Overview of Pharmacodynamics

Psychology 472: Pharmacology of Psychoactive Drugs

Pharmacodynamics

- Generally defined as effects of drugs on a system
- Can be associated with any system
- Neural, Heart, Liver, Endocrine System, etc.
- Lots of issues influence pharmacodynamics
  - Amount 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

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

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

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
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

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 \( K_d \)
   - Is the concentration of ligand at which 50% of all bindings sites are occupied
   - Larger \( K_d \) values indicate lower affinities
   - 200mM vs 20mM
2. \( B_{max} \)
   - Is the total amount of binding
3. Competition \( K_i \)
   - Is the concentration at which ½ of a radioactive ligand is displaced
   - Add a drug, and knock of the ligand
   - Is called competition
**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

**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.

**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.

**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$_{50}$

**Different Drugs**

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

<table>
<thead>
<tr>
<th>Drug</th>
<th>LD$_{50}$</th>
<th>Organism</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dilaudid</td>
<td>51-84</td>
<td>Mice</td>
<td>Baxter</td>
</tr>
<tr>
<td>Morphine</td>
<td>226-318</td>
<td>Mice</td>
<td>H Helper</td>
</tr>
<tr>
<td>Heroin</td>
<td>22</td>
<td>Mice</td>
<td>H Helper</td>
</tr>
<tr>
<td>Codeine</td>
<td>300</td>
<td>Mice</td>
<td>H Helper</td>
</tr>
</tbody>
</table>

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

**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.
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
  - New receptors are created
  - Increases sensitivity initially.
- 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, etc.

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.

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

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

Conclusions

- Know what the systems are
- Understand these basic concepts