Pharmacokinetics

Pharmacodynamics: What drugs do to the body
Pharmacokinetics: What the body does to drugs

- Absorption
- Distribution
- Metabolism
- Excretion
Drug level vs. time curve

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Absorption

- Different routes available
- Rate varies
- Bioavailability varies
- Time-release preparations
Midbrain Dopamine Neurons

Nucleus accumbens

Ventral tegmental area
Dopamine signals unexpected rewards

Signal (bursts per second)

Time (seconds)

Eats peanut
Dopamine signals predicted/expected rewards

First trial:

Tenth trial:

“Good monkey”

Eats peanut

“Good monkey”

Eats peanut

Time (seconds)
Dopamine signals error in prediction

Tenth trial:

“Good monkey”

Eats peanut

No peanut:

“No peanut”

“Good monkey”

Time (seconds)
The dopamine burst motivates the animal

The dopamine motivates the child, focuses the child’s attention on the goal, and facilitates the behavior (truck chasing) that will lead to reward.
Drugs of abuse mimic natural reward

First dose:
- Sees cocaine
- Snorts cocaine

Fiftieth dose:
- Sees cocaine
- Snorts cocaine
- Sees cocaine

Time (seconds)
Why does seeing cocaine cause dopamine release? Remember how conditioning normally works:

First trial:

Tenth trial:

“Good monkey” Eats peanut

“Good monkey” Eats peanut

Time (seconds)
Drugs of abuse mimic natural reward

When an addict sees cocaine, the dopamine burst *produced by his own cells* motivates him to get cocaine and snort it.

The pleasure an addict actually feels from snorting cocaine is decreased over time, due to tolerance.
Drug addicts are insensitive to non-drug motivators

Normal person:

"Wash my car or go to prison"

The incentive of freedom triggers a dopamine burst, which motivates the person to wash the car.

Addict:

"Stay clean or go to prison"

The addict has tolerance to both cocaine and their own dopamine, so they cannot be motivated by normal incentives.

What will the addict do?

Sees cocaine

Time (seconds)
Liking versus wanting

Addicts don’t like doing drugs as much as they used to
Addicts want to do drugs
Addicts don’t want to do anything else
Speed of onset and addiction

Drugs which take effect quickly are more addictive, because a fast spike in dopamine more closely mimics natural rewards and the drug-taking behavior is more closely associated with the reward if they come close together
Speed of onset and addiction

Faster onset, more addictive:
- Crack cocaine
- Injected heroin
- Smoked meth (ice)

Slower onset, less addictive:
- Powder cocaine (snorted, has an 11 minute absorption half-time)
- Snorted heroin (absorbed faster than snorted cocaine. Why?)
- Snorted meth (even less addictive: swallowed meth)
Speed of onset and addiction

Faster onset, more addictive:
Xanax (the fast elimination and need for more doses also increases addiction potential. Why do frequent doses lead to stronger addiction? Discuss.)

Slower onset, less addictive:
Klonopin, Librium
# Speed of onset and addiction

<table>
<thead>
<tr>
<th>Faster onset, more addictive:</th>
<th>Slower onset, less addictive:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Snorted Ritalin</td>
<td>Oral Ritalin</td>
</tr>
<tr>
<td>Vicodin</td>
<td>OxyContin</td>
</tr>
<tr>
<td>Abused (chewed, crushed and snorted) OxyContin</td>
<td>Properly used (intact time-release tablets) OxyContin</td>
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ADHD

ADHD is treated with stimulants that boost dopamine (and norepinephrine), why does this work?

Dopamine normally facilitates goal-directed behavior by:

- Increasing motivation
- Focusing attention on the goal
- Providing energy to work towards the goal
- Speeding learning and reinforcing memory
ADHD

Why does dopamine speed learning and reinforce memory?
Discuss
That was absorption. What came next?
Distribution

• Where does the drug go?
• How fast does it get there?
One-compartment model

The body is a bathtub with the faucet running and the drain open.
Two-compartment model

The body has two pieces:
Tissues that absorb drug fast (roughly the blood, brain, vital organs)
Tissues that absorb drug slow (fat)
(Muscle is medium-fast)
Levels in different tissues

Levels in tissues

- Plasma
- Brain
- Viscera
- Lean tissue
- Fatty tissue

mg/L vs. Minutes
Drugs with funky distribution

Sodium pentothal (thiopental, amytal, truth serum)

Marijuana (maybe, maybe not)

Many opioids may have an especially intense initial rush due to distribution
What’s next after distribution?

Do you remember?
Metabolism

This is how your body chemically modifies drugs.

Metabolism occurs mostly in the liver, or else it is widely distributed.

Metabolism produces metabolites

Some metabolites are active drugs
Prodrugs

Prodrugs are inactive chemicals that turn into drugs in the body, because of metabolism:
GBL (gamma-butyrolactone, becomes GHB)
1,4-Butanediol (becomes GHB, found in toys)
Vyvanse (becomes amphetamine, why is it good to have a prodrug in this case?)
Levodopa (discuss why it is often mixed with carbidopa)
Prodrugs

Psilocybin (becomes psilocin)

Codeine (becomes morphine, although this conversion is much slower in some people. Codeine itself is active)

Hydro- and oxycodone become hydro- and oxymorphone respectively

Clorazepate (becomes nordazepam)
Downside to metabolism

Hepatic portal circulation:
It often cuts down on bioavailability
This is called first-pass metabolism
BuSpar has only 5% bioavailability due to first-pass metabolism
First-pass metabolism

Bypassed by:

Suppositories (only 50% portal circulation, less portal circulation closer to the orifice BUT higher risk of falling out)

Sublingual, intranasal, intravaginal (no portal circulation at all, BUT these tissues are sensitive and the extremely high concentration of drug in a very small patch can be very hurtful)
Image removed due to copyright restrictions.

View a photo of the effects of cocaine-induced vasoconstriction.
What’s next?

Do you remember?
Excretion

• In feces (how did it get there? Discuss)
• In urine (Kidneys)
Drugs with funky excretion

Amphetamine:
A large amount of amphetamine is excreted renally without being metabolized.
Amphetamine is a weak base with a pKa near urine’s pH.

Acidic urine causes fast excretion
Alkaline urine causes slow excretion
Playing with ADME:

• Alcohol enemas
• Taking a huge amount of baking soda with amphetamine
• Taking Tagamet (cimetidine) with MDMA (ecstasy), opioids, many other drugs. Tagamet inhibits liver enzymes, thus inhibiting A, D, M, or E?
• Taking grapefruit juice
Playing with ADME:

• Snorting everything
• Smoking everything
• Injecting everything
• Depot injections (inject a month’s worth of drugs into the muscle, design for slow absorption)
• Chewing time-release pills
• Dissecting time-release pills (Concerta)
Playing with ADME:

• Snorting Viagra before snorting something else (especially before snorting something vasoconstrictive, like what?)

• Inhaling albuterol before smoking crack (yes, people do this)

• Taking MAOIs with your DMT to enable absorption – this is called ayahuasca and was discovered hundreds of years ago
Playing with ADME:

• Taking MAOIs (eg. Selegiline) with your phenethylamine (purchased at GNC) to get an amphetamine-like high. Warning: Causes tachycardia, and possibly other catastrophic side effects.