SP.236 / ESG.SP236 Exploring Pharmacology
Spring 2009

Pharmacokinetics

Pharmacodynamics: What drugs do to the body

Pharmacokinetics: What the body does to drugs

- Absorption
- Distribution
- Metabolism
- Excretion

ADME

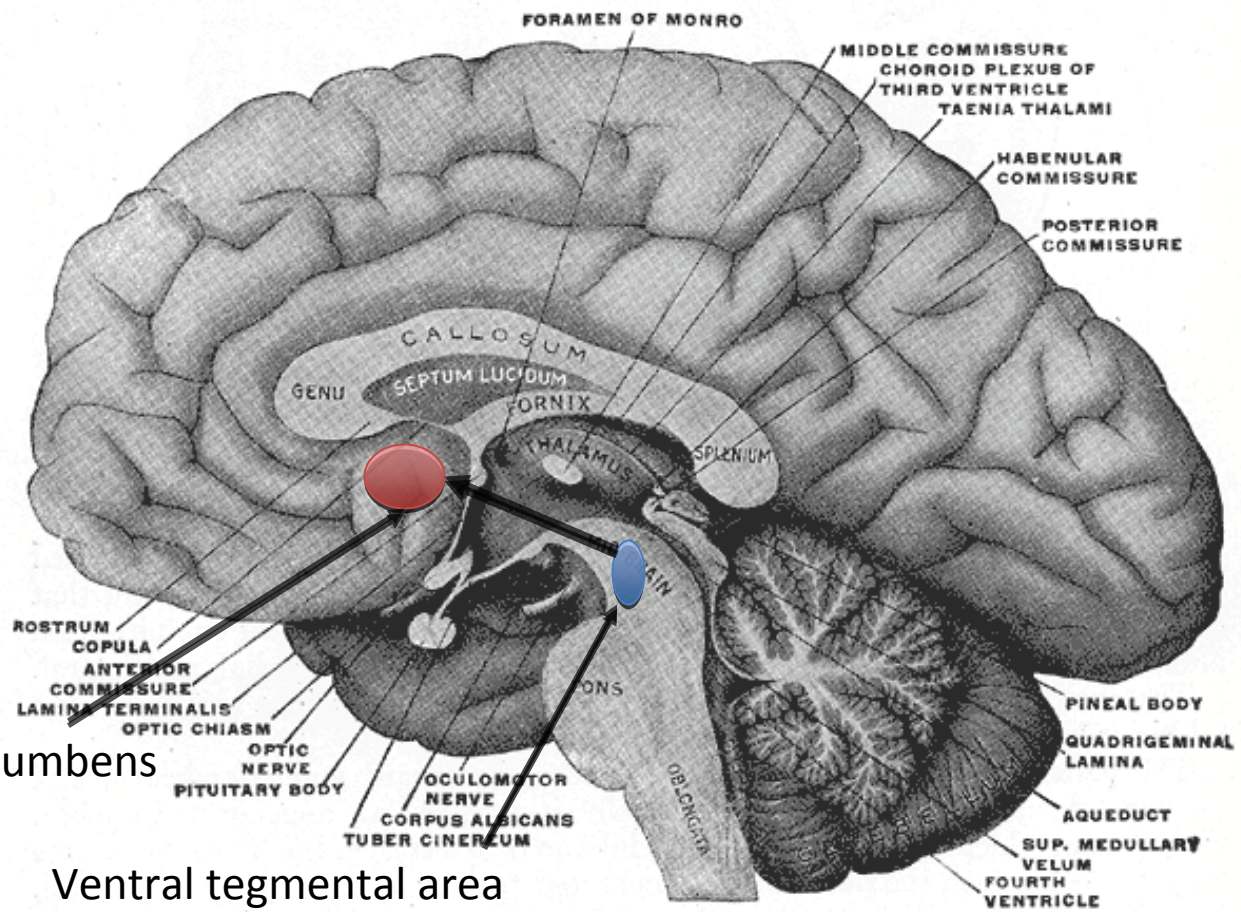
Absorption

- Different routes available
- Rate varies
- Bioavailability varies
- Time-release preparations

Dopamine and Reward

One of the most-studied examples of a neurotransmitter encoding behavior

Midbrain Dopamine Neurons

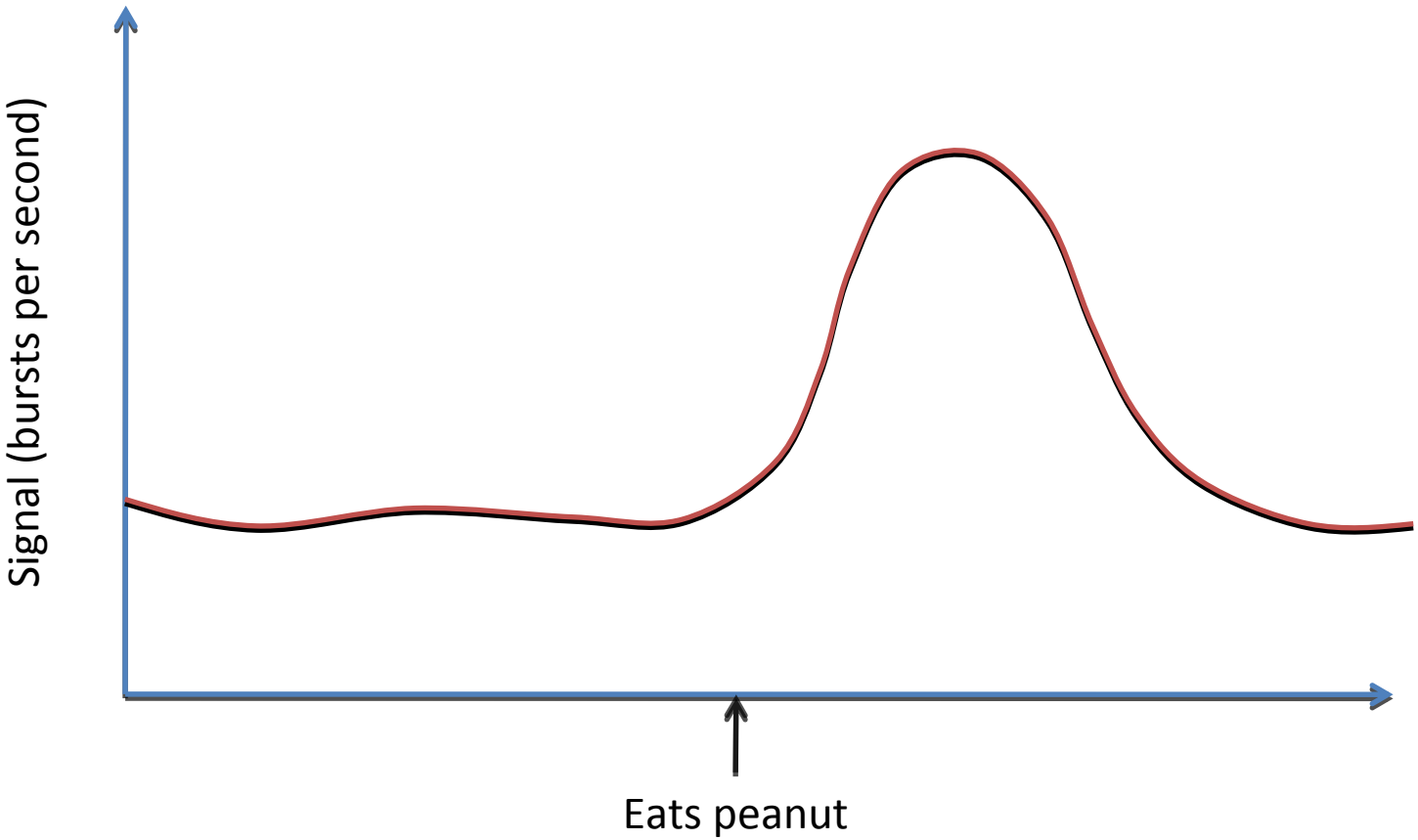


Nucleus accumbens

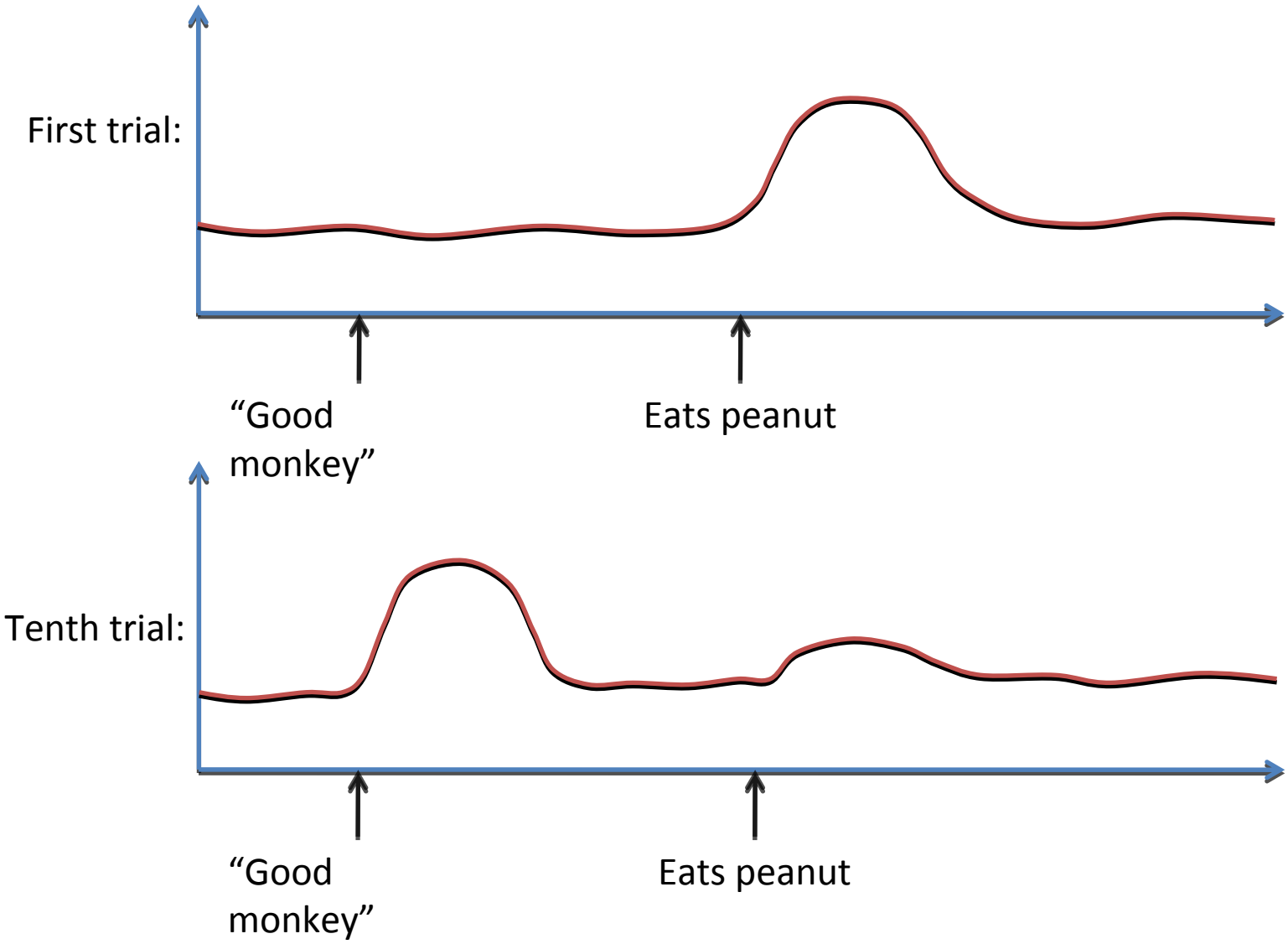
Ventral tegmental area

Picture: In public domain worldwide,
http://commons.wikimedia.org/wiki/File:Mozok.gif

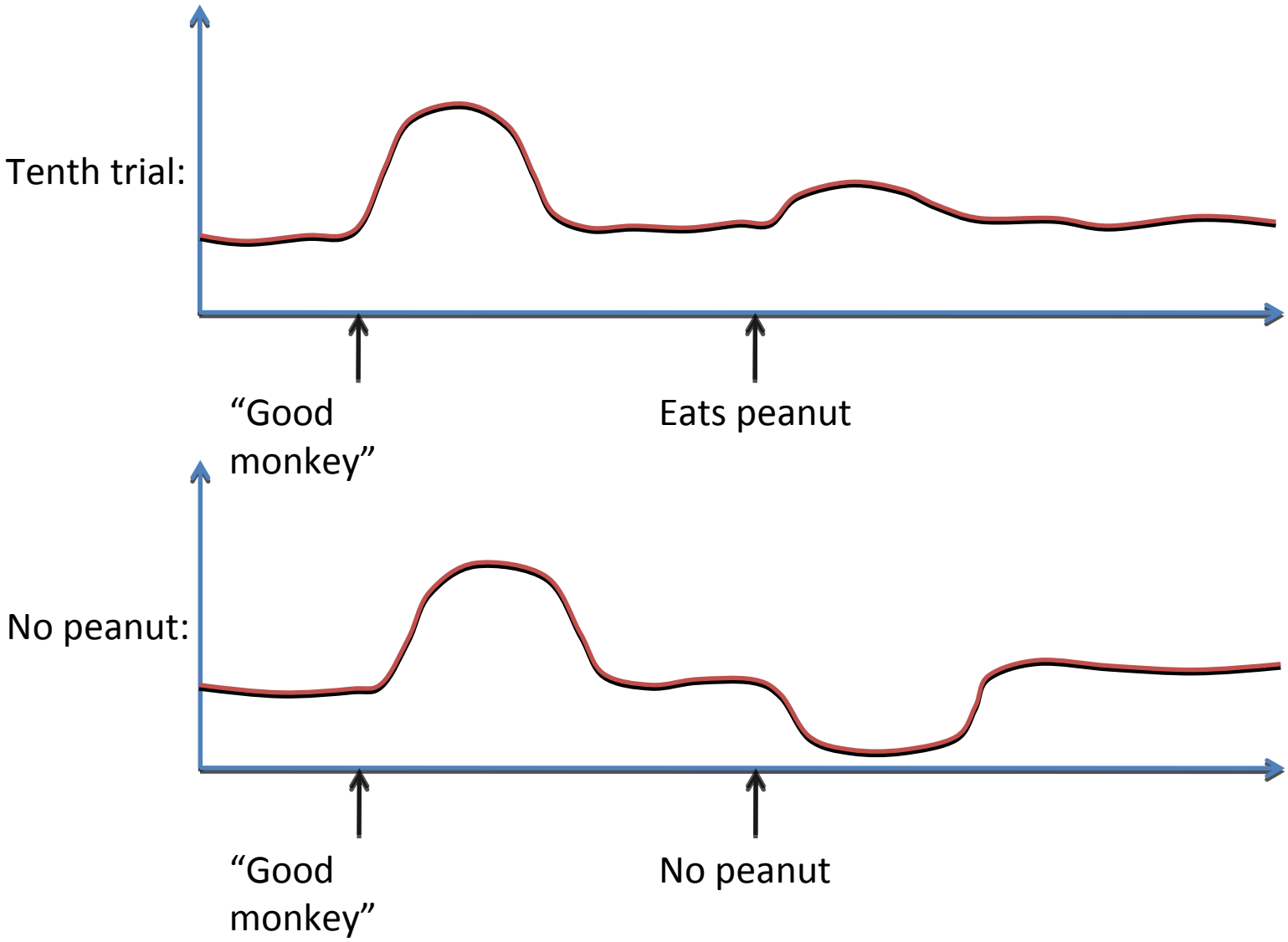
Dopamine signals unexpected rewards



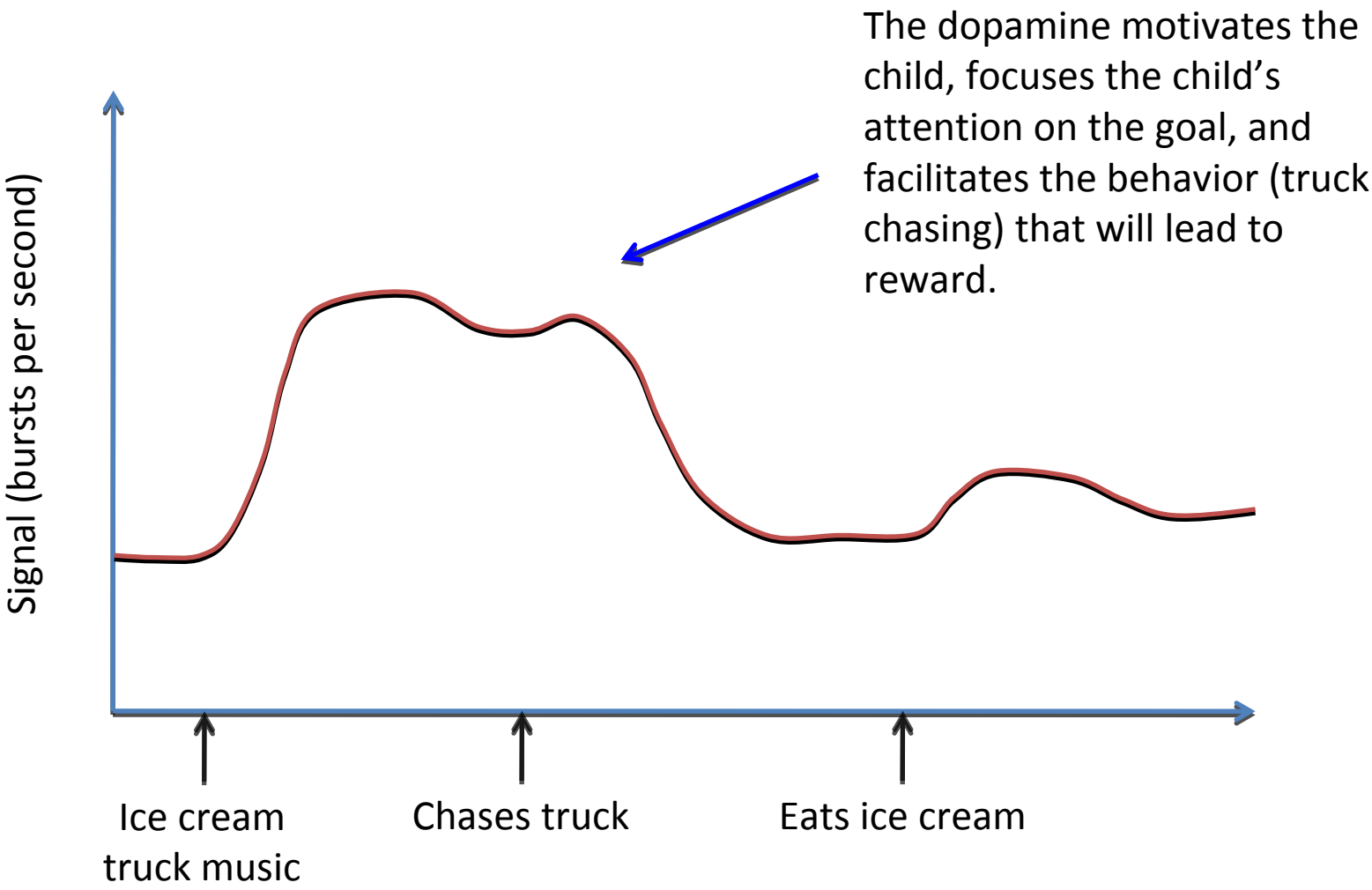
Dopamine signals predicted/expected rewards



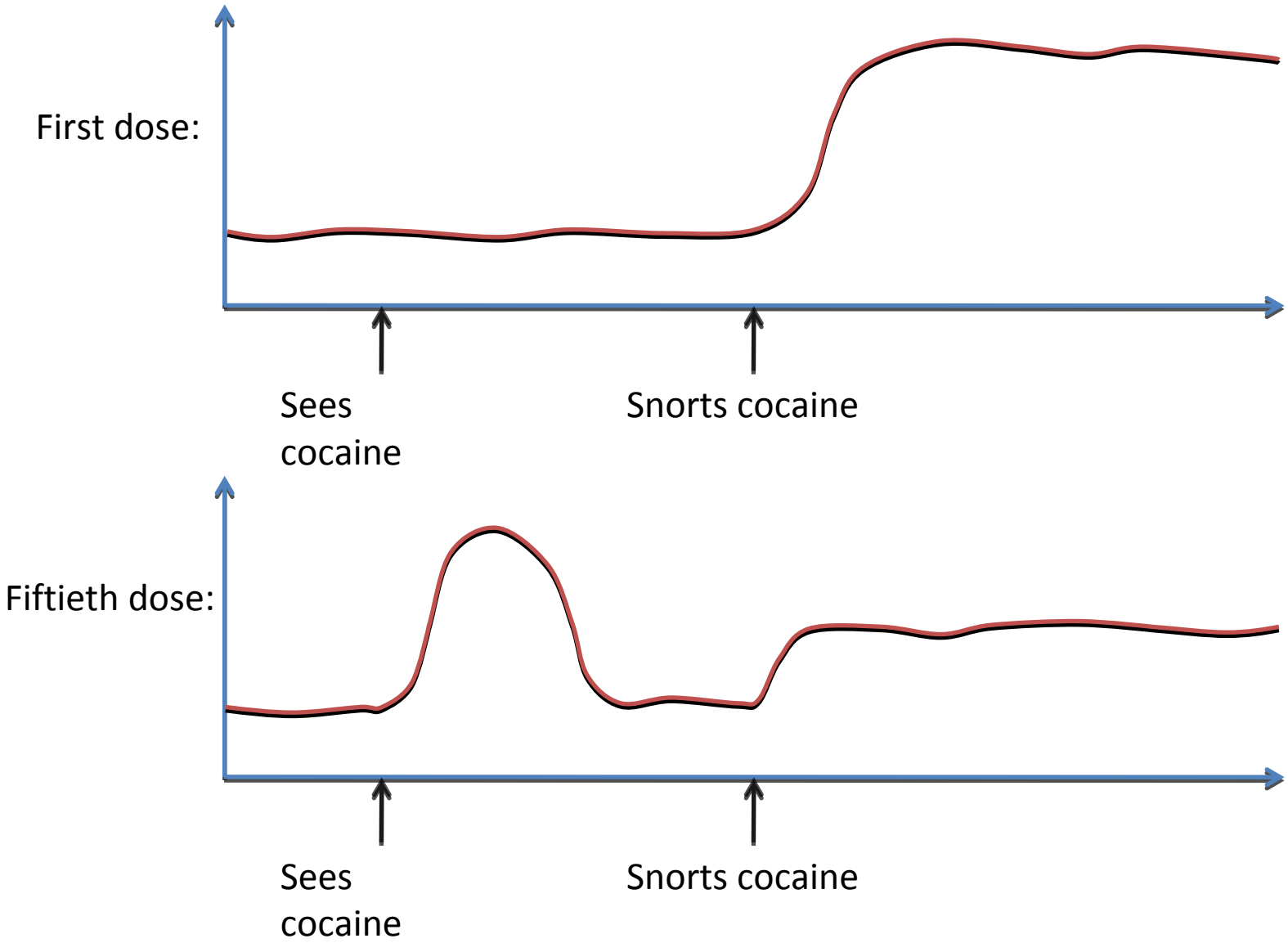
Dopamine signals error in prediction



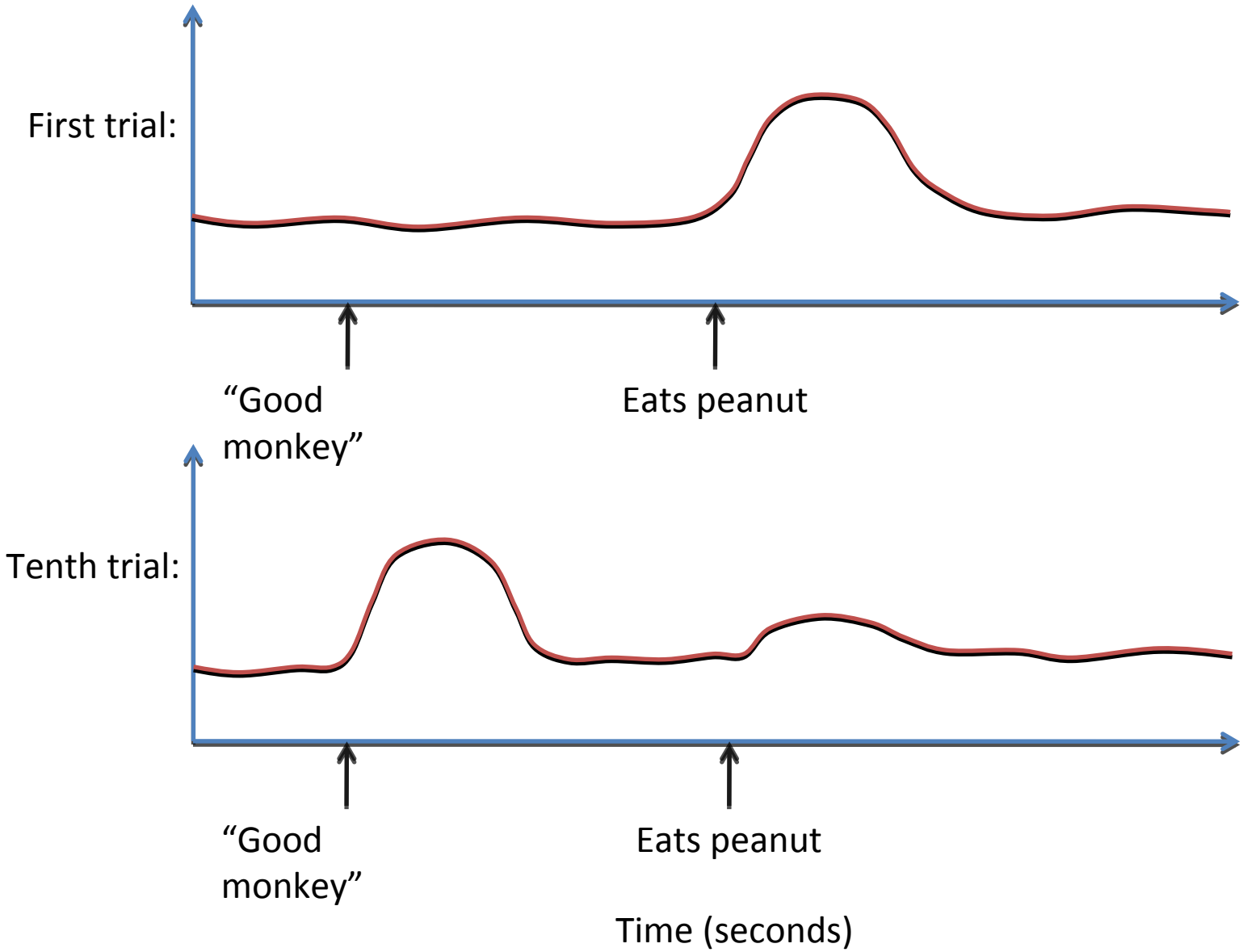
The dopamine burst motivates the animal



Drugs of abuse mimic natural reward



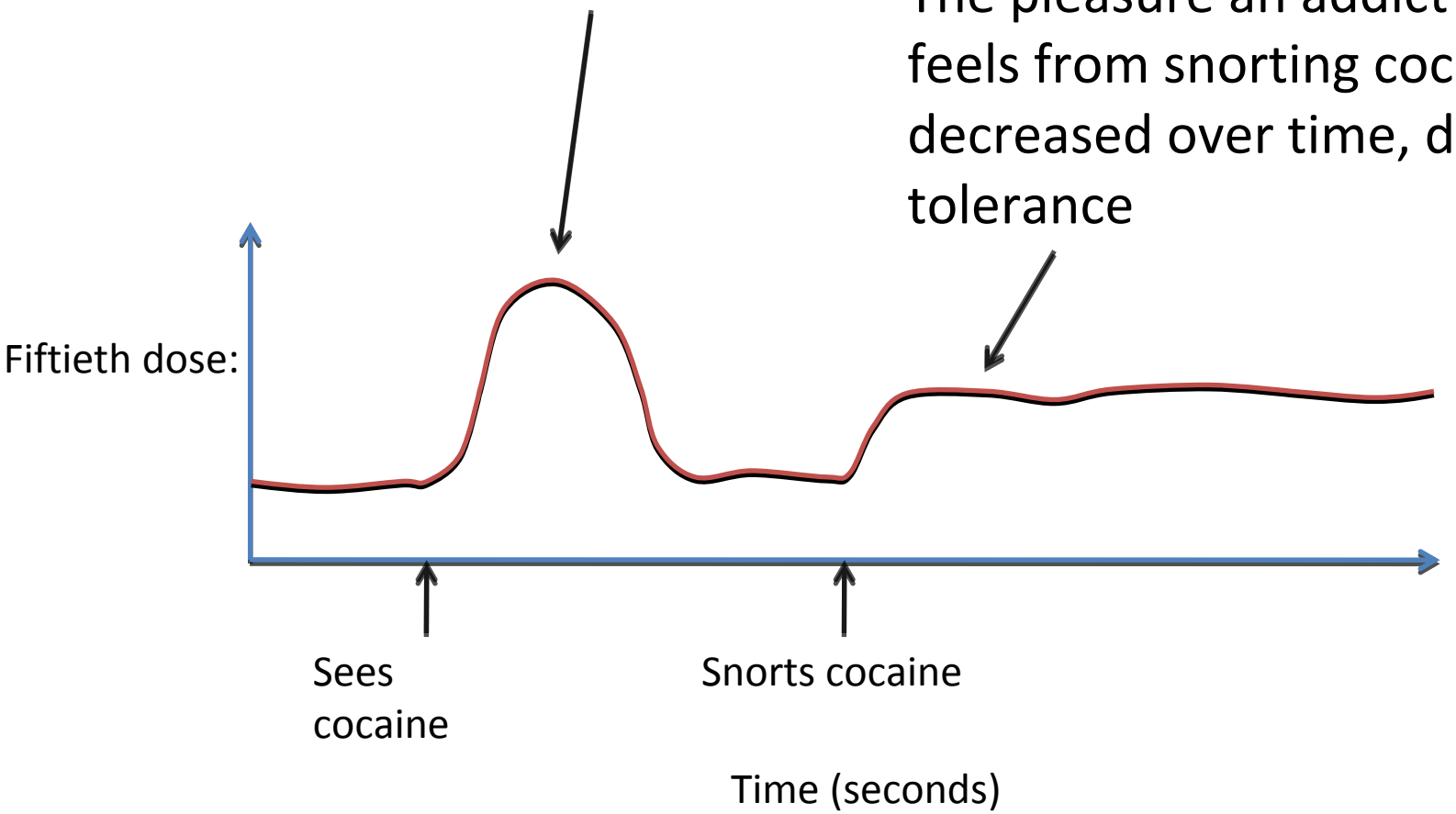
Why does seeing cocaine cause dopamine release?
Remember how conditioning normally works:



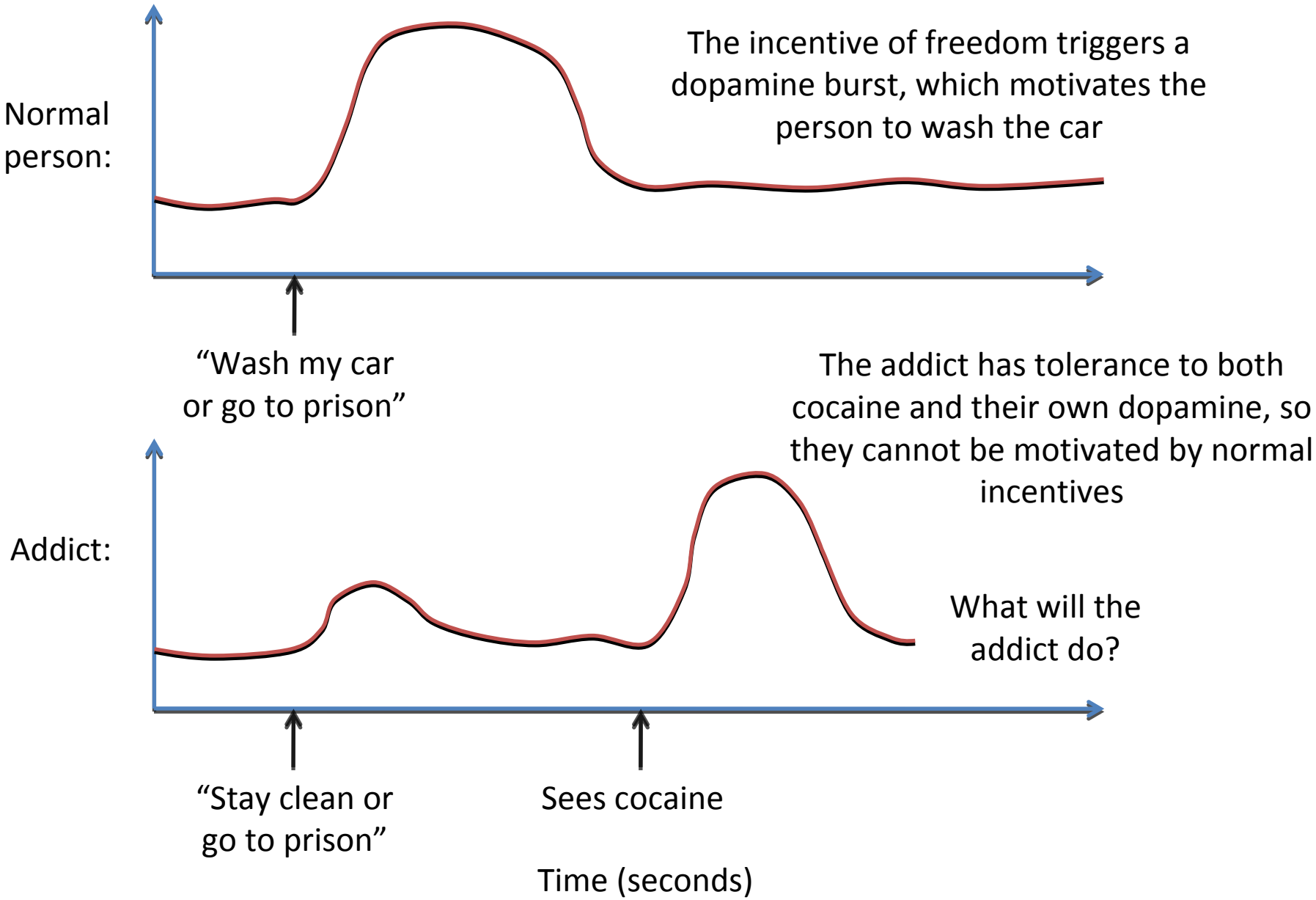
Drugs of abuse mimic natural reward

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



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

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

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

Faster onset, more addictive:

Snorted Ritalin

Vicodin

Abused (chewed, crushed and snorted) OxyContin

Slower onset, less addictive:

Oral Ritalin

OxyContin

Properly used (intact time-release tablets) OxyContin

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

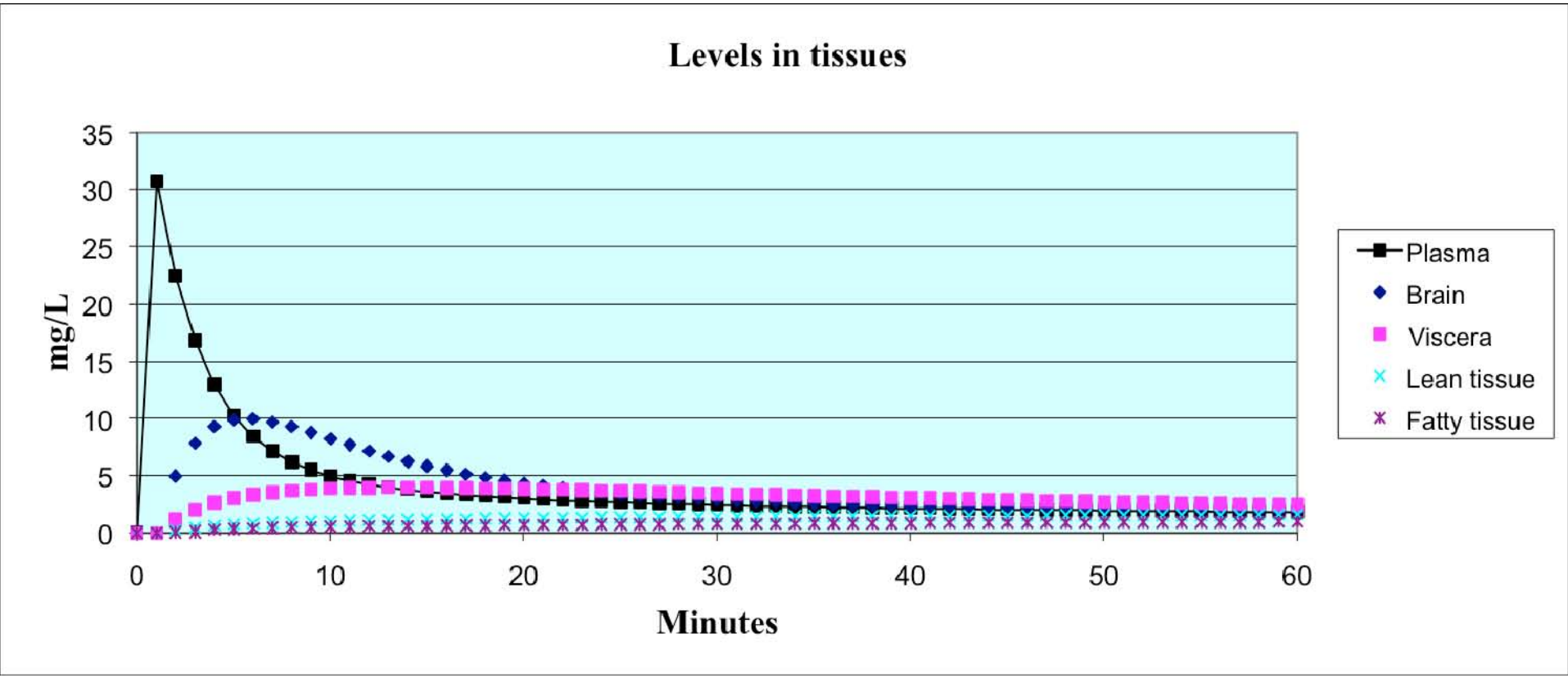
The body has two pieces:

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



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)

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