Overview of Pharmacodynamics

Psychology 472: Pharmacology of Psychoactive Drugs

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Pharmacodynamics

- Generally is defined as effects of drugs on a systems
- Can be associated with any system
  - Neural, Heart, Liver, Endocrine System, etc.
- Lots of issues influence pharmacodynamics
  - Amt of drug available
  - Past drug use - Tolerance
  - Drug Stability
    - How long a drug lasts in the body before it is metabolized
- Drug Consistency
  - Does it need metabolized before it can be used
    - L-Dopa vs. Dopamine

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Bioavailability

- Determines how much of a drug that actually reaches a target organ or structure
- Effects can depend on
  - Gastrointestinal loading (decreases absorption)
  - Liver metabolism (First Pass)
  - Binding to plasma proteins that makes the drug unavailable to the target
  - Cannot penetrate the Blood-Brain Barrier
  - Cannot penetrate other cell membranes

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Effects on Target Binding Site

- All drugs bind on some receptor site
- Causes some effect on the target site
- Creates some behavioral effect
  - Called Main Effect
- Also has other unintended effects
  - Called Side Effect

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Dose-Response Relationships

- Examine several doses of some drug and measure the change in some response (behavioral, neuronal, or structural)
- Relationship between *dose* and *response* is called the dose-response curve (DRC).
- Several types

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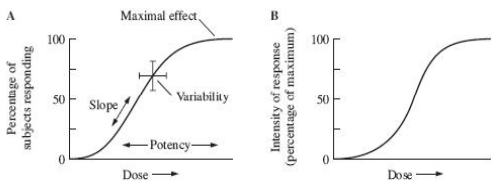
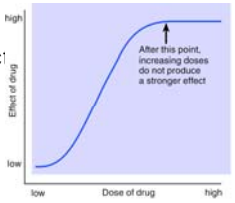


From Julien Text

Dose Response Curves

- Depicts the relation between drug dose and magnitude of drug effect
- Drugs can have more than one effect
- Drugs vary in effectiveness
  - Different sites of action
  - Different affinities for receptors



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Slope of Curves

- Indicates how the effect changes with each change in dose.
- Usually relates to the central part of the curve;
  - Small change in dose produces a large change in effect, the slope is steep.
  - If large changes in dose produce small changes in effect, the slope is shallow.
- Provides information about three variables

Tolerance and Sensitization

- Tolerance: Repeated drug administration results in diminished effect
  - Effect can be at the receptor or behavioral level
- Sensitization: Repeated drug administration results in heightened drug effectiveness
- Relates to Up and Down Regulation of the receptors

Potency

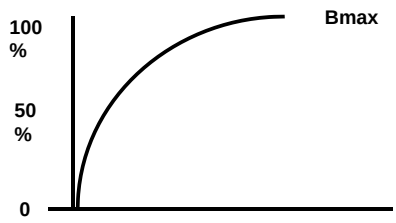
Relates to how well drug molecules attach to receptors

- More potent drugs have greater affinity or bind better on receptors than less potent drugs
- Less potent drugs may have lower affinity for a receptor.
  - Can be knocked off easier by other drugs

Concepts

- 1. Affinity Kd
  - Is the concentration of ligand at which 50% of all bindings sites are occupied
  - Larger Kd values indicate lower affinities
  - 200mM vs 20mM
- 2. Bmax
  - Is the total amount of binding
- 3. Competition Ki
  - Is the concentration at which ½ of a radioactive ligand is displaced
  - Add a drug, and knock of the ligand
  - Is called competition

Plot of Bound Ligand



Example

- Opiates bind on Mu receptors in Medulla
  - Can cause respiratory depression and death
- Naloxone (Narcan)
  - Is a narcotic antagonist
  - Blocks opiate receptor sites
  - Opiate cannot bind to the receptor
  - Reverses respiratory depression and death
- Different drugs may bind to the same receptor but with different affinities

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Efficacy of the Drug

- Is the maximum effect obtainable
- No additional doses produce any effect.
  - A drug may be potent but might never be able to produce a peak response no matter how much drug is given.
- A drug that is more effective (efficacious) produces a greater peak (maximum) effect than a drug that is less efficacious.

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Example Morphine and Heroin

- Both are potent analgesics
- Have equal efficacy but heroin is more potent - Need less of the drug to get an analgesic effect.
- Note: Although heroin may be more potent, the user may prefer morphine because of the behavioral effects it produces.

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Drug Safety vs. Drug Effectiveness

- Effective Dose = ED_{50}
  - Drug dose that produces the desired effect in 50 percent of test subjects
- Lethal Dose = LD_{50}
  - Drug dose that is the lethal dose for 50 percent of test subjects
- Therapeutic Index = Ratio of LD_{50} to ED_{50}

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Different Drugs

- Drugs have different therapeutic indexes
- Drugs also have different LD even in same drug group

Drug	LD_{50}	Organism	Source
Dilaudid	51-84	Mice	Baxter
Morphine	226-318	Mice	H Helper
Heroin	22	Mice	H Helper
Codeine	300	Mice	H Helper

https://www.accessbutler.com/msdsimages/A0003015.pdf
http://www.heroinhelper.com/curious/chemistry/stats.shtml

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Therapeutic Index

- TI = LD_{50} / ED_{50}
  - The greater the TI, the safer the drug
  - If two drugs have the same effect, the better drug is the one with the greater TI
- **The lower the ED_{50}, the greater the potency; but, the lower the TI, the lower the safety.**

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Neuronal Plasticity

- Is the process by which neurons adapt over time to a chronic disturbance
- To understand the effects of a drug, must understand
  - Immediate effects
  - Intraneuronal effects that occur over time
  - Signals between neurons
  - How neurons in brain circuits work and function

Autoreceptors

- Are receptors located in the presynaptic element
- Influence neurotransmitters and neuromodulators
- Ultimately change the number of receptors on the Post Synaptic Element
- Can change the amount of NT release

Up and Down Regulation

- Up regulation - Increase the number of receptors on the post synaptic element
  - New receptors are created
  - Increases sensitivity initially.
- Down regulation – Decrease the number of receptors on the post synaptic element.
  - Receptors are degraded
  - Results in reduced sensitivity initially.

Implications

- Relates to tolerance.
  - More drug, get down regulation
    - Need more drug to get the same effect
    - Stop drug, behavioral effect is opposite of what the drug did. - Withdrawal

Example - Alcohol

- Is a depressant
- Get Up-regulation – increased number of receptors
- Stop drug
  - Lots of receptors
  - Get increased stimulation initially
    - Shakes, seizures, DT's, ect.

Example – Methamphetamine

- Is a stimulant
- Get Down regulation – Decreased number of receptors
- Stop Drug
  - Fewer receptors
  - Result – Get depression initially
    - Sleep, lethargy, etc.

Finally

- After a few days, the system begins to re-regulate the number of receptors
- Result, withdrawal effects decrease.
- Can take weeks to months to achieve final effects.

- Withdrawal effects are usually the opposite of the drug's effect.

Agonists, Antagonists, and Inverse Agonists

- Needs to be viewed on a continuum
- Agonist – Mimics the endogenous NT
  - Causes the same conformational change
  - Creates the same biological response
  - All NT are receptor agonists (enkephalins)

- Antagonists
  - Are inherently inert
  - Exerts biological effect by interfering with a endogenous ligand
  - Example - Naloxone

Partial Agonists

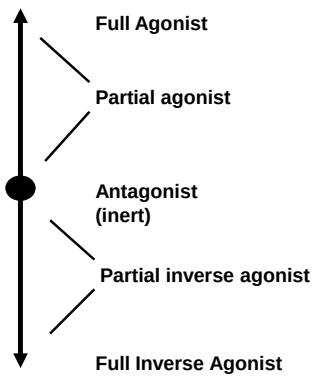
- Most drugs fall here.
- Occurs when a drug binds to a receptor and elicits only a partial biologic response.
- Is assumed to:
  - Lack some molecule required to get the full effect.
  - Binds differently on the receptor site.

Continued

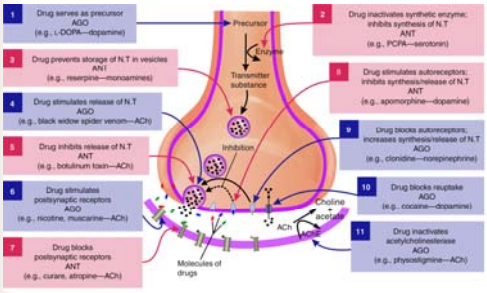
- Can have different effects at different potencies
  - Low – get mild agonist effect
  - High – also get a mild effect because of molecule properties (shape)
  - Can also be an antagonist a full agonist (e.g., NT)
  - Why, affinity is greater than full agonist.

Example - Buprenorphine

- Is a partial agonist for opioid receptors
- Low doses, used in chronic pain
- High doses, fails to get stronger effect.
  - Limits ability for pain control
- Antagonizes the action of full opiates
  - Discourages the use



Drug Action on Synaptic Transmission



Agonist drugs are in red, Antagonists are in blue

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Conclusions

- Many different drugs
- ED, LD, and TI may vary depending on
  - Organism species
  - Age of person
  - Metabolism of the person
  - Genetics
  - Other
- Use levels will influence up or down regulation and withdrawal symptoms

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Implications for Treatment Providers

- A thorough history is mandatory
- Need to understand interactions of compounds
- Need to note interactions of drugs
- Need to note dose rates by the user
- Different dealers may have different purities of their product
- Levels and duration will influence withdrawal symptoms

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Conclusions

- Know what the systems are
- Understand these basic concepts

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