black widow venom
  - An agonist: leads to an increase in ACh release
  - Leads to overstimulation of muscle fibers and convulsions: leads to the neuron “running out” of release ACh and paralysis
- Botulin
  - An antagonist: leads to a decrease in ACh
  - Leads to paralysis

Examples: Effects on NT Receptors

- Curare
  - Used on arrowheads and darts
  - Occupies nicotinic ACh receptors and leads to paralysis
Examples: Effects on NT Reuptake

- Dopamine reuptake inhibitors
  - Cocaine, amphetamine, Ritalin
- Serotonin reuptake inhibitors
  - Prozac
- More on this later in the class

Basic Principles of Drug Effects

- Drugs may or may not have different effects depending upon their method of administration
- Frequently the level of drug in the body is different based upon the method of administration
- Also, different side effects may occur
  - Cocaine
    - Snorting may cause bowel gangrene
    - Snorting causes nasal bleeds, problems swallowing etc
  - Injecting may cause liver problems and allergic reactions

Placebo Effects

- When pharmaceutical companies are testing drugs, must worry about placebo effects
- When patients are told they are getting a new depression drug, dopamine levels rise and may contribute to a lessening of the depression (before the drug even takes place)
- Give subjects a placebo instead (sugar pills, saline)
- Don’t tell subjects whether they are receiving the drug or the placebo
  - Controls for placebo effects

Experimenter Effects

- Some doctors may view a subject as less depressed if on the drug than if not
- Power of suggestion
- Studies are frequently run as double blind
  - Neither the subject nor the experimenter knows whether the subject is getting the placebo or the drug
  - Records are kept by a second experimenter that doesn’t have contact with the subjects

Tolerance

- Tolerance
  - Changes in the body’s response to the drug to maintain a constant environment
    - i.e. If a drug causes an increase in heart rate, the body may prepare for the drug by decreasing its heart rate
    - This causes users to gradually increase the amount of the drug to get the same effects

Interesting Note about Tolerance

- Imagine that every day for a year you injected heroin in your arm at 5:45 outside of the door before this class
- As the year went on, you would progressively need more and more heroin to get the same effect (tolerance)
- One day, you decided to skip class and injected heroin in front of your neighborhood McDonalds instead
  - There is a very high danger of overdose here
  - Why?
Why is there a higher danger of overdose?

- Because your tolerance is not just to the drug but to the situation
- Your body, when you see the classroom, begins to prepare for the drug well before you bring out the needle
- It sees the situation and knows what is coming
- Once the situation is changed, the body does not prepare itself as well, and your tolerance is lowered
- This leads to an increase in overdoses

Tolerance

![Classically conditioned tolerance to heroin graph]

Withdrawal

- Similar to tolerance
- Occurs after a user stops using
- Occurs because the body is trying to maintain a constant environment and is preparing for the drug (that never comes)

Addiction

- Compulsive need for repeated use of the drug
- Linked to neural reward systems
  - Dopamine
  - Nucleus accumbens
- Some drugs don’t activate this circuit
  - LSD: no strong addictions usually

Addiction

- Removal of nucleus accumbens or damage to this dopaminergic circuit leads to reductions in addiction
  - Not a viable option for treating addicts
  - May lead to no feelings of reward

Treatment

- Very hard to end an addiction
  - Once you’re an alcoholic you always are alcoholic
- Relapses are very common
- Multistep programs addressing many different areas seem to be the most affective
Treatments

- Drugs are being developed to try and help addicts
  - may cause unpleasant effects when addict takes the drug
  - Unpleasant effects become associated with taking the drug and the addict quits
  - May block the drug from working
    - The addict loses interest in taking the drug

Types of Psychoactive Drugs

- Stimulants
- Opiates
- Marijuana and other Hallucinogens
- Alcohol

Stimulants

- Typical Effects
  - Increase heart rate
  - Increase blood pressure
  - Increase alertness
  - Increase concentration
  - Increase mobility

Caffeine - FMRI

Subjects performing a task without caffeine
Subjects performing a task after taking caffeine

Stimulants

- Caffeine!!!
  - Mechanism not completely understood
  - Antagonist to adenosine
  - Adenosine is an inhibitory NT
    - Eliminates the inhibition – thus things speed up
  - May cause an increase in reward feelings, arousal, and reaction time
  - Caffeine use is actually correlated with decreases in Parkinson’s Disease

Stimulants

- Nicotine
  - Acts upon nicotinic cholinergic neurons
  - 50% of cigarettes consumed are by people with mental disorders
    - May be self medicating
    - May also be that nicotine contributes to mental disorders
Implications of Smoking on Nicotinic Receptors

- An ionotropic receptor
- Smokers report an increase in functioning capabilities
  - Increase in auditory capabilities
  - Memory functions
- Nicotine may be a substitute for ACh but it is not a very good one
- After longer use, nicotine actually deadens the receptors

Stimulants

- Cocaine
  - Works as a Dopamine reuptake inhibitor
- Amphetamine
  - Stimulates dopamine and norepinephrine (at dopaminergic neurons) release and inhibits reuptake as well
  - Very addictive: due to their power on the dopaminergic reward system
  - A single dose could cause addiction in mice
- May lead to hallucinations
  - May be due to an overstimulation of the sensory systems

Why is Cocaine so addictive?

Temporary Effects in certain areas

Cocaine on the Brain

Cocaine also blocks Sodium receptors, in some areas; Long term effects are a decrease in activity

Stimulants

- Ecstasy
  - Aka MDMA
  - Relative to amphetamine
  - Stimulates the release of serotonin
  - Over stimulates serotonin synapses and may lead to the death of serotonin receptors
  - Since serotonin is one of the main mechanisms for happiness, prolonged ecstasy use leads to depression

Effects of ecstasy on the brain
Opiates

- Typical Effects
  - Pain management
  - Relaxation
  - Euphoria
  - Endorphines
    - Natural opiates

Morphine

- Mechanisms of action are unclear
  - Opiates have their own receptors
  - Recent evidence points to increasing the release of serotonin
    - Leads to feelings of pleasure
  - When coupled with magnesium, NMDA receptors appear to be blocked
    - MAY lead to the pain relieving effects found
  - Codeine is a relative to morphine
    - Has similar effects
    - Not quite as strong

Heroin

- Heroin is actually a prodrug
  - It is inactive as a drug in its normal state
- Once in the body, it is metabolized into morphine

Hallucinogens

- Marijuana
  - A hallucinogen at high levels
  - May cause excitement and euphoria or depression and social withdrawal
  - Contains over sixty different psychoactive substances
- Amanita Mushrooms
  - GABA agonist
- Lysergic Acid Diethylamide
  - Similar to serotonin
  - Produces feelings of pleasure
  - Mechanism for hallucinations not understood

PET of marijuana users

Marijuana abuser: a long term user of marijuana

Cannabinoid Receptors all over

- Rat cortex:
Alcohol

- Dilates blood vessels
- Relieves anxiety
- Reduces behavioral inhibitions
- Works at GABA receptors, dopaminergic receptors, NMDA receptors
- Tolerance develops very quickly
- Great effects in the cerebellum
  - Leads to movement deficits

PET study of alcohol and tobacco

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<tr>
<th>Addicts</th>
<th>Non-addicts</th>
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Presence and severity of characteristic withdrawal symptoms

- Reinforcement: A measure of the substance's ability, in human and animal tests, to get users to take it again and again, and in preference to other substances.
- Tolerance: How much of the substance is needed to satisfy increasing cravings for it, and the level of stable need that is eventually reached.
- Dependence: How difficult it is for the user to quit, the relapse rate, the percentage of people who eventually become dependent, the rating users give their own need for the substance and the degree to which the substance will be used in the face of evidence that it causes harm.
- Intoxication: Associated with addiction and increases the personal and social damage a substance may do.