Lecture 5 – Pharmacokinetics Companion

Pharmacokinetics vs. Pharmacodynamics:

Pharmacodynamics is what drugs do to your body – what receptors the drugs bind to, whether they are agonists or antagonists

Pharmacokinetics is what your body does to drugs:

Absorption
Distribution – spreading throughout your various tissues
Metabolism – breaking down drugs
Excretion

Absorption:

Bioavailability: What percentage of the drug makes it into the blood

Playing with bioavailability: Drugs which are much better absorbed by injection than orally will be requested as pills and then injected by addicts. Examples:
Hydromorphone (Dilaudid): 5 times stronger IV
Oxymorphone (Opana): 10 times stronger IV
Methylphenidate (Ritalin): 2-3 times stronger IV or snorted

Speed of onset: How fast a drug gets absorbed, and thus how fast it kicks in
Faster onset means more euphoria. We will see why later

Different routes of administration:

Benefits of each?
Hazards of each?
Examples of each?

Oral

Intranasal (snorted)

Inhalation (smoking, inhalers)

Rectal (suppositories, enemas, gels and liquids)

Transdermal (patches)

Parenteral (into bloodstream):

Intravenous

Intramuscular

Subcutaneous

Intraarterial

Spinal:

Epidural – right outside the spinal cord

Intrathecal – into the cerebrospinal fluid inside the spinal cord

Absorption >
Dopamine and **reward:**
See slides

Dopamine released in a special place (the **nucleus accumbens**) signals **good outcomes**
Sex
Food

Dopamine signals **unexpected rewards**

Dopamine **reinforces** the behavior that led to the good outcome
This is **learning**
Behaviors which cause dopamine release will be **repeated**

Dopamine **motivates** behavior
Provides energy
Focuses attention on the goal

Absorption > Dopamine and Reward > Addiction:

Seeing the drug causes more DA release than **taking** the drug
Thus seeing the drug will **motivate** the behaviors needed to acquire and take the drug, it will boost focus

Addictive drugs cause more DA release than **natural rewards**, and thus:
Natural rewards do not please addicts
Natural rewards cannot motivate addicts
Punishments cannot deter addicts

The addictive drug is **much more salient** than any other motivators

Liking vs. Wanting:

Different pathways

Addicts **don't like (enjoy) drugs**, not as much as they used to

Addicts **do want drugs**

Addicts **don't want or like anything else**

Faster onset means **more euphoric** and **more addictive**

Why?

Fast spike mimics natural reward

Closer temporal correlation leads to **more learning**, especially unconscious association of the drug-taking behavior with the reward

Examples:

Methadone – it is a full opioid agonist, every bit as potent as heroin or morphine, but it is less addictive because it kicks in slowly. Also, it lasts a long time, which prevents

withdrawal, and leads to less frequent drug taking. Taking drugs more often means **more opportunities for learning**.

Crack vs. powder cocaine

IV vs. snorted heroin

Smoked vs. snorted meth

See slides…

Absorption > Dopamine and Reward >
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

Why does DA speed learning and increase motivation?

Why aren't ADHD drugs addictive?

Distribution:

Multicompartment redistribution: The drug level in the brain **spikes** up very high and very fast, but the drug levels **quickly fall** as the drug **redistributes** into other tissues and thus gets **diluted**

Why does this happen?
Blood gets the drug first
Then brain

Then viscera
Then muscles
Then finally fat

What is required to make a drug with a funky spike and then redistribution?

Fast absorption (IV or maybe smoked)
Fast crossing of **blood-brain-barrier**

Examples:

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: Chemicals that are inactive, but are metabolized into active drugs

Examples:

GBL and 1,4-BD – The latter was found in children's toys

Hepatic portal circulation: All chemicals in the stomach and small intestines **must** go through the liver before reaching the regular bloodstream

It often cuts down on bioavailability
This is called first-pass metabolism

Why did this evolve?

Ways to bypass:

Intranasal (snorting)
Inhalation
Injection
Intrarectal (only 50% bypasses portal circulation)
Intravaginal

Why are intranasal, intrarectal, and intravaginal administration hazardous?

Excretion:

In feces

How did it get there?

In urine (kidneys)

Amphetamine excretion depends on urine pH.

How can we modify urine pH?

What chemistry technique is this reminiscent of?[1]

Playing with ADME:

See slides

What phase of ADME is being modified in each of these examples?

1 Extraction – when you have two solvents and you let the solute **distribute** between the two according to the **partition coefficient**, the ratio indicating how much of the solute can "fit" in each of the two liquids.

ES.S10 Drugs and the Brain

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