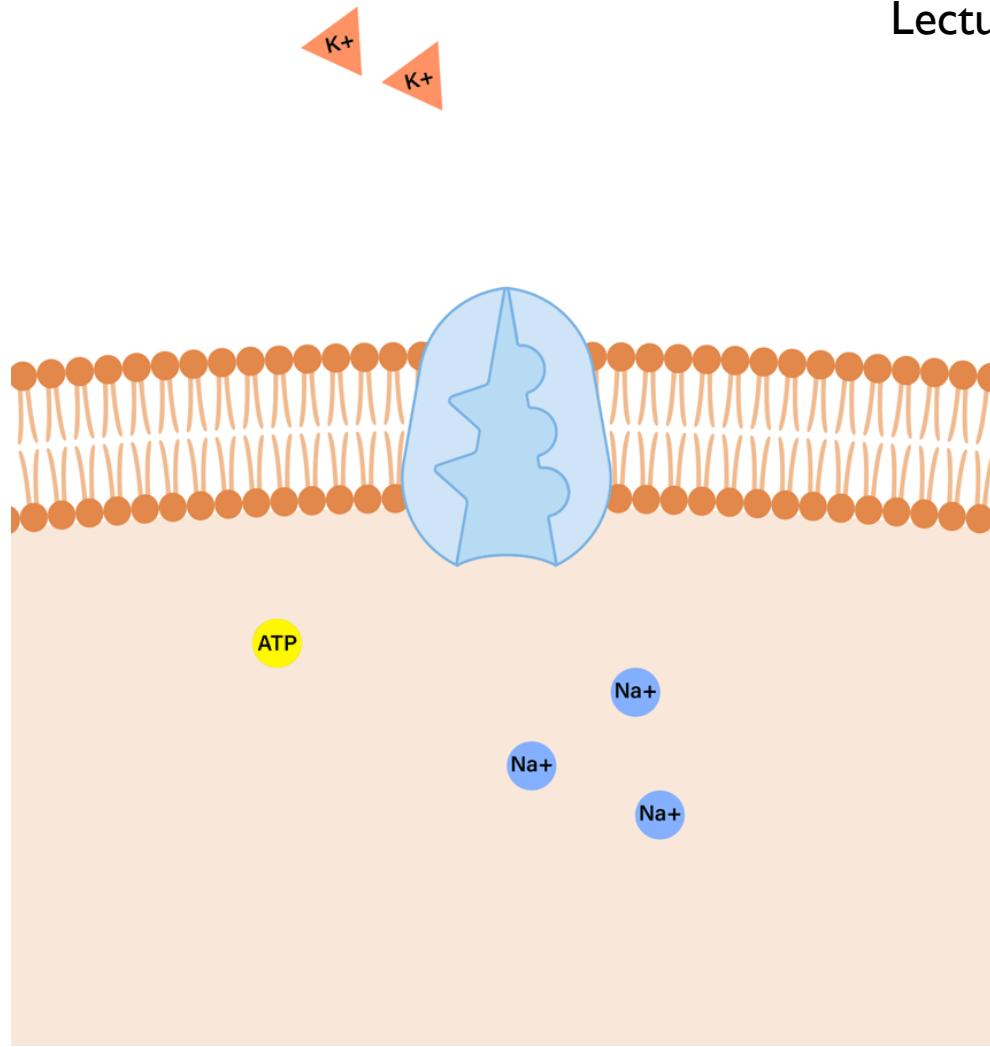


LECTURE 4

BEHAVIORAL PHARMACOLOGY BASICS

(Na^+) / (K^+) SODIUM POTASSIUM PUMP

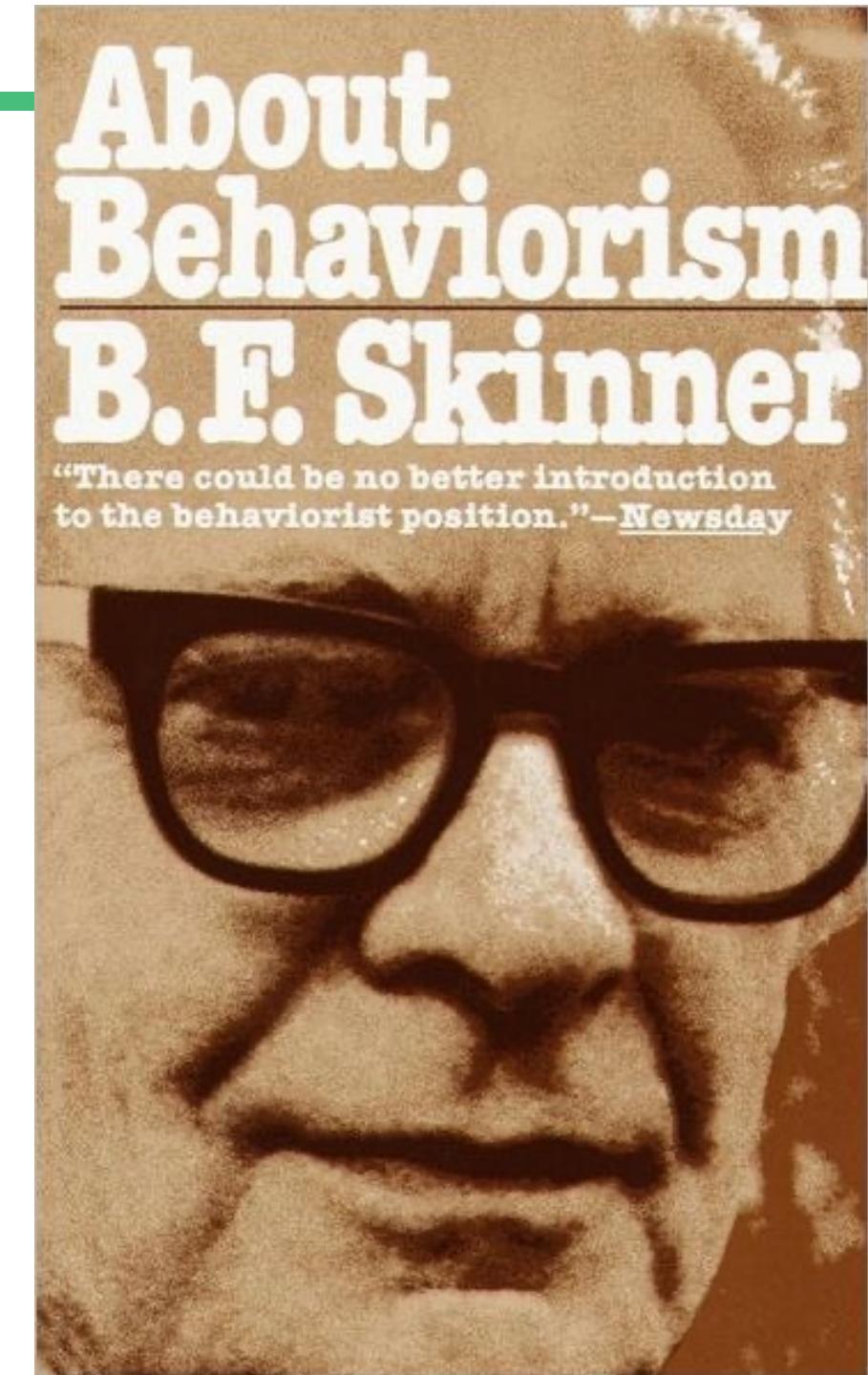
- A sodium-potassium pump is an enzyme found in the membrane of most neurons.
- It is a way to transport sodium and potassium ions across the cell membrane, against their concentration gradient (low to high concentration), resetting the membrane potential back to its hyperpolarized state



One thing to add to
Lecture 3 ***

BEHAVIORAL PHARMACOLOGY BASICS

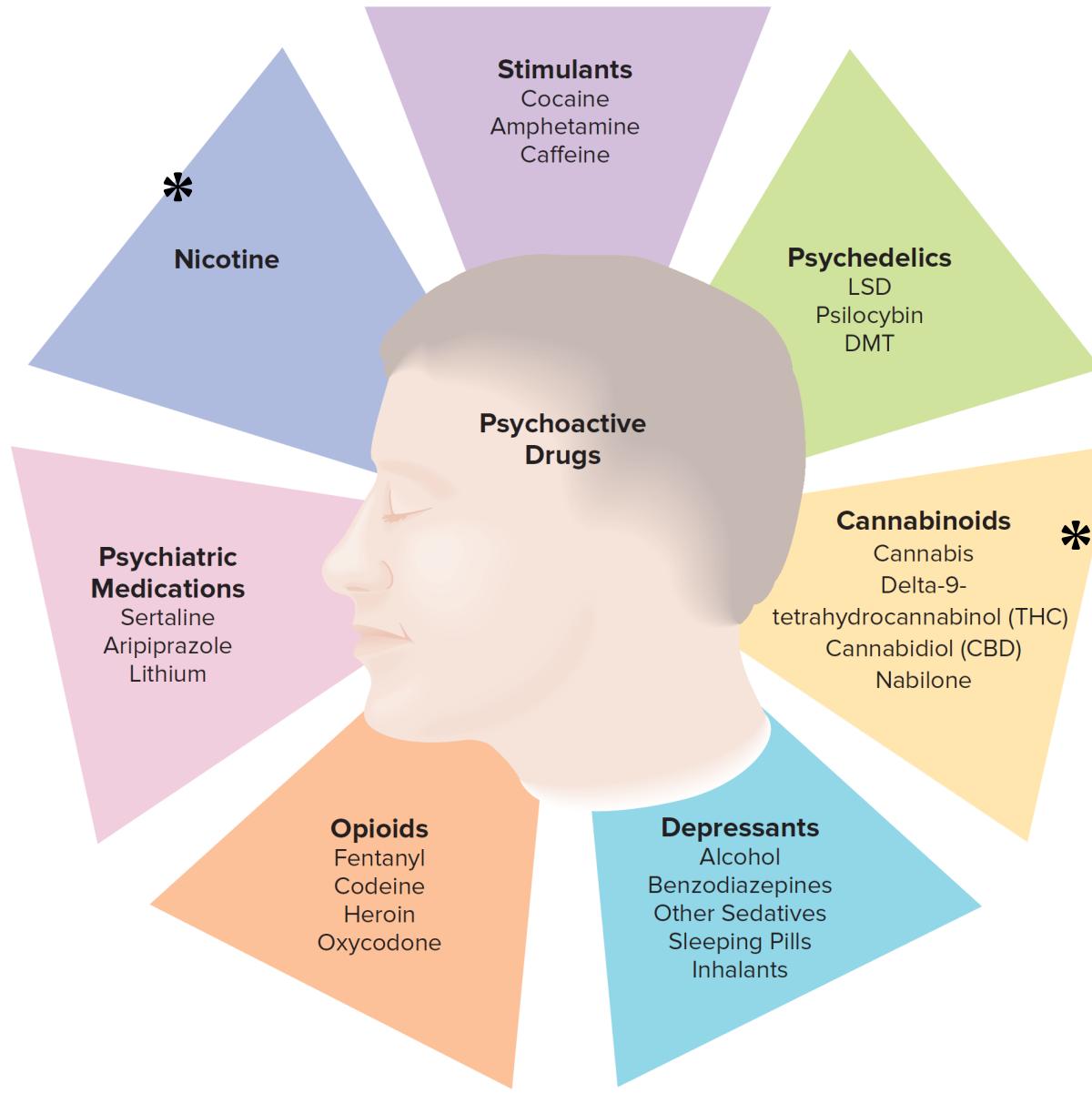
- How do behavioral pharmacologists classify drugs?
 - By their behavioral effects
 - By their effects on the brain
 - By their chemical composition



6 PRIMARY PSYCHOACTIVE DRUG CLASSES

- 1) Psychostimulants** - produce wakefulness and a sense of energy and well-being.
- 2) Depressants** - slow nervous system activity.
- 3) Opioids** - produce a relaxed, dreamlike state.
- 4) Psychedelics (Hallucinogens)**- produce perceptual and emotional changes.
- 5) Psychotherapeutics** - prescribed to treat symptoms of mental disorders.
- 6) Cannabinoids** – produce feelings of relaxation and psychoactive mood changes.

FIGURE 5.1: CLASSIFICATION OF PSYCHOACTIVE DRUGS



Some drugs belong to multiple categories.
Examples: Cannabis and nicotine.

FYI - NOT TECHNICALLY DRUG CLASSES – RELATED TERMS

- Narcotic
- Sedative
- Tranquilizer
- Analgesic
- Anesthetic
- Anxiolytic
- Euphoric
- Rewarding
- Reinforcing

NAMES OF DRUGS

- **Chemical name.**

- Gives a complete chemical description of the molecule.
- Derived from the rules of organic chemistry for naming any compound.

- **Street name.**

NAMES OF DRUGS

- **Brand/Trade name.**
 - Specific formulation trademarked by manufacturers.
 - Patented drugs can be manufactured and sold for 20 years without direct competition by the companies that discovered and patented them.
 - Example: **Concerta**, or methylphenidate.
- **Generic** name.
 - Official or legal name of drugs.
 - Listed in the **United States Pharmacopeia**, or USP.
 - Cannot be trademarked.

DRUG IDENTIFICATION

<https://www.pdr.net/>

- Physicians can tell from appearance of the drug the exact drug and dose.
 - The Physician's Desk Reference, or PDR, includes color photographs of legally manufactured pharmaceuticals.
- Illegal drugs are sometimes marked, packaged, or labeled in an identifiable way.
- Drugs can also be tested and identified through chemical analyses.



Drug Information

Prescribers' Digital Reference®

PDR Drug Information
Fully searchable
Fully digital

Trusted by generations of healthcare providers, PDR.net decisions and patient adherence to improve health.

tylenol

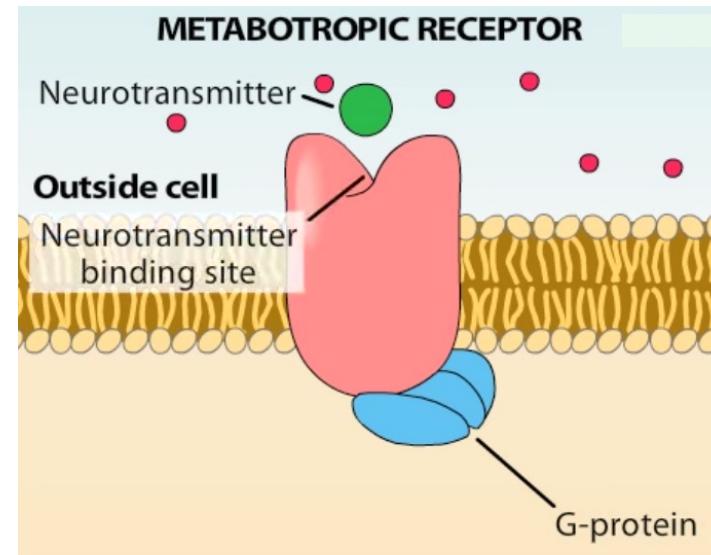
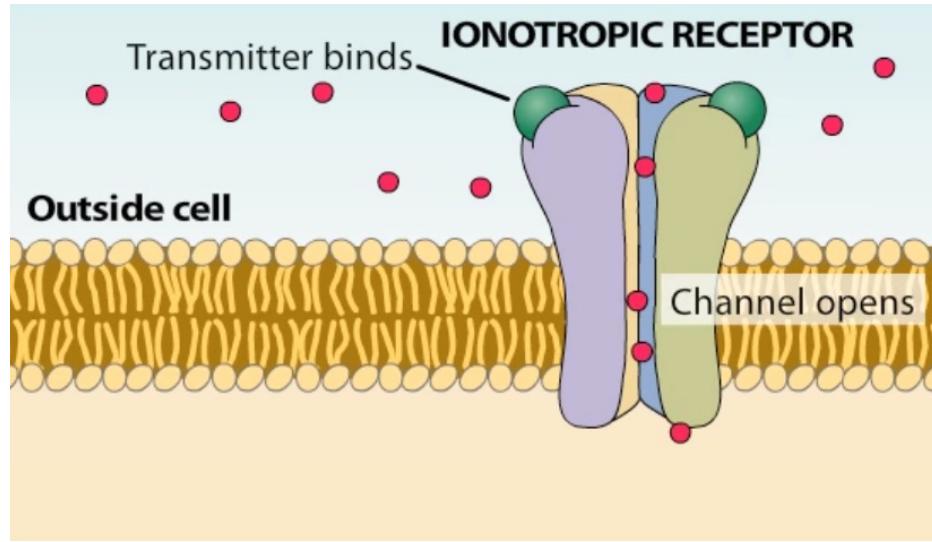
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PHARMACODYNAMICS - MECHANISMS OF DRUG ACTION

- **Pharmacodynamics** – the mechanisms by which a **drug** exerts its effects on the body
- Drugs may affect neurons by...
 -altering the electrical characteristics of the neuron.
 - ... changing the availability of a neurotransmitter by shifting the transmitter chemical's rate of:
 - **Synthesis.**
 - **Release** from storage vesicles.
 - **Reuptake** into the releasing neuron.
 - **Metabolism.**
 - ... activating (**agonist**) or preventing the activation (**antagonist**) specific neurotransmitter receptors.

PHARMACODYNAMICS: RECEPTOR SUBTYPES

IONOTROPIC VS METABOTROPIC RECEPTORS



- **Ionotropic –**
 - Fast (within a 1-2 milliseconds!)
 - Multimer proteins that create a ion pore across the membrane
- **Metabotropic / “G-protein Coupled” –**
 - ‘slow’ (100 milliseconds – sometimes longer)
 - Have intracellular ‘G-proteins’ that are either **stimulatory (G_s or G_q)** or **inhibitory (G_i)**

PHARMACODYNAMIC EFFECTS

Not all effects observed are caused by the pharmacological actions of the drugs themselves.

- Specific Effects

- Pharmacological or chemical effects of drug on brain/body
 - Depend on the presence of a chemical at certain concentrations in the target tissue.

- Nonspecific Effects

- Effects not due to drug's pharmacological actions on the brain/body
 - “Placebo effects” are generally, “good” non-specific effects
 - “Nocebo effects” are usually, “bad” non-specific effects

STUDYING DRUGS CLINICALLY: BALANCED PLACEBO DESIGN

		<u>Told</u>	
		Nicotine	Placebo
Given	Nicotine	Group 1	Group 3
	Placebo	Group 2	Group 4

Due to both specific and non-specific effects

Table 4
Cigarette Ratings Across the Experimental Conditions

	Conditions (Given/Told)				Effects			
	Nicotine/ Nicotine	Nicotine/ Placebo	Placebo/ Nicotine	Placebo/ Placebo	Main effect nicotine	Main effect instructions	Nicotine X instructions	
	Mean (SEM)	Mean (SEM)	Mean (SEM)	Mean (SEM)	F	η^2	F	η^2
Satisfying	5.40 (0.24)	4.30 (0.23)	3.17 (0.24)	2.29 (0.25)	$F^a = 78.68^{***}$	0.546	$F = 17.16^{***}$	0.119
Tastes good	4.41 (0.25)	3.70 (0.24)	2.53 (0.25)	1.94 (0.26)	$F = 52.85^{***}$	0.367	$F = 6.66^*$	0.046
Enjoyable sensations in throat and chest	3.86 (0.26)	3.48 (0.25)	3.17 (0.26)	2.29 (0.27)	$F = 13.36^{***}$	0.093	$F = 6.05^*$	0.042
Calming	4.46 (0.22)	3.43 (0.22)	2.89 (0.23)	1.86 (0.23)	$F = 49.05^{***}$	0.341	$F = 21.26^{***}$	0.148
Less irritable	3.68 (0.25)	2.58 (0.24)	2.50 (0.25)	1.77 (0.26)	$F = 15.54^{***}$	0.108	$F = 13.27^{***}$	0.092
Helped Concentrate	3.43 (0.24)	2.88 (0.23)	2.28 (0.25)	1.80 (0.25)	$F = 20.88^{***}$	0.145	$F = 4.50^*$	0.031
Reduced craving	4.86 (0.27)	4.00 (0.26)	3.81 (0.27)	2.11 (0.28)	$F = 29.74^{***}$	0.207	$F = 22.40^{***}$	0.156
Less anxious	3.78 (0.23)	2.65 (0.23)	2.75 (0.23)	1.69 (0.24)	$F = 18.97^{***}$	0.132	$F = 22.95^{***}$	0.159
More alert	3.10 (0.21)	2.48 (0.20)	2.19 (0.21)	1.97 (0.21)	$F = 11.80^{***}$	0.082	$F = 4.31^*$	0.030
More awake	3.38 (0.24)	2.75 (0.23)	2.25 (0.24)	2.00 (0.24)	$F = 15.79^{***}$	0.110	$F = 3.45^\dagger$	0.024
Reduced hunger	2.30 (0.22)	2.45 (0.21)	1.94 (0.22)	1.34 (0.22)	$F = 11.26^{**}$	0.078	ns	ns
Different from usual brand	4.59 (0.23)	4.85 (0.22)	6.31 (0.23)	6.49 (0.23)	$F = 54.63^{***}$	0.379	ns	ns
Dizzy	2.73 (0.27)	2.83 (0.26)	1.83 (0.27)	1.57 (0.28)	$F = 15.72^{***}$	0.109	ns	ns
Nauseous	1.38 (0.17)	1.58 (0.16)	1.64 (0.17)	1.94 (0.17)	$F = 3.49^\dagger$	0.023	ns	ns

Note. SEM = Standard Error.

^a df (1,144) for all analyses.

[†] $p < .08$. * $p < .05$. ** $p < .01$. *** $p < .001$.

Due mainly to specific effects

STUDYING DRUGS CLINICALLY: DOUBLE-BLIND PROCEDURE

- Neither the experimental participants nor the researchers know whether a subject is receiving a placebo or an experimental drug.
 - The relevant individuals are informed about which participants comprised the drug conditions after the experiment is over.
 - In combination, experiments that control non-specific effects (e.g., balanced placebo experiments and **double-blind** experiments) are best methods to isolate specific effects AND test for the effectiveness of a new drug.

THE “UNBLINDING PROBLEM” IN PSYCHIATRIC RESEARCH

OTHER CHALLENGES IN BEHAVIOURAL PHARMACOLOGY

At the end of a trial, research subjects usually figure out which condition they are in. How?

1) Side effects.

- Unintended effects that accompany specific therapeutic effects.

2) Expectancy Effects.

- Derive from the user’s unique background and particular perception of the environment.

ARTICLE

OPEN



Microdosing with psilocybin mushrooms: a double-blind placebo-controlled study

Federico Cavanna^{1,2}, Stephanie Muller¹, Laura Alethia de la Fuente ^{1,3}, Federico Zamberlan^{1,4}, Matías Palmucci¹, Lucie Janeckova⁵, Martin Kuchar ^{5,6}, Carla Pallavicini^{1,2,8} and Enzo Tagliazucchi ^{1,7,8✉}

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The use of low sub-perceptual doses of psychedelics ("microdosing") has gained popularity in recent years. Although anecdotal reports claim multiple benefits associated with this practice, the lack of placebo-controlled studies severely limits our knowledge of microdosing and its effects. Moreover, research conducted in standard laboratory settings could fail to capture the motivation of individuals engaged or planning to engage in microdosing protocols, thus underestimating the likelihood of positive effects on creativity and cognitive function. We recruited 34 individuals starting to microdose with psilocybin mushrooms (*Psilocybe cubensis*),

one of the materials most frequently used for this purpose. Following a double-blind placebo-controlled experimental design, we investigated the acute and short-term effects of 0.5 g of dried mushrooms on subjective experience, behavior, creativity (divergent and convergent thinking), perception, cognition, and brain activity. The reported acute effects were significantly more intense for the active dose compared to the placebo, but only for participants who correctly identified their experimental condition. These changes were accompanied by reduced EEG power in the theta band, together with preserved levels of Lempel-Ziv broadband signal complexity. For all other measurements there was no effect of microdosing except for few small changes towards cognitive impairment. According to our findings, low doses of psilocybin mushrooms can result in noticeable subjective effects and altered EEG rhythms, but without evidence to support enhanced well-being, creativity and cognitive function. We conclude that expectation underlies at least some of the anecdotal benefits attributed to microdosing with psilocybin mushrooms.

EXPECTANCY AND NONSPECIFIC DRUG EFFECTS

- They can be produced by an inactive OR active chemical that the user believes to be a drug.
 - Be careful... non-specific != side effects
- **Discussion:**
 - Antidepressants - some researchers suggest that for many, their therapeutic benefits are largely due to non-specific effects...
 - <https://www.youtube.com/watch?v=Zihdr36WVi4> (Start-7:15)



DISTINGUISHING BETWEEN SPECIFIC AND NON-SPECIFIC EFFECTS

Textbook says: “Perhaps the strongest demonstration of the specific effects of a drug is obtained when the dose of the drug is varied and the size of the effect changes directly with the drug dose.”

Why?

In the dose is the poison...

DRUG EFFECTS AND TOXICITY: HOW DO WE MEASURE IT?

Toxicity → the physical or psychological harm that a drug might present to the user

- **Dose-response curve** - Graph depicting the relationship between the drug dose and the resulting drug effects.
 - Different dose-response curves can be created for different drug effects.
 - Some response systems have higher thresholds.
 - Some drugs have an all-or-none dose-response relationship.
- **Threshold** - The lowest dose at which an effect is observed.

ANATOMY OF A DOSE-RESPONSE CURVE

■ Dose

- Amount of drug, goes on X-axis
- Usually metric weights, i.e., grams (g), milligrams (mg), micrograms (mcg or “ μ g”)
- Often adjust for bodyweight (e.g., “mg/kg”), but not always
 - Or metric volumes, e.g., liters, milliliters, etc.
 - Sometimes imperial units, e.g., ounces, pounds, pints, etc.

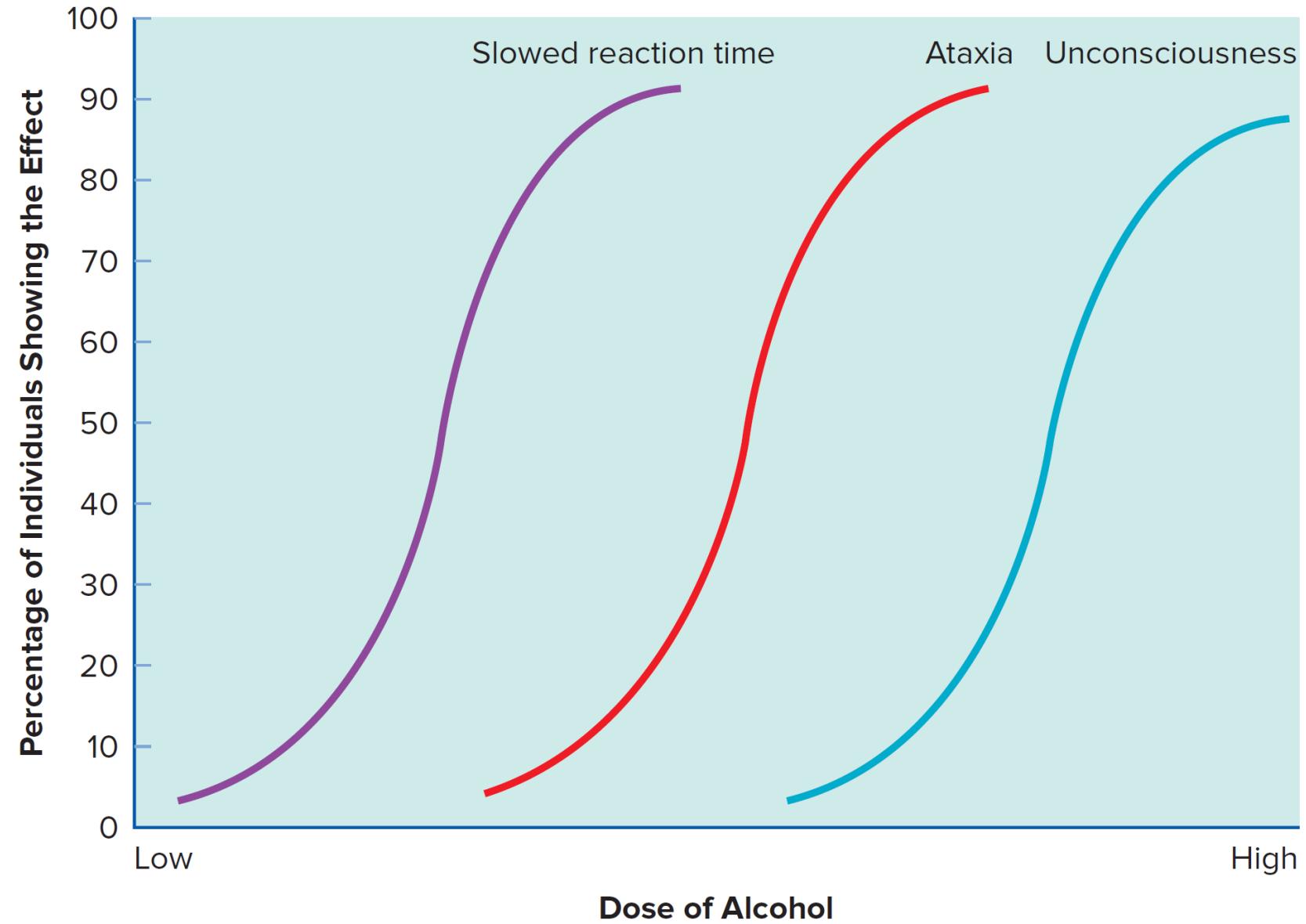
ANATOMY OF A DOSE-RESPONSE CURVE

(...aka dose-effect curves)

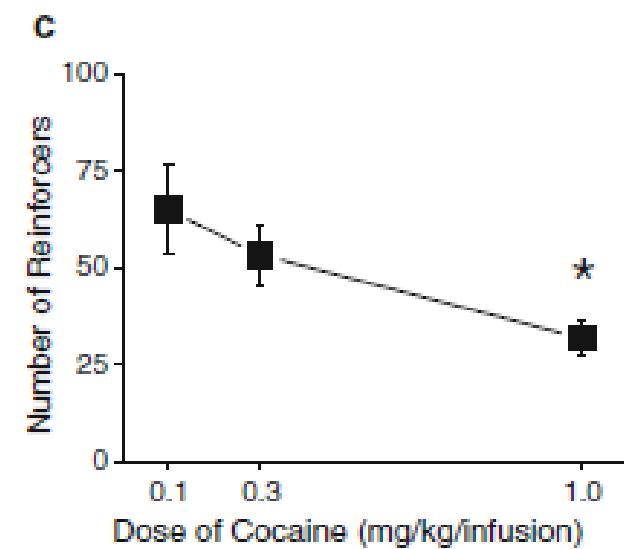
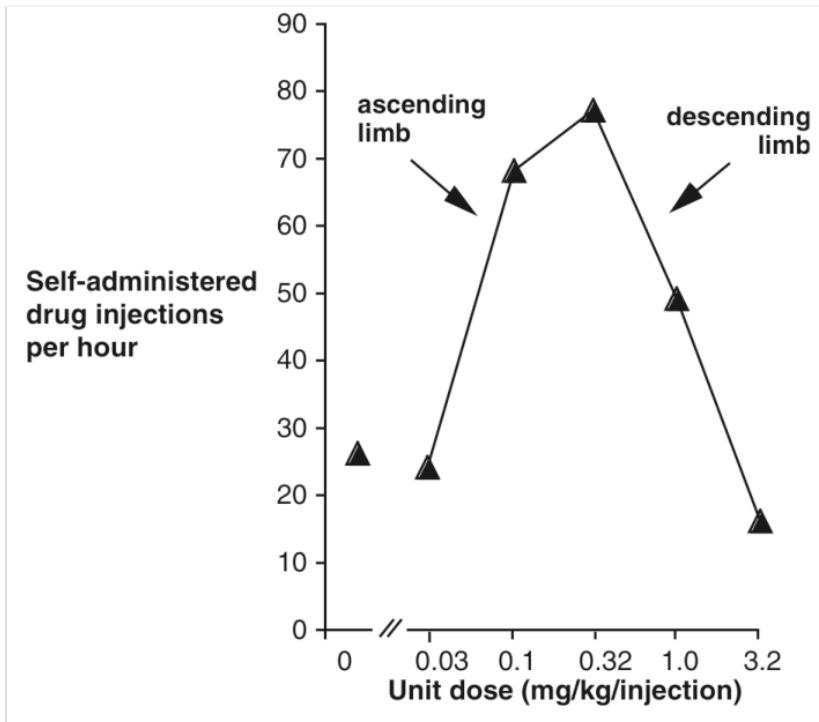
■ Response or Effect

- Goes on Y-axis
- Drugs have multiple different effects, so always make sure to specify which one you're talking about
 - E.g., analgesia, which could be operationally defined as latency to flick tail when under hot light
- Response could be % of subjects showing some behavior
- Or it could be the strength of a response measured
 - e.g., "how much do you like this drug on a scale of 1 to 7?"

FIGURE 5.2: RELATIONSHIP BETWEEN ALCOHOL DOSE AND MULTIPLE RESPONSES



EXAMPLES: OTHER DOSE-RESPONSE CURVES

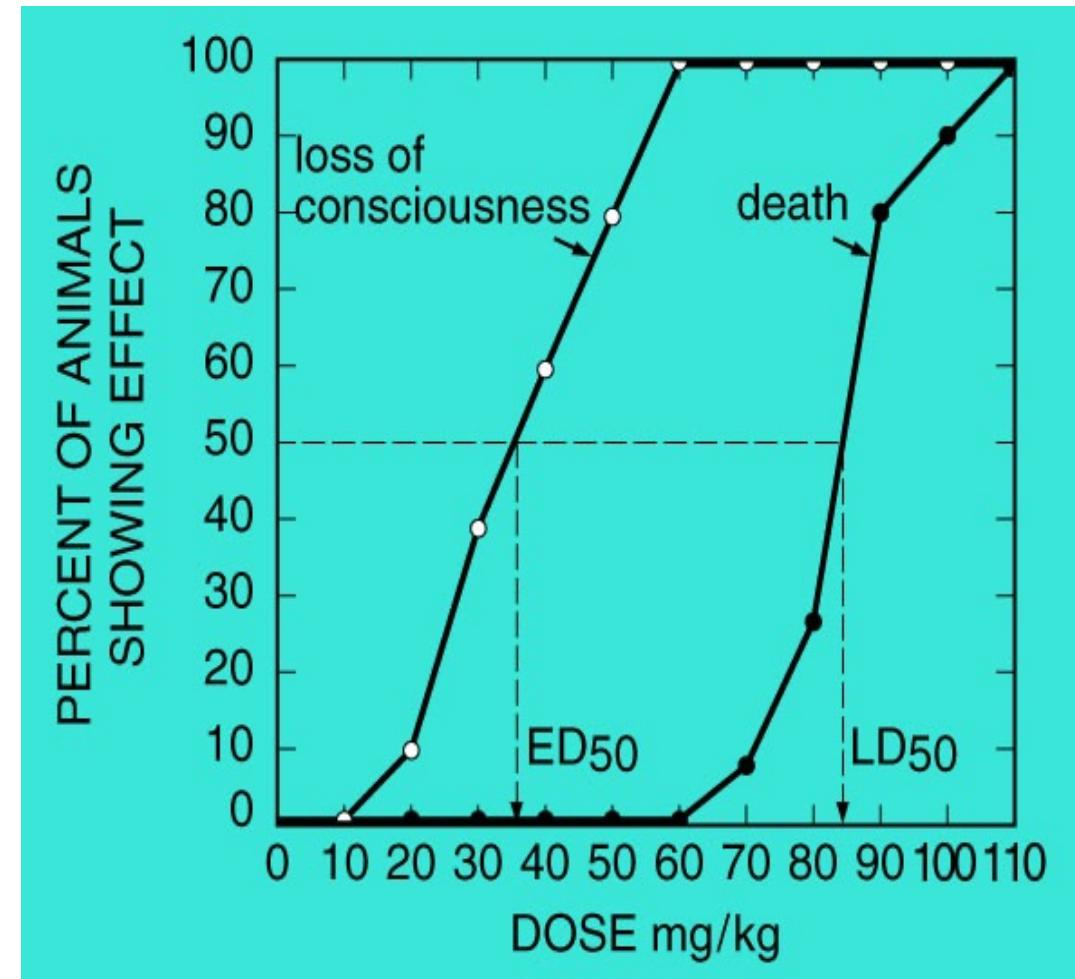


WHAT CAN WE LEARN FROM DOSE-RESPONSE CURVES?

- Median effective dose (ED_{50})
- Median lethal dose (LD_{50})
- Therapeutic index
- Margin of safety
- Potency
- Efficacy

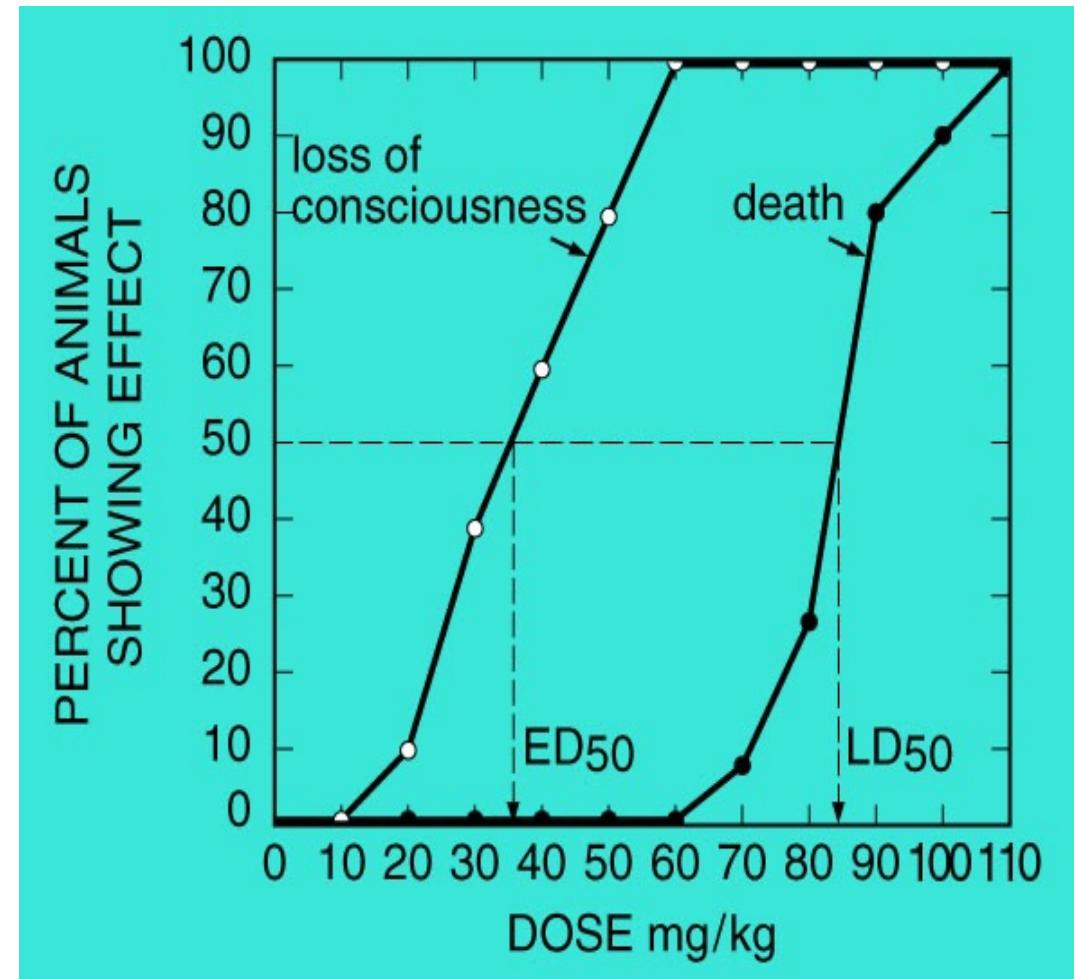
EFFECTIVE DOSE, OR ED.

- Dose of a drug that produces a meaningful **effect** in some percentage of test subjects.
- **ED₅₀**
 - ED₅₀ is an amount (g, mg, ounces, ml, etc).
 - Amount that produces effect (i.e., “effective dose”) in half of subjects
 - Amount that produces a half maximal effect.
- What is the ED₉₅ for this example?



LETHAL DOSE, OR LD.

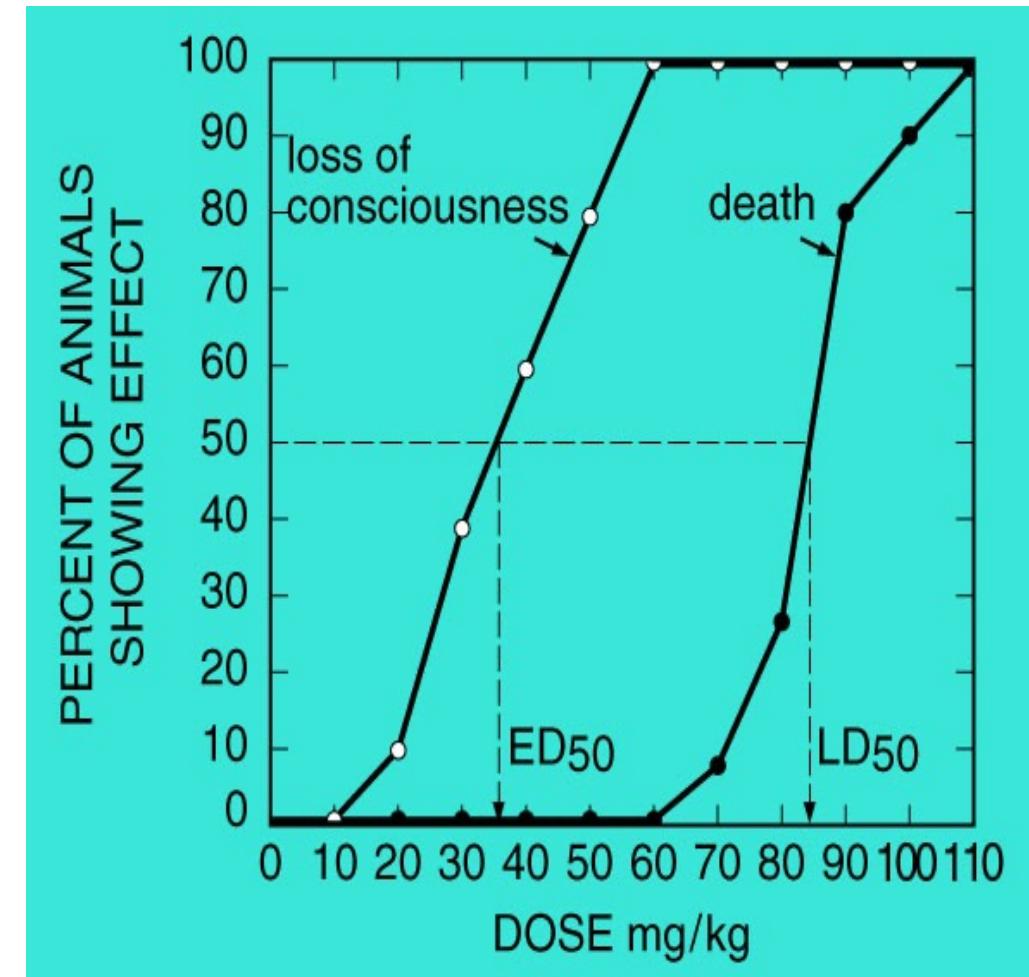
- Dose of a drug that has a lethal effect in some percentage of test subjects.
- **L D₅₀** is the lethal dose for half (50%) of the subjects
 - Most drugs have an L D₁ well above the E D₉₅ level.



(yes, this graph shows a very dangerous drug)

THERAPEUTIC INDEX, OR TI.

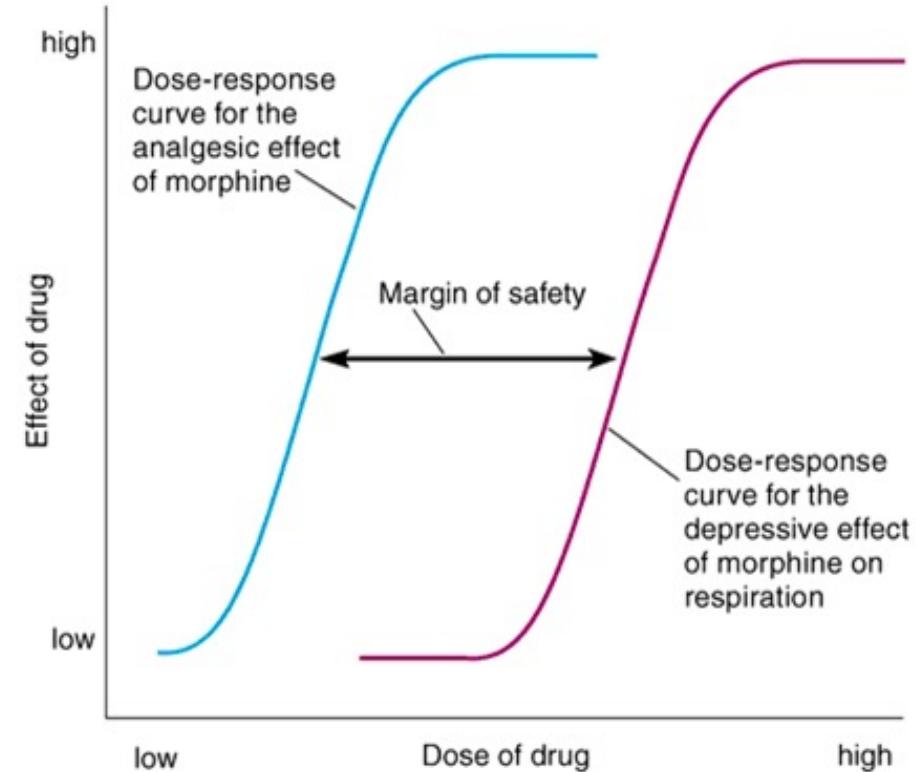
- Therapeutic Index = LD_{50}/ED_{50}
 - So, this is one amount divided by another amount
 - Should always be greater than one.



MARGIN OF SAFETY

- **Safety margin.**
 - dose producing unacceptable toxic minus dose that is effective in most people

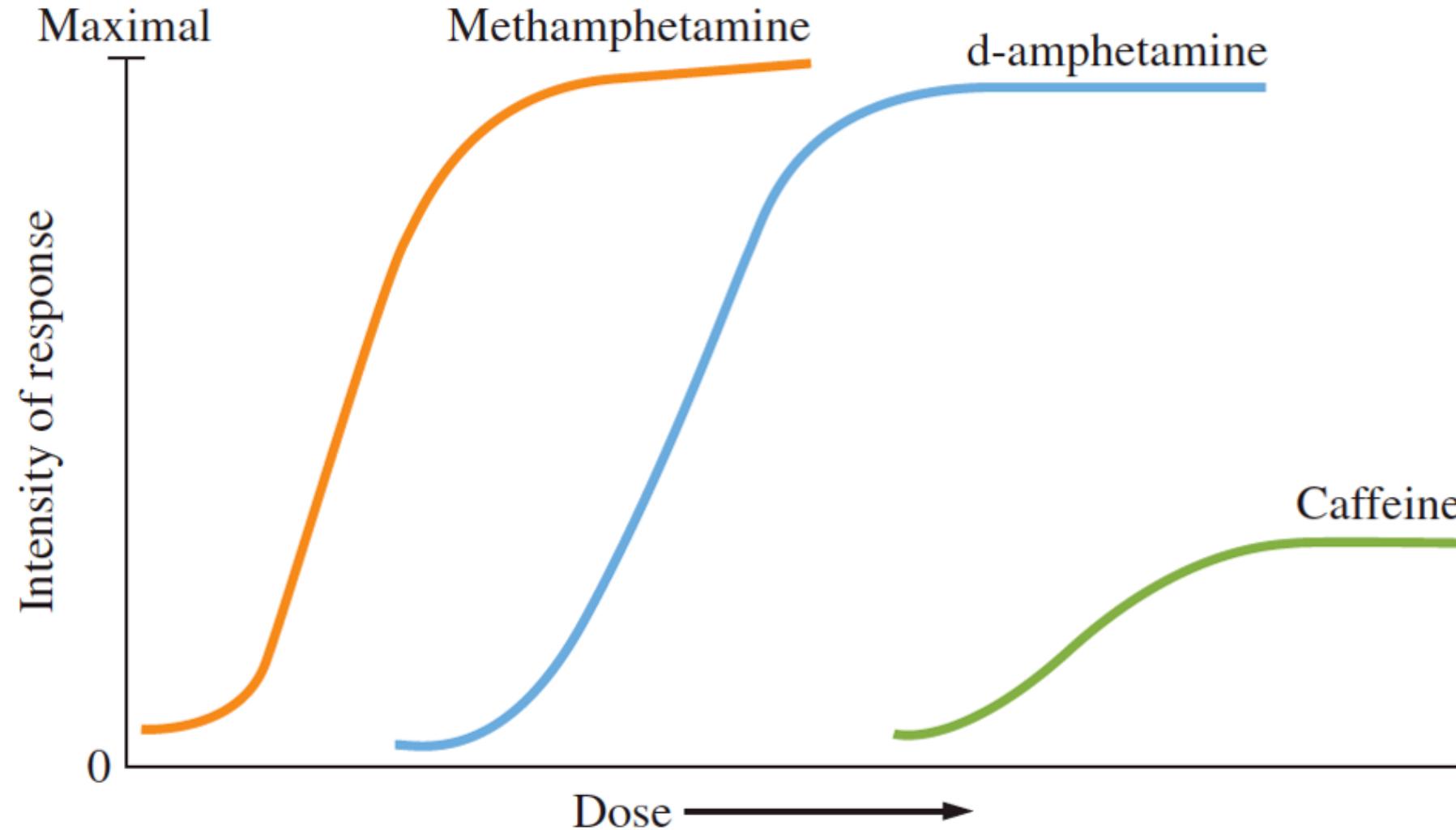
► Dose-Response Curves for the Analgesic and Depressant Effects of Morphine



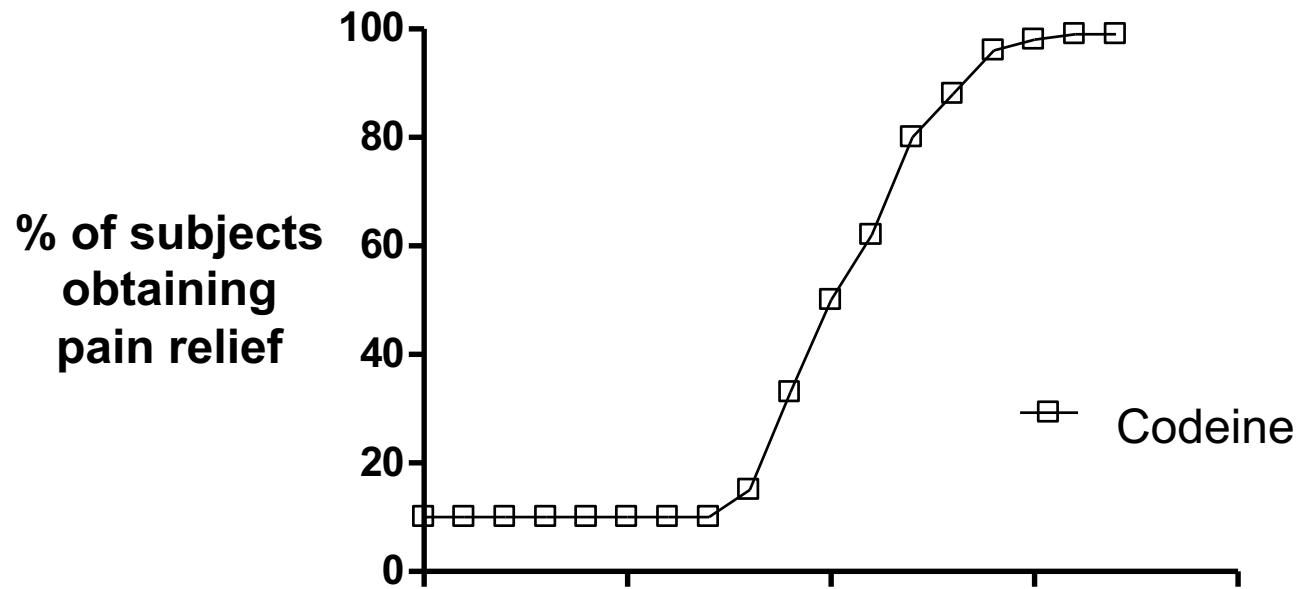
POTENCY AND EFFECTIVENESS

- **Effectiveness (or “Efficacy”): Maximum effect a drug can have at any dose**
 - an inherent characteristic of the drug.
- **Potency:** the **amount** of drug required to **produce** an effect.
 - Codeine < morphine < heroin < fentanyl

LET'S LOOK AT THIS FOR SOME STIMULANTS...



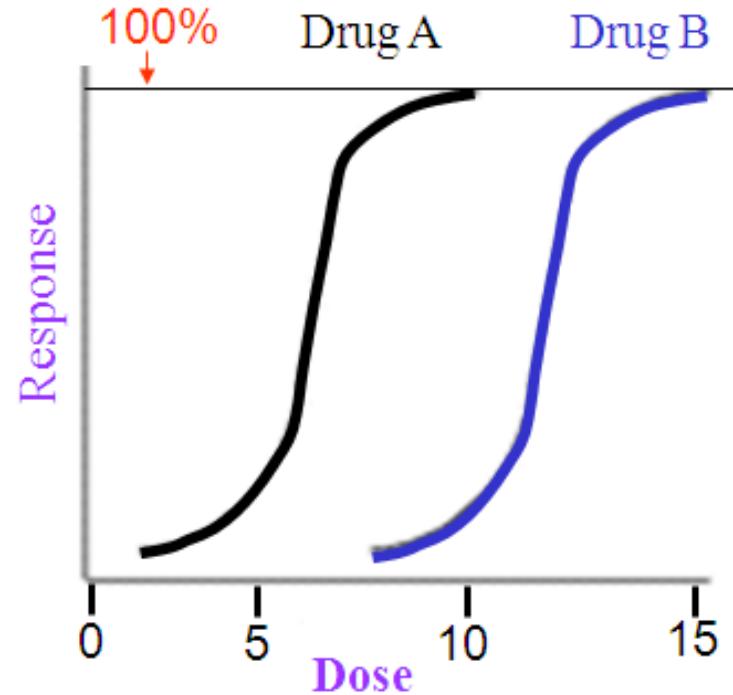
**What might a dose-response curve representing codeine and morphine look like?
Presume Codeine's ED_{50} = 100mg and morphine is ~6x more potent**



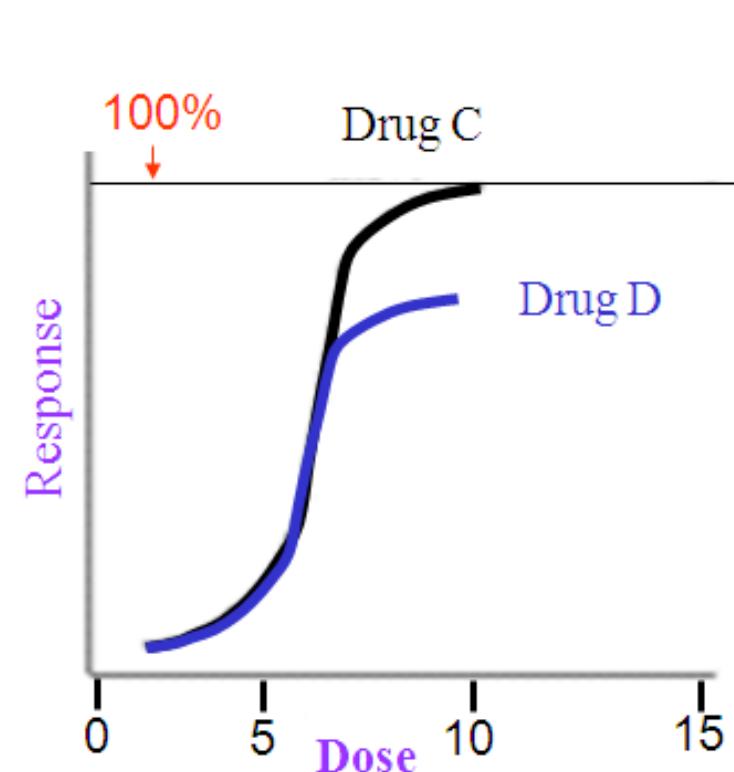
(remember to plot ED_{50})

POTENCY VS. EFFECTIVENESS

- Be careful - People confuse this often



These drugs differ in potency,
but **have same effectiveness**



These drugs have the **same potency**,
but differ in effectiveness

PHARMACOKINETICS

- How the body handles/interacts with drugs
- The time course of a drug's effect depends on 3 major factors:
 - 1) **Absorption** (how to get drug into blood)
 - Routes of administration
 - 2) **Distribution** (of drug around body)
 - 3) **Metabolism (or Elimination)**

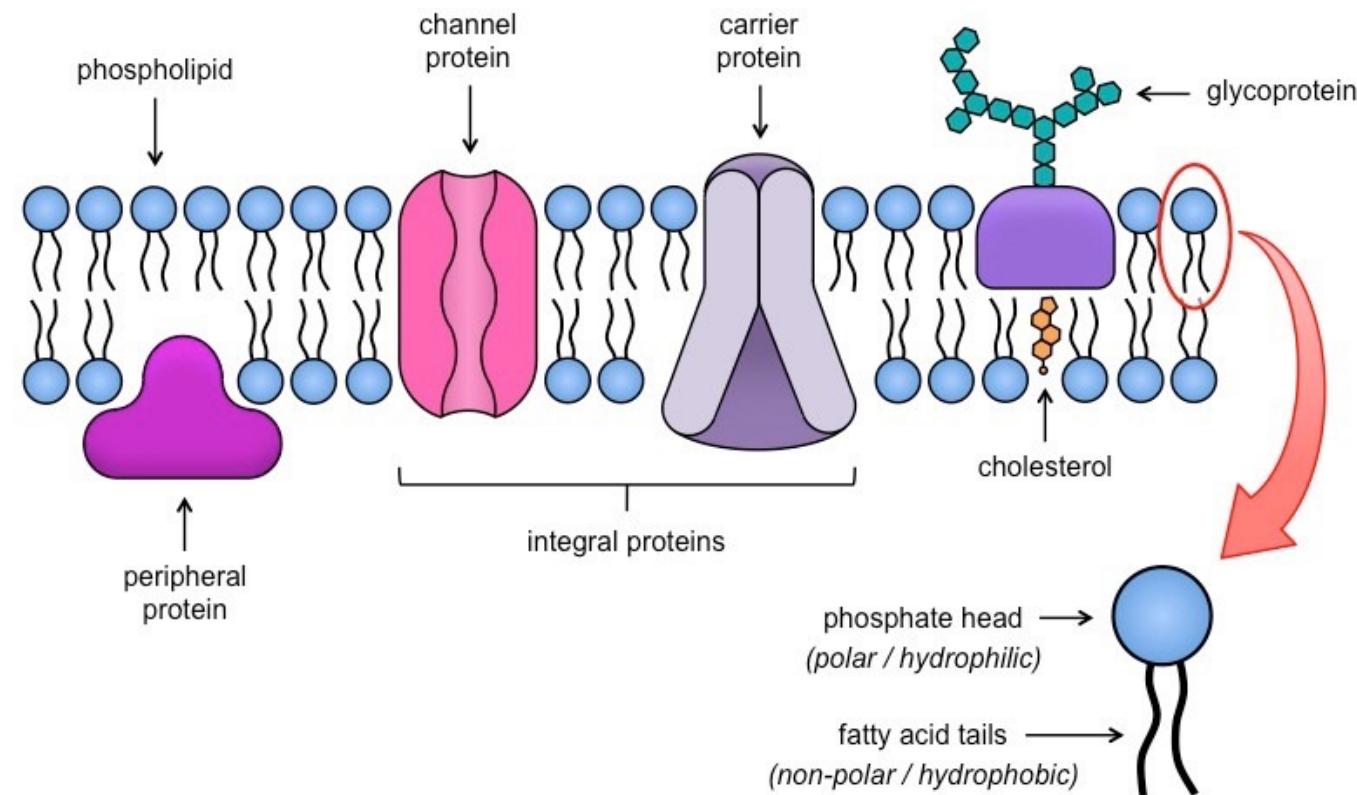


ABSORPTION

/ ADMINISTRATION

ABSORPTION

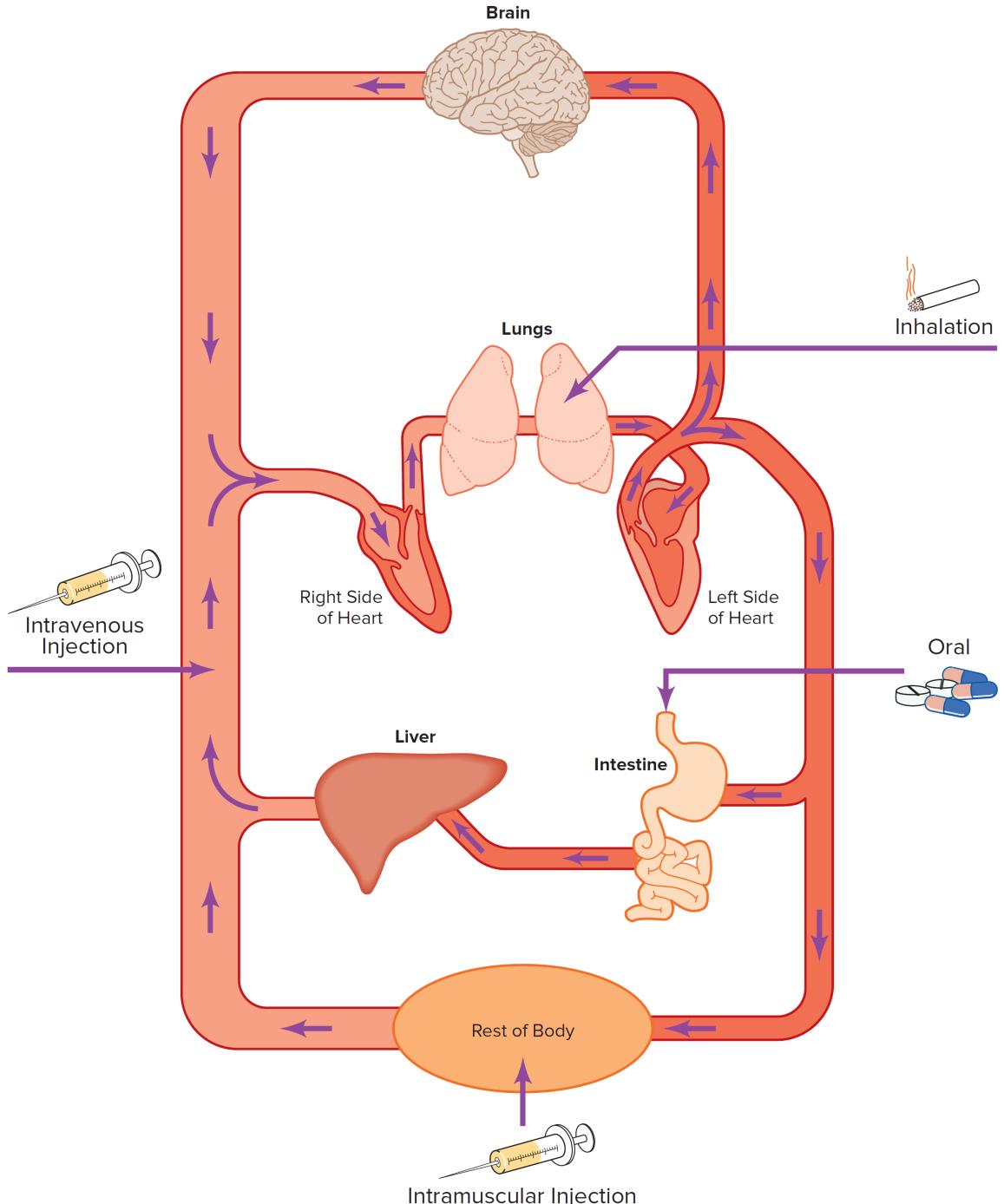
- **Lipid solubility** (extent to which a psychoactive drug dissolves in oils and fats) important at each stage:
 - To get into capillaries in body,
 - To get out of capillaries in the brain so that drug can act on neurons



ROUTES OF ADMINISTRATION

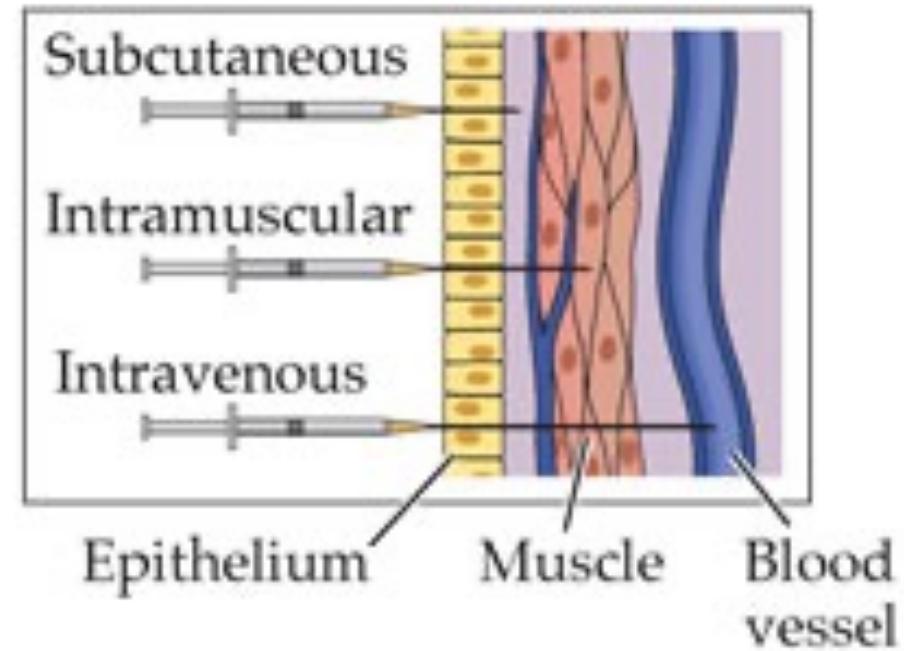
Administration route is a critical factor in how quickly a drug is absorbed.

- Most common routes:
 - 1) Injection (3x types)
 - 2) Oral administration
 - 3) Inhalation
- Other common routes:
 - 4) Intranasal
 - 5) Sublingual
 - 6) Transdermal



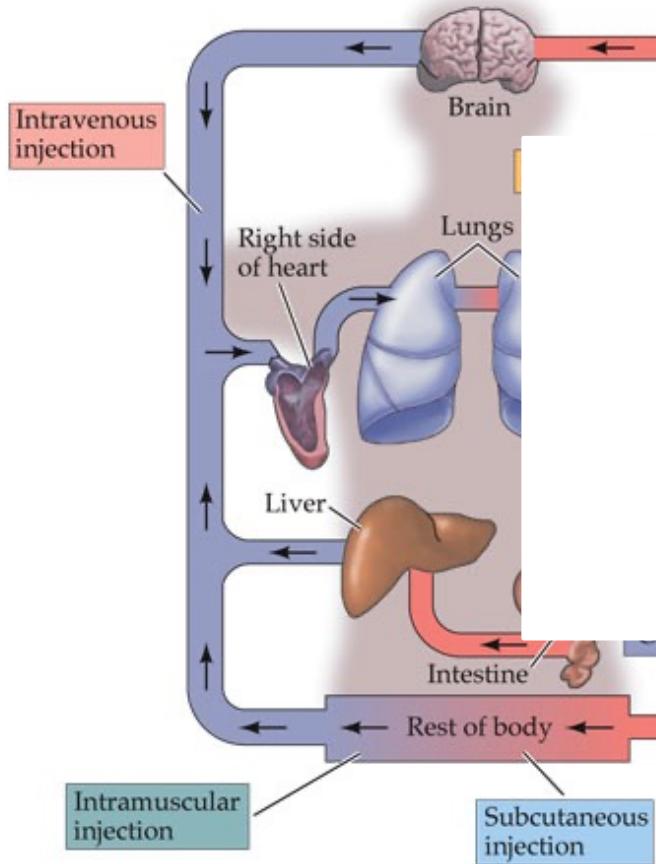
INJECTION

- 3 types:
 - 1) intravenous (i.v.) injection
 - 2) intramuscular (i.m.) injection
 - 3) subcutaneous (s.c.) injection



I) INTRAVENOUS INJECTION

- **Intravenous Injection** - Drug is delivered directly into the bloodstream.
 - Irritating material may be injected this way, because blood vessel walls are relatively insensitive
 - Doesn't have to dissolve across capillaries
- Pros.
 - High concentrations can be delivered.
 - Results in a rapid onset of its effects than does with oral administration or with other means of injection.
- Cons/Risks.
 - Veins may become damaged over time.
 - Blood-borne diseases (HIV, hepatitis) spread easily.



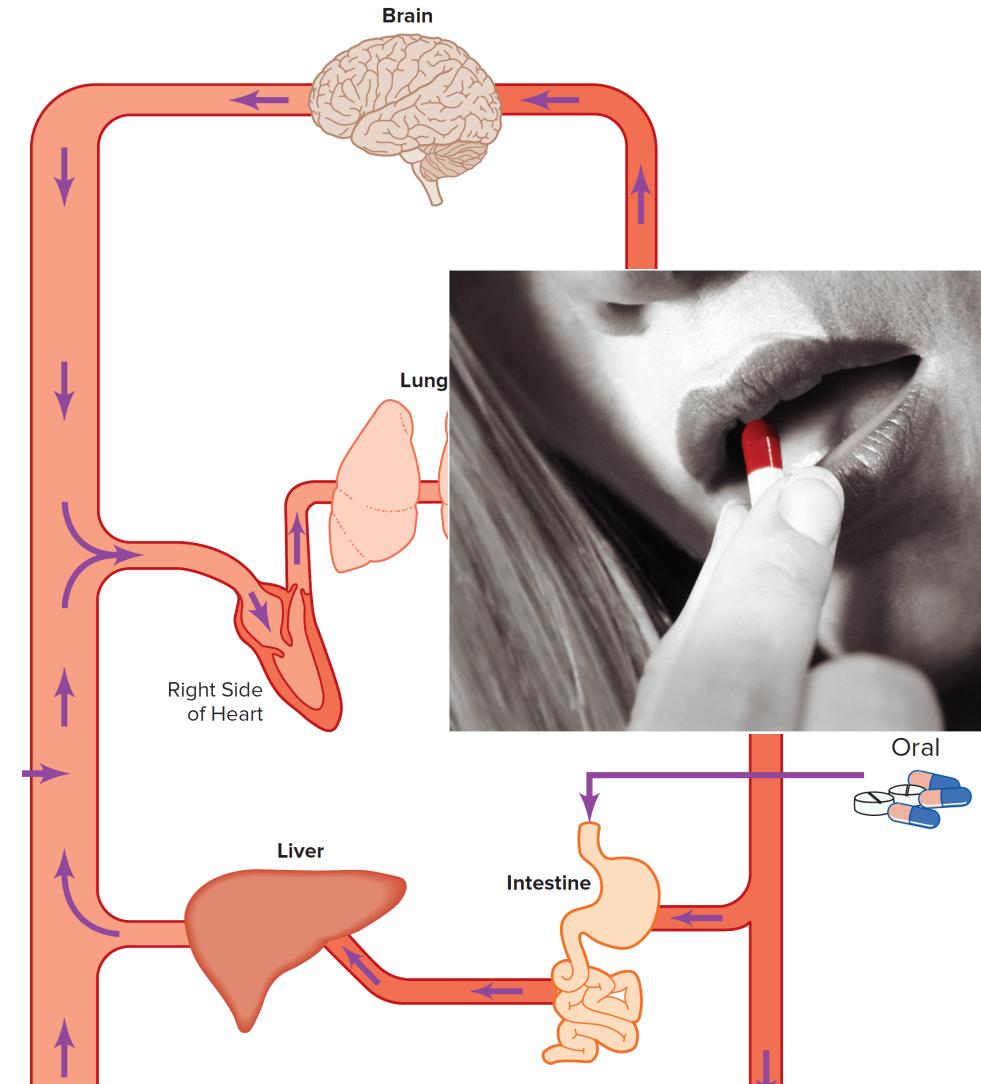
2-3) SUBCUTANEOUS AND INTRAMUSCULAR INJECTIONS

- **Subcutaneous injection.**
 - Injection under the skin, good for hormone/lipophilic drugs.
 - Potential for pain and necrosis from irritating substances around the site of injection
- **Intramuscular injection.**
 - Absorption is more rapid from intramuscular injection than from subcutaneous injection because of the greater blood supply in muscles.
 - most rapid when the injection is into the deltoid muscle of the arm and least rapid when the injection is in the buttock.
 - Drug absorption can be unpredictable or unusual in very obese and emaciated individuals



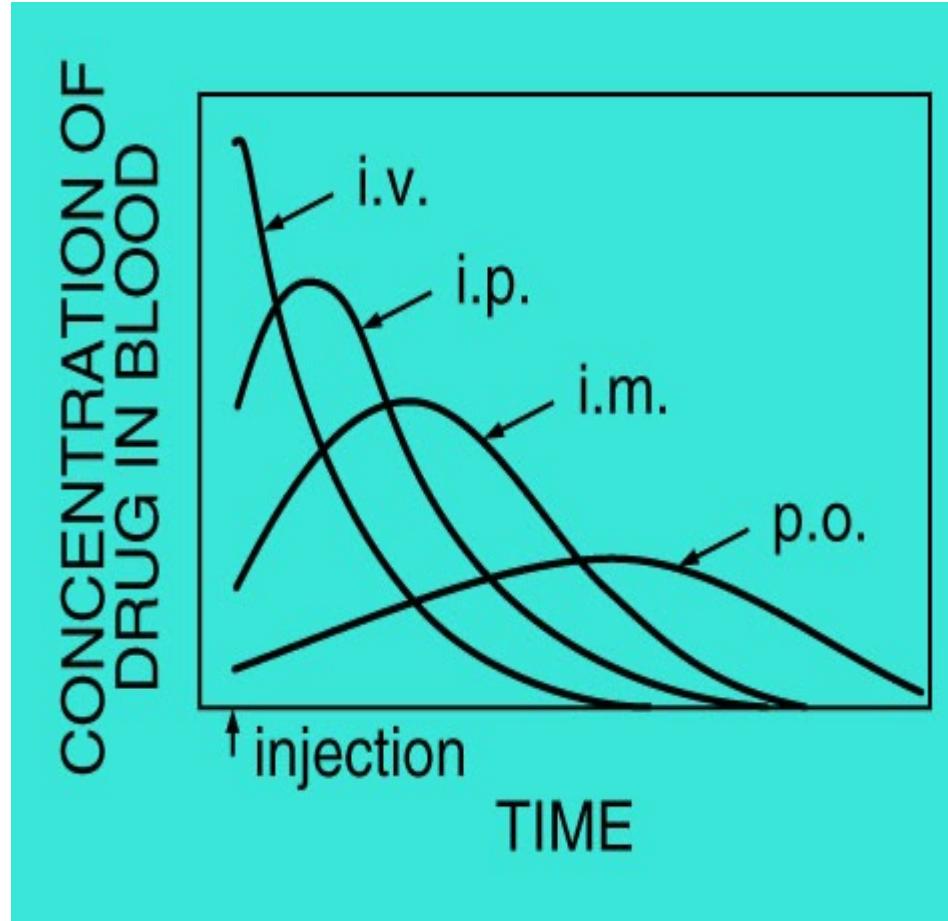
ORAL ADMINISTRATION

- Easiest for humans, but the gastrointestinal tract is the most complicated way to enter the bloodstream:
 1. Drugs must withstand digestive processes and not be deactivated by food in the stomach before they are absorbed.
 - Rate of absorption depends on what else is in stomach
 2. Drugs must then pass through the cells lining the gastro-intestinal tract and into the blood capillaries
 3. **First-pass Metabolism** - then drugs pass through the liver.
 - Oral is only route where blood goes to liver first, which breaks down some drug, before going to general blood circulation



***Very little may get into circulation if the drug gets metabolized rapidly...

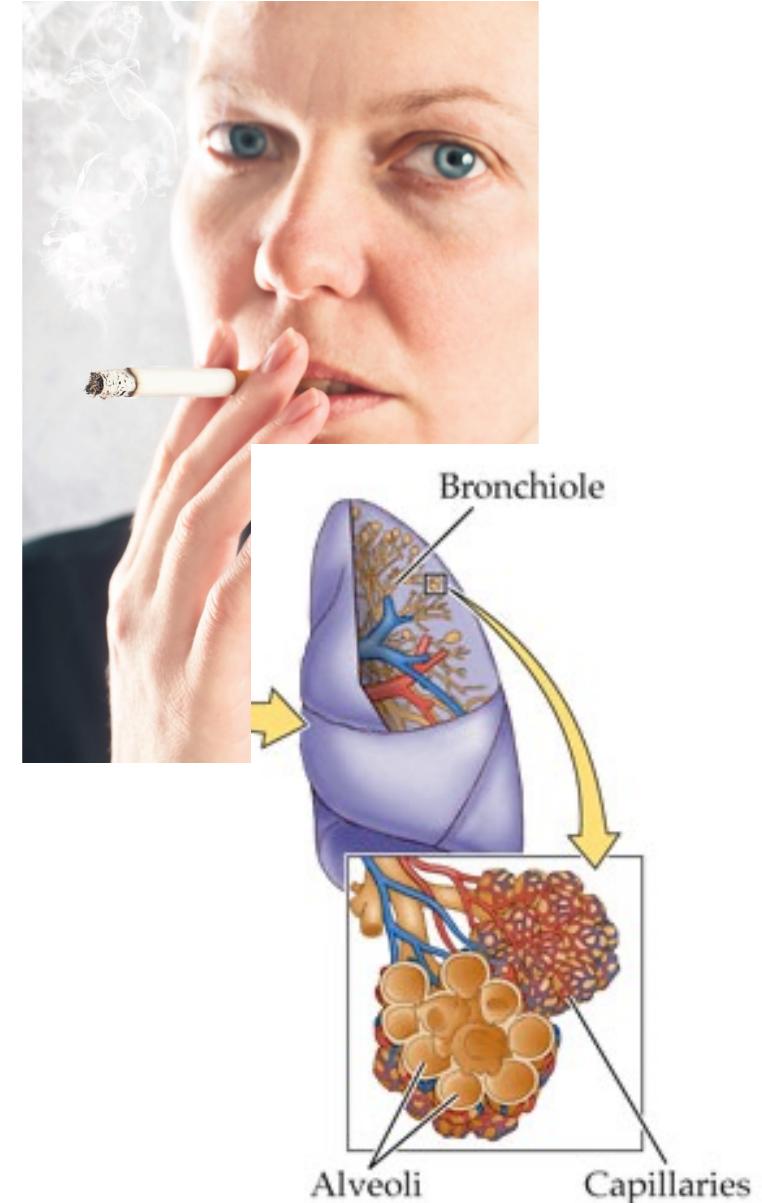
PHARMACOKINETICS



Time courses for i.v.,
i.m., and p.o. routes
(p.o. = “per oral” = by
mouth = swallowing)

INHALATION

- Aka, smoking.
 - FASTEST, highly efficient way of delivering a drug.
 - Onset of drug effects is rapid because the capillary walls are accessible in the lungs, and the drug thus enters the blood quickly.
- Produces more rapid effects for psychoactive drugs than intravenous administration.
 - Blood from the lungs, which contains the drug, moves directly to the brain.



INTRANASAL/INSUFFLATION



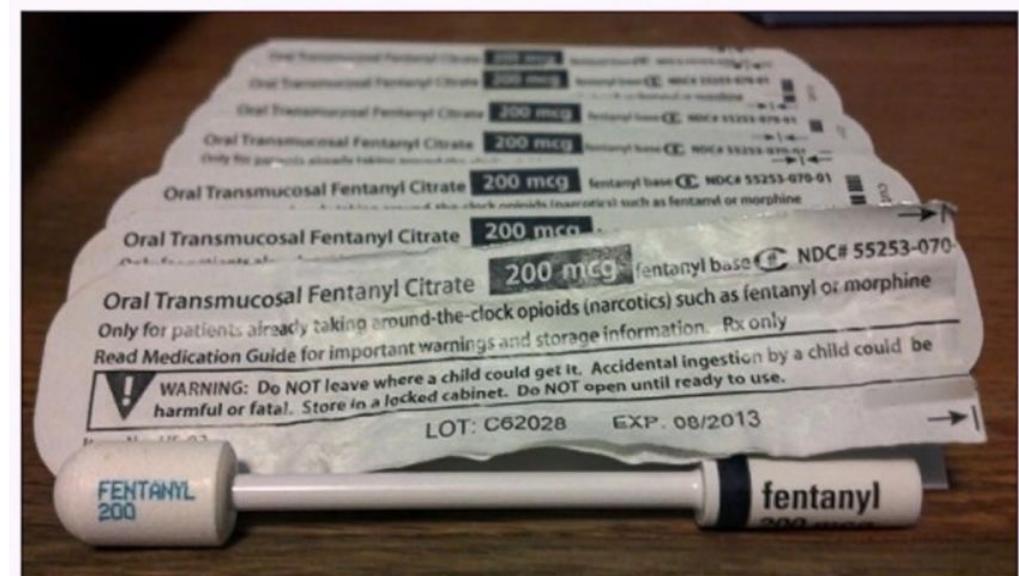
- Also called... **Insufflation** (aka “snorting”)
 - Onset of effects is faster than it is for oral administration.
 - Absorption through mucous membranes into the bloodstream occurs rapidly, bypassing the liver.
 - Not as fast as i.v. or inhalation
 - Drawback associated with intranasal drug use includes nasal necrosis, or death of cells in the septal region.



SUBLINGUAL

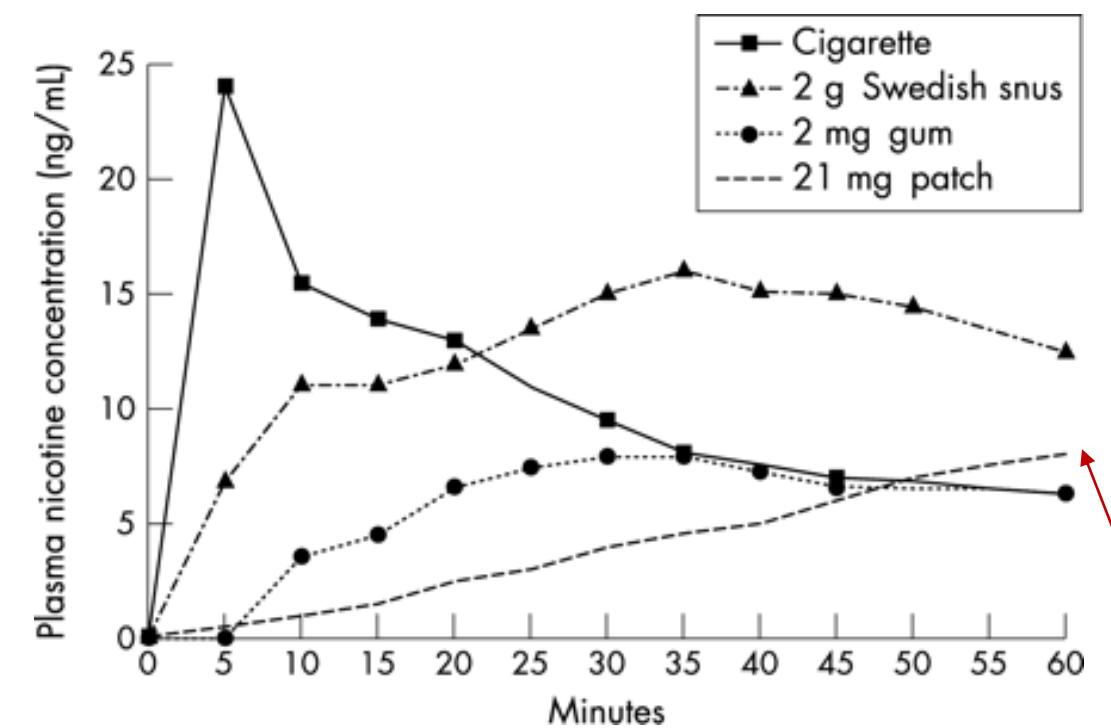
■ Buccal/transmucosal/sublingual

- The drug is placed under the tongue.
- Don't actually swallow the substance
- After dissolving through mucous membranes in mouth it is absorbed directly into the bloodstream.
- Results in a rapid onset of drug effects, comparable to that which is observed after intranasal dosing.



TRANSDERMAL

- Drugs are delivered across the skin to enter the bloodstream
 - Can be a patch, cream, gel, or spray
 - Patches typical for drugs that aim for slow and continuous delivery - drug will be delivered as long as the patch is worn
- Pros:
 - Convenient - Most patches can just be adhered to the skin
 - Non-invasive
- Cons:
 - Not all drugs can be absorbed through the skin
 - Some patches cause irritation



Blood levels of nicotine still rising for transdermal, when blood levels are falling for other routes

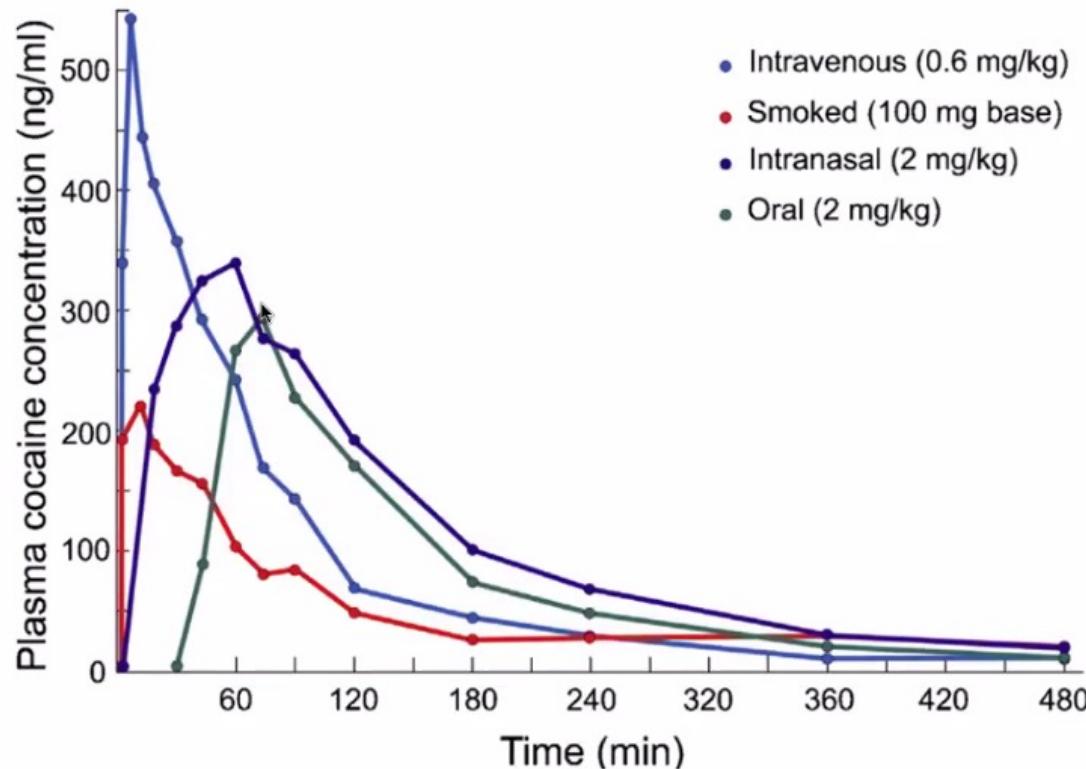
TABLE 5.1: SOME CHARACTERISTICS OF ROUTES OF DRUG ADMINISTRATION

Route	Advantages	Disadvantages
Oral	<ul style="list-style-type: none">• Usually more safe• Convenient	<ul style="list-style-type: none">• Absorption rate can be unpredictable• Slow onset of drug effects
Intranasal	<ul style="list-style-type: none">• Liver metabolism avoided• Rapid drug effects• Reliable and convenient	<ul style="list-style-type: none">• Potential for nasal necrosis
Intravenous injection	<ul style="list-style-type: none">• Liver metabolism avoided• Rapid drug effects	<ul style="list-style-type: none">• Increased risk of adverse effects: Direct (for example, overdose) and indirect (for example, potential for blood-borne diseases)• Potential for collapsed veins

TABLE 5.I: SOME CHARACTERISTICS OF ROUTES OF DRUG ADMINISTRATION ₂

Route	Advantages	Disadvantages
Subcutaneous injection	<ul style="list-style-type: none">Drug absorption can be slow and constant providing a sustained drug effect	<ul style="list-style-type: none">Potential for pain and necrosis from irritating substances
Intramuscular injection	<ul style="list-style-type: none">Drug effects are more rapid than subcutaneous route	<ul style="list-style-type: none">Drug absorption can be unpredictable or unusual in very obese and emaciated individuals
Smoked (Inhalation)	<ul style="list-style-type: none">Liver metabolism avoidedRapid drug effects	<ul style="list-style-type: none">Increased risk of direct adverse effectsPotential for lung toxicity
Sublingual	<ul style="list-style-type: none">Liver metabolism avoidedRapid drug effectsReliable and convenient	<ul style="list-style-type: none">Some drug formulations don't work using this route (for example, extended-release formulations)

ROUTE OF ADMINISTRATION IS A CRUCIAL FACTOR IN DRUG REWARD



- Faster drug injections results in:
 - increased limbic activity, more self admin, faster rise in dopamine neurotransmitter levels



DISTRIBUTION

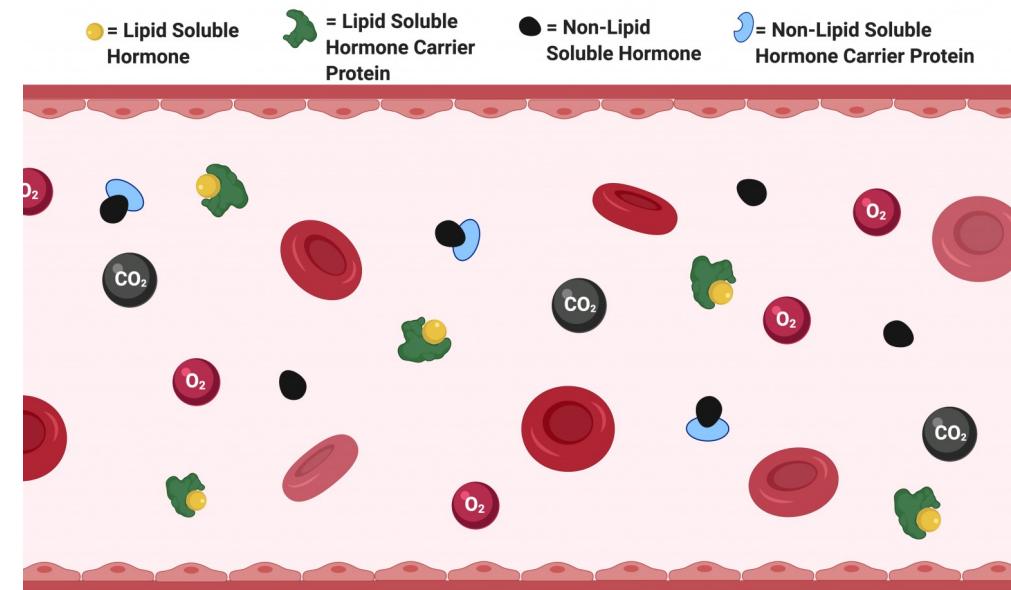
HOW DO DRUGS MOVE FROM THE BLOOD TO BRAIN?

Drugs need to move into the **Body** → **Blood** → **Brain**

- Blood transport: once in the bloodstream, drug molecules attach to protein molecules.
 - Most common protein involved is albumin.
 - Inactive in this state and cannot leave the blood.
 - Protected from inactivation by enzymes.

TRANSPORT IN THE BLOOD

- Drugs vary in their affinity for binding with plasma proteins.
 - A drug with high affinity will displace a drug with low affinity, and thus, the drug with low affinity exists in the unbound form.
 - Increase in the unbound drug concentration helps move the drug out of the bloodstream to the sites of action faster.
- Free, or unbound, drug molecules can move to sites of action in the body.
 - Release of protein-bound drug occurs to maintain the proportion of bound to free molecules.



HOW DO DRUGS MOVE FROM THE BLOOD TO BRAIN?

Drugs need to move from outside the **Body** → **Blood** → **Brain**

- Once in the bloodstream, drug molecules attach to protein molecules.

However, still 2 factors to overcome –

- I) Drug depots**
- 2) Blood-brain barrier**

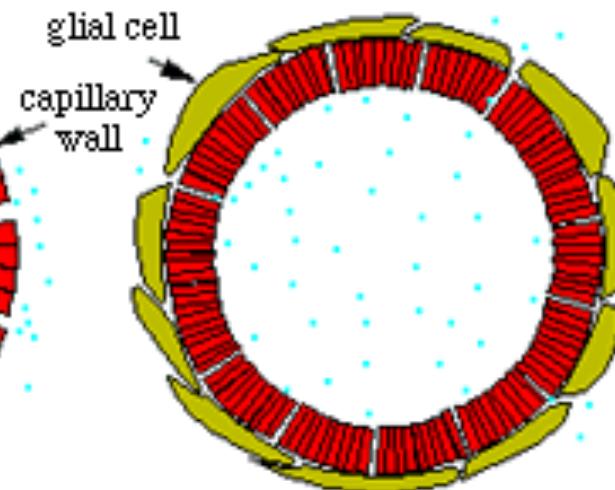
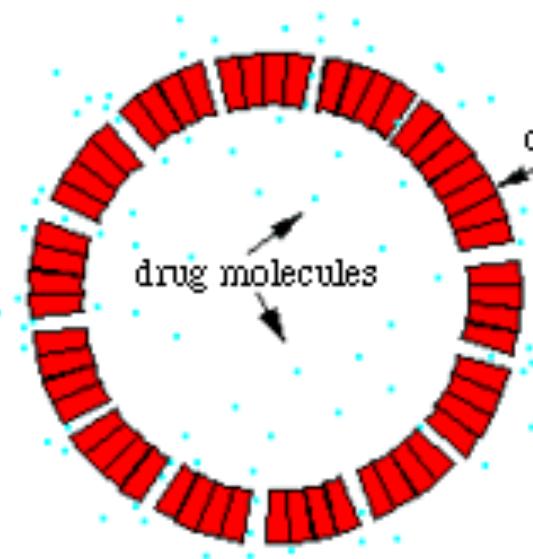
DRUG DEPOTS

- Drug depots act to slow down pharmacokinetics
 - Inactive storage spots in the body effecting a drugs' distribution and elimination
 - Blood proteins (e.g., albumin) can bind to ("stick to") drug, temporarily
 - When bound, drug can't cross blood-brain barrier
 - Typically occurs in fat, occasionally muscle, sometimes bone:
 - Some drugs (e.g., THC) dissolve into body fat, temporarily

BLOOD-BRAIN BARRIER (BBB)

- In general, only small **lipophilic** molecules enter the brain.
- About 85 percent of brain capillaries are covered with **astrocytes**, and there is little extracellular space next to the blood vessel walls.
 - Active transport systems may be needed to move chemicals in and out of the brain.
 - BBB also does not cover area of the brain – tends to be absent in hypothalamus and medulla in the “area postrema” (vomiting the center of the brain)

A capillary in body,
outside of brain



A capillary in the
brain



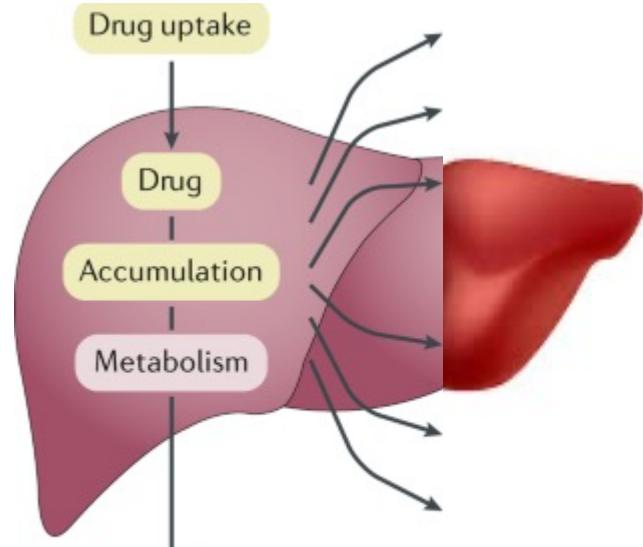
METABOLISM / ELIMINATION

METABOLISM

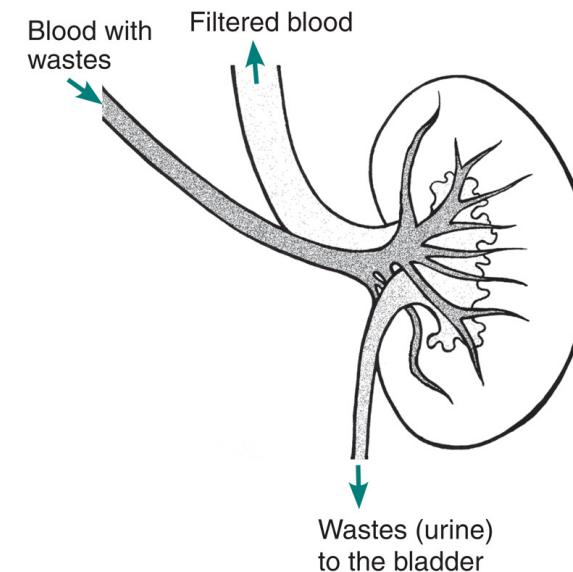
3. Elimination (Drug Deactivation)

- A drug ceases to have an effect when it is either
 - I) chemically changed or 2) excreted unchanged from the body.

Enzymes in the liver

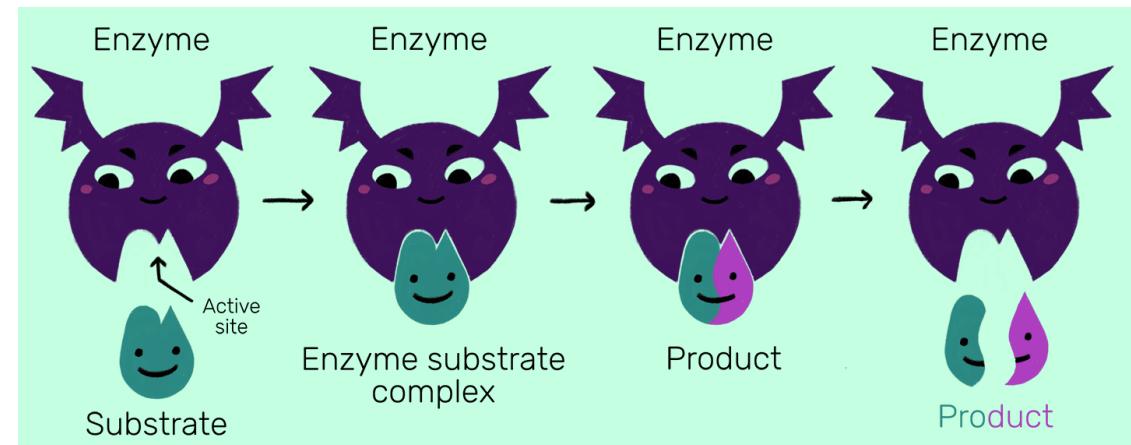


Kidneys filter blood

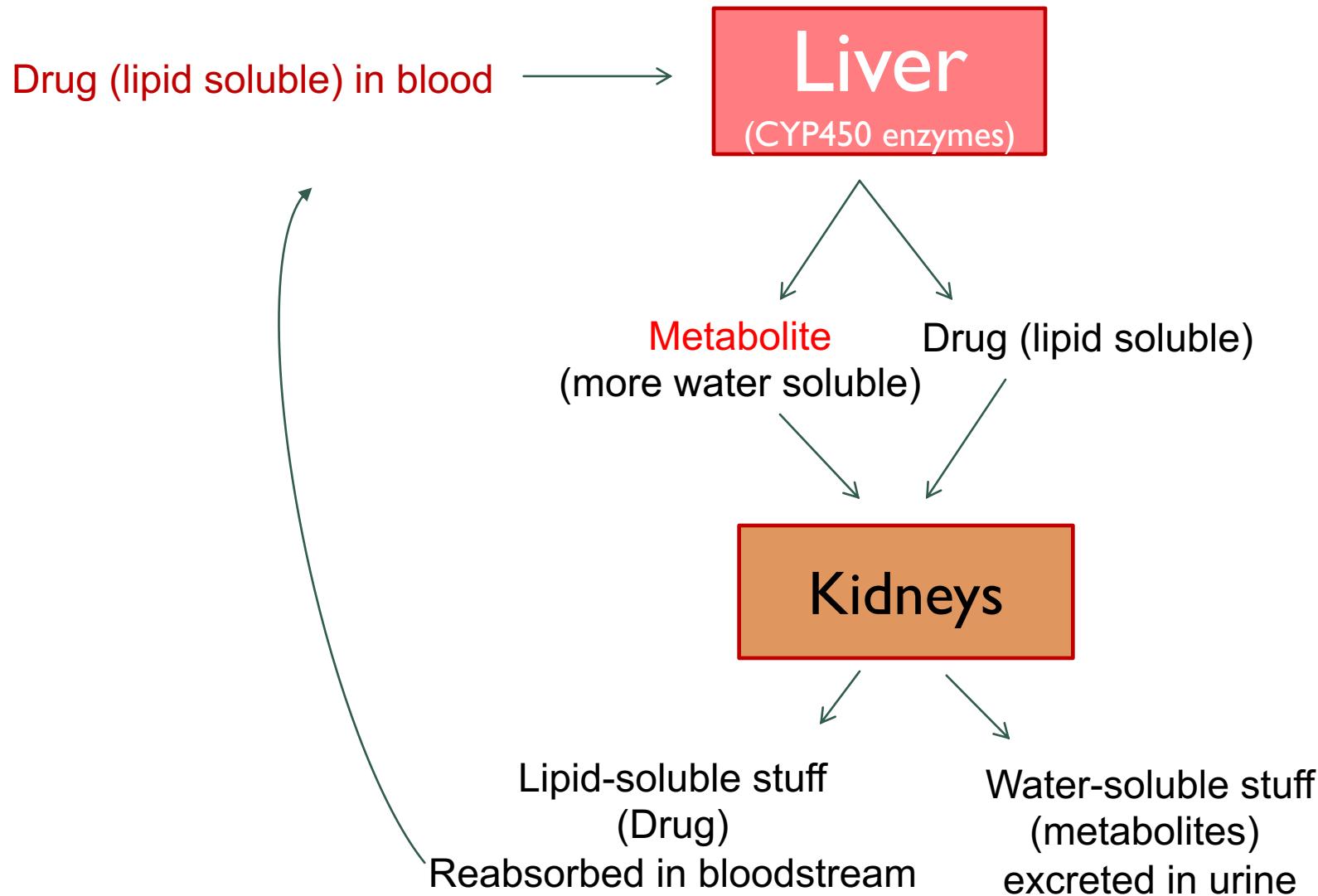


LIVER FUNCTION AND CYTOCHROME P450

- **CYP450** – a family of liver enzymes specialized for inactivating various general kinds of foreign chemicals ingested.
 - Turn **drugs** into less lipid-soluble (i.e., more water-soluble) molecules called **metabolites**.
 - Many drugs have active **metabolites** that produce effects similar to those of the original drug and prolong the effects considerably.



DRUG DEACTIVATION

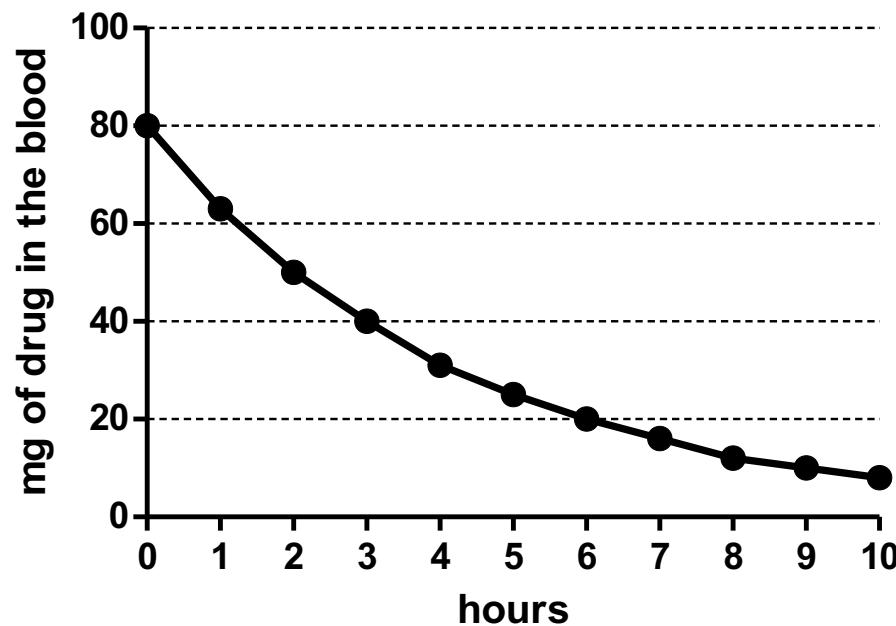


DRUG HALF LIFE AND FIRST ORDER KINETICS

Half-life: time needed for $\frac{1}{2}$ of amount of drug in body to be eliminated.

Typical Drug Half Lives:

- Cocaine = 1 hour
- Morphine = 2 hours
- Nicotine = 2-3 hours
- Caffeine = 3 hours
- Marijuana = 19 hours
- PCP = 20+ hours



DRUG HALF LIFE AND FIRST ORDER KINETICS

First-order kinetics: Constant proportion of drug eliminated from body per unit time
(most drugs eliminated this way)

(b) First-order kinetics

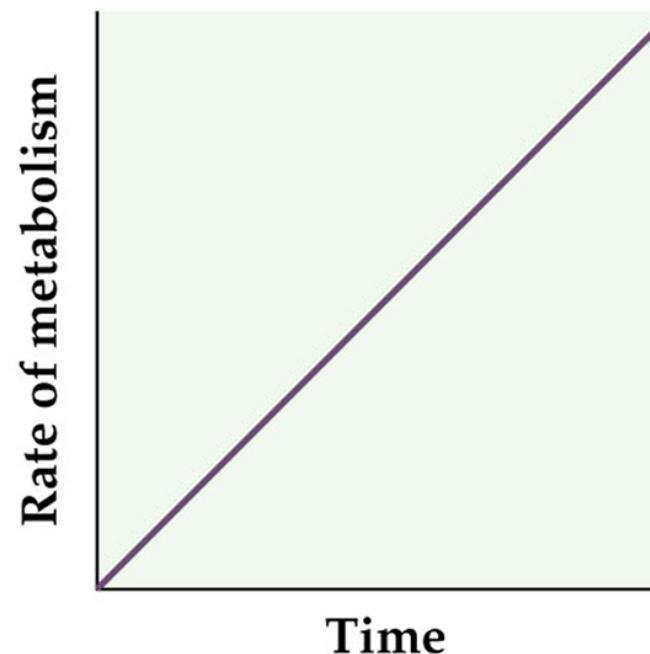


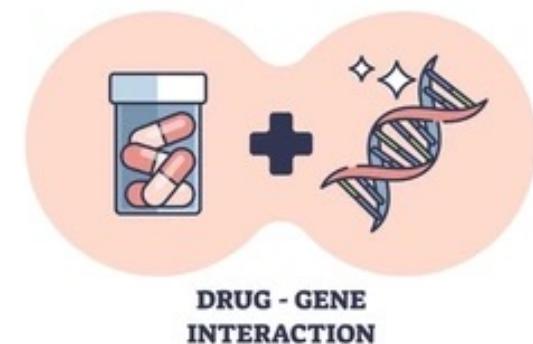
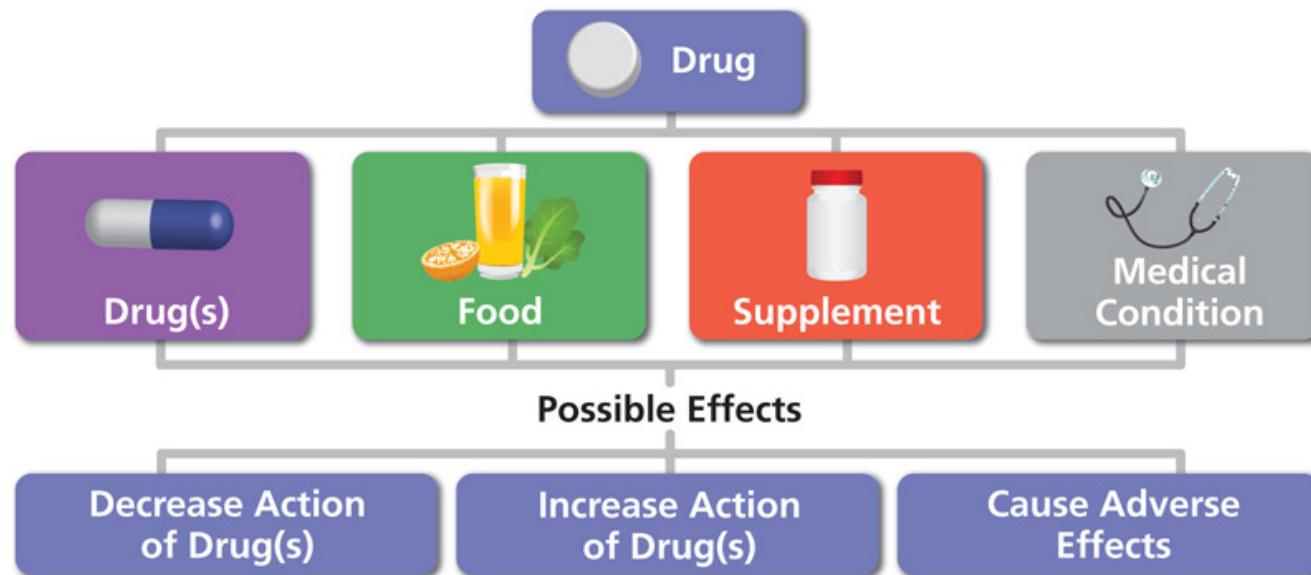
FIGURE 4.3. Zero-order kinetics. Alcohol undergoes zero-order kinetics (a) in which the rate of metabolism is independent of the concentration of alcohol. Most other drugs undergo first-order kinetics (b), in which the rate of metabolism is proportional to the concentration of the drug.

OTHER FACTORS DETERMINING THE BEHAVIORAL IMPACT OF DRUGS

How does pharmacokinetics play into **pharmacodynamics**?

- 1) Drug Interactions
- 2) Tolerance

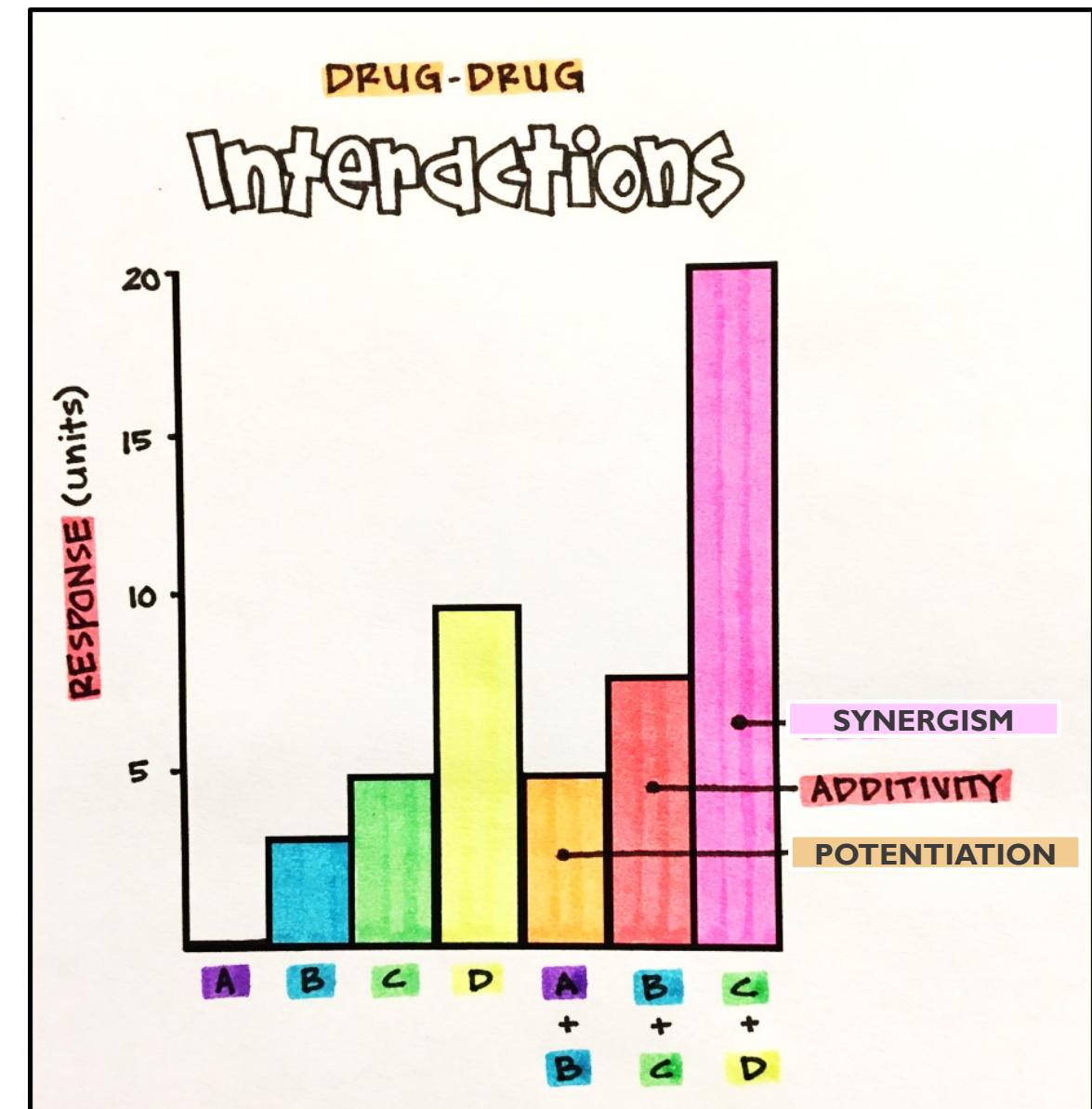
I) DRUG INTERACTIONS



- Additionally, taking multiple doses of drugs too close together will increase the maximum blood level with each dose, which can result in **cumulative effects**.

DRUG-DRUG INTERACTIONS

- Effects may vary depending on whether you are looking at drugs in a similar (e.g., depressant drugs and alcohol) or opposite category (e.g., stimulant drugs like methamphetamine and with depressants like alcohol)
 - Additivity
 - Synergism
 - Potentiation
 - Antagonistic **

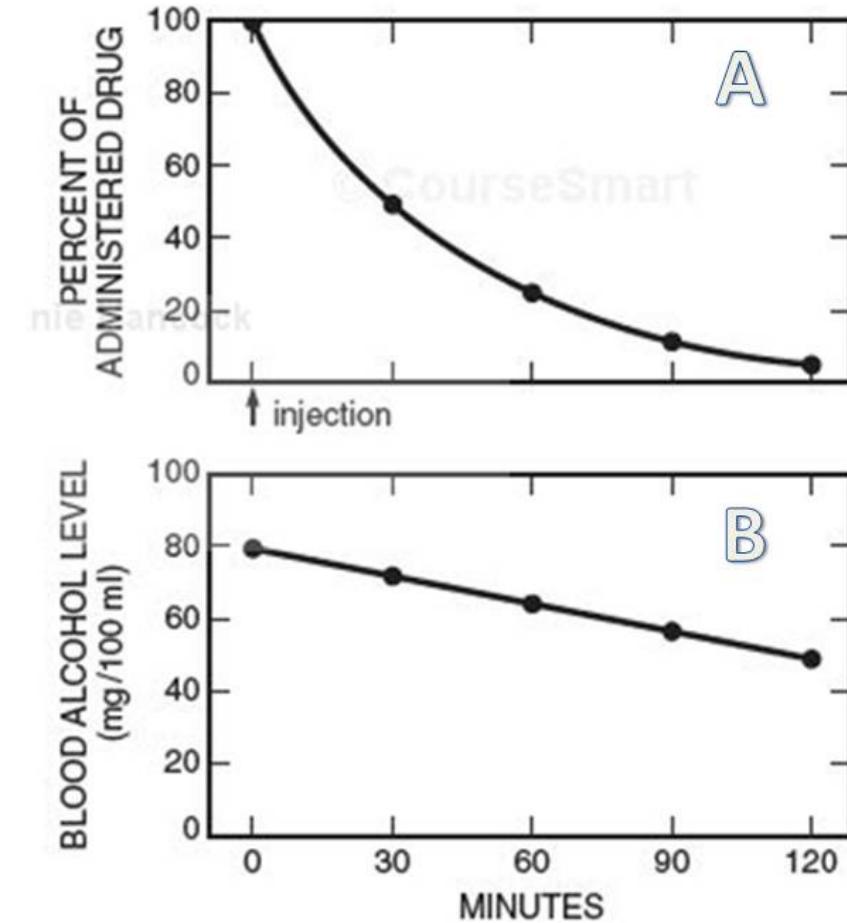


POSSIBLE MECHANISMS OF DRUG TOLERANCE

- **1) Drug Disposition Tolerance (Metabolic)**
 - aka “Pharmacokinetic Tolerance”, due to enzyme induction
- **2) Behavior Tolerance (Behavioral)**
 - Learning to adjust behavior to compensate for drug effects
- **3) Pharmacodynamic Tolerance (Cellular)**
 - Neurons adapt to long-term drug exposure

METABOLIC TOLERANCE

- **Drug disposition, or pharmacokinetic/metabolic, tolerance.**
 - Increased metabolism or excretion may reduce or alter the effect of the subsequent dose.
 - May relate to enzyme activity or the alteration of the pH of the urine.



BEHAVIOURAL TOLERANCE

■ Behavioral tolerance.

- Drug continues to have the same biochemical effect but with a reduced effect on behavior.
 - Reduced behavioral effect is a result of a drug user learning to compensate.

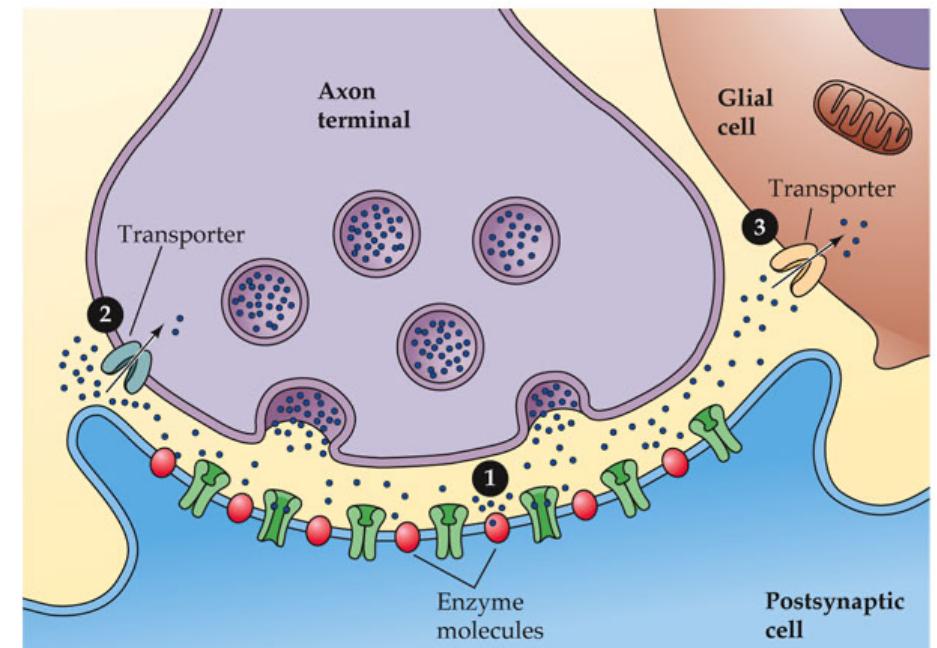


CELLULAR TOLERANCE

■ Pharmacodynamic tolerance.

- Leads to a reduced effectiveness of the drug.
- Neurons adapt to long-term drug exposure
- Causes withdrawal symptoms.

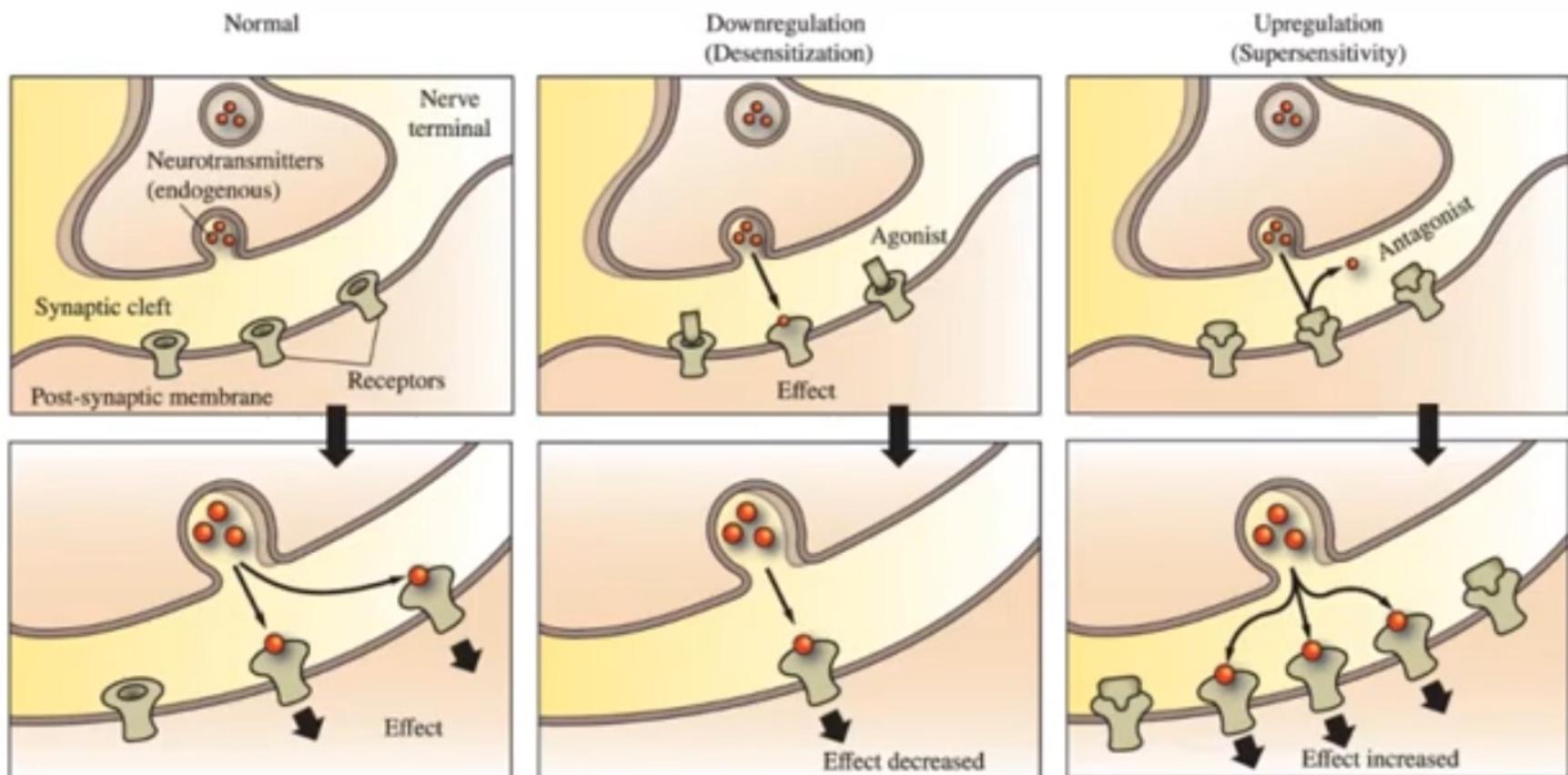
How might a neuron with overstimulated receptors adapt to this overstimulation? What about understimulation? →



PHARMACODYNAMIC AND BEHAVIORAL TOLERANCE

Down-regulation:
decreased number of
receptors in response to
overstimulation
(desensitization)

Up-regulation:
increased number of
receptors in response to
understimulation (**hyper-
or super- sensitivity**)



BRINGING IT ALL TOGETHER - MECHANISMS OF DRUG ACTION

- Today we've reviewed both:
 - **Pharmacodynamics** – the mechanisms by which a drug exerts its effects on the body
 - **Pharmacokinetics** – how the body handles drugs (absorption, distribution, metabolism/elimination)

<https://www.youtube.com/watch?v=lOqCxGINGPs>