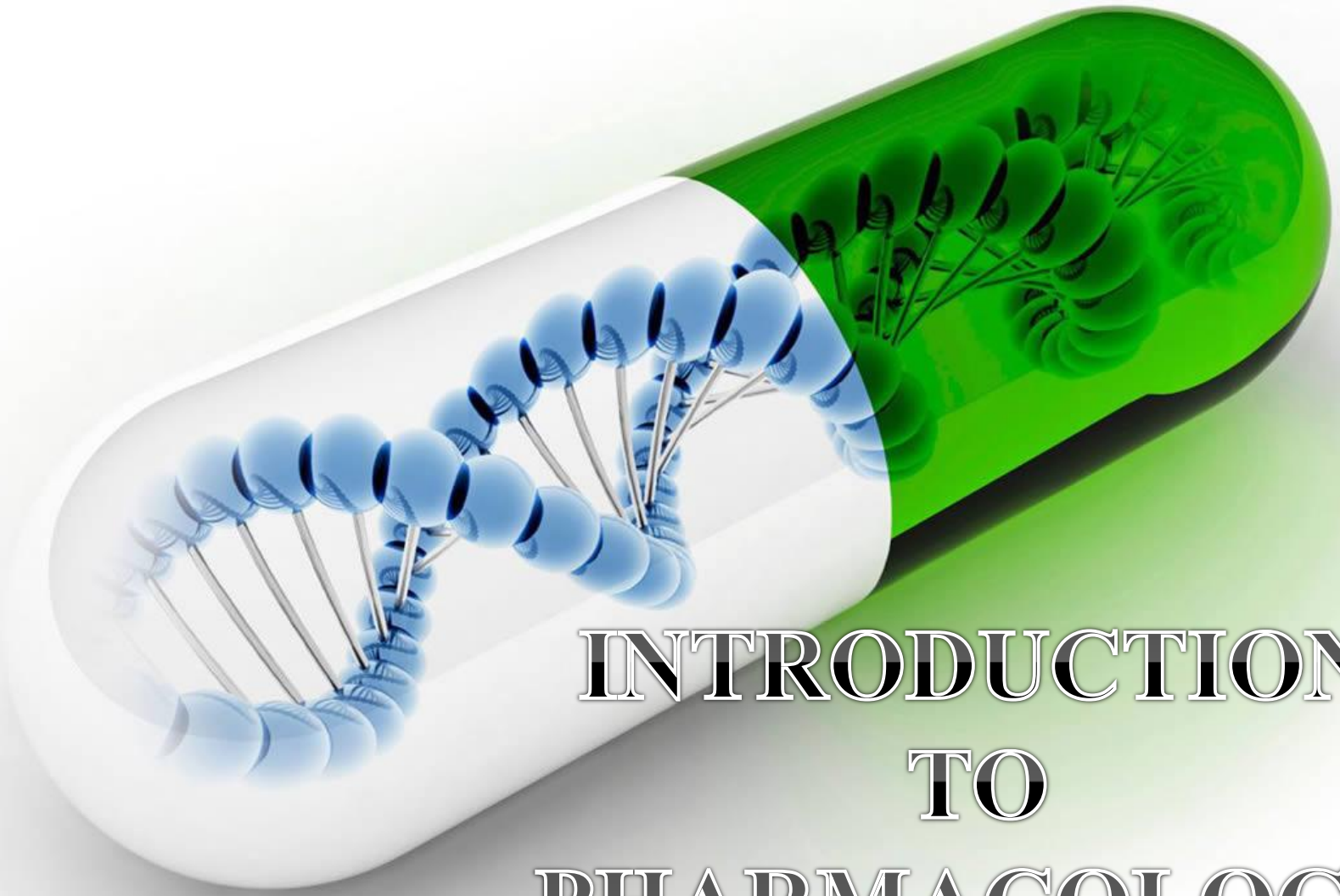
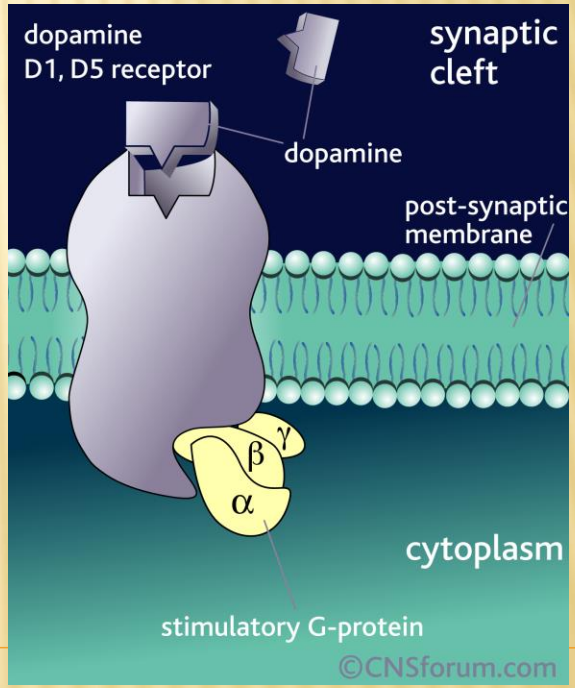


INTRODUCTION TO PHARMACOLOGY

(UNIT 1st)

PHARMACOLOGY BASICS



DEFINITIONS

- Pharmacokinetics
  - The process by which a drug is **absorbed**, **distributed**, **metabolized** and **eliminated** by the body
- Pharmacodynamics
  - The **interactions** of a drug and the receptors responsible for its action in the body

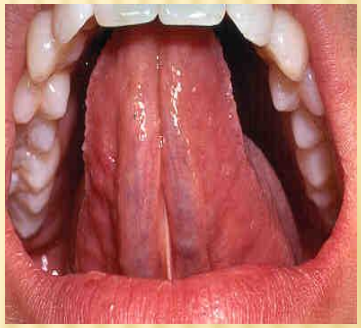
THE LIFE CYCLE OF A DRUG (PHARMACOKINETICS)

- Absorption
- Distribution
- Degradation
- Excretion

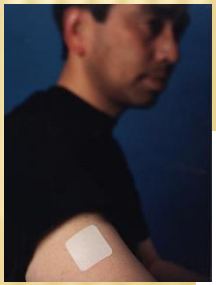
SLOW ABSORPTION

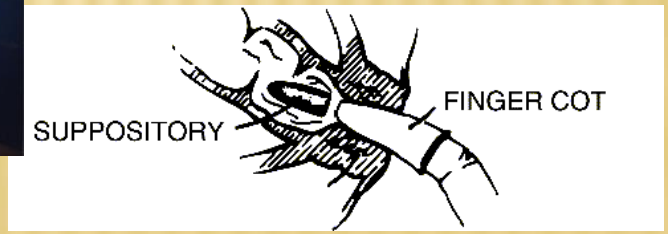
- Orally (swallowed)

- through Mucus Membranes
  - Oral Mucosa (e.g. sublingual)
  - Nasal Mucosa (e.g. insufflated)



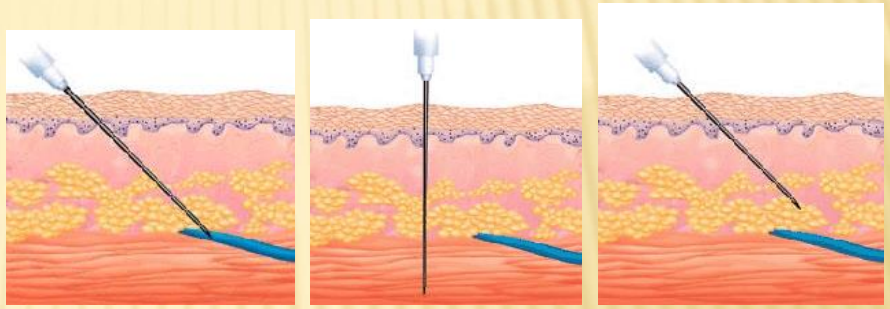
- Topical/Transdermal (through skin)
- Rectally (suppository)





FASTER ABSORPTION

- Parenterally (injection)
  - Intravenous (IV)
  - Intramuscular (IM)
  - Subcutaneous (SC)
  - Intraperitoneal (IP)



- Inhaled (through lungs)

FASTEST ABSORPTION

- Directly into brain
  - Intracerebral (into brain tissue)
  - Intracerebroventricular (into brain ventricles)

General Principle: The faster the absorption, the quicker the onset, the higher the addictiveness, but the shorter the duration

ABSORPTION: SOLUBILITY

- Water-soluble
  - Ionized (have electrical charge)
  - Crosses through pores in capillaries, but not cell membranes
- Lipid(fat)-soluble
  - Non-ionized (no electrical charge)
  - Crosses pores, cell membranes, blood-brain-barrier

Dissociation constant or pKa → indicates the pH where 50% of the drug is ionized (water soluble) and 50% non-ionized (lipid soluble);

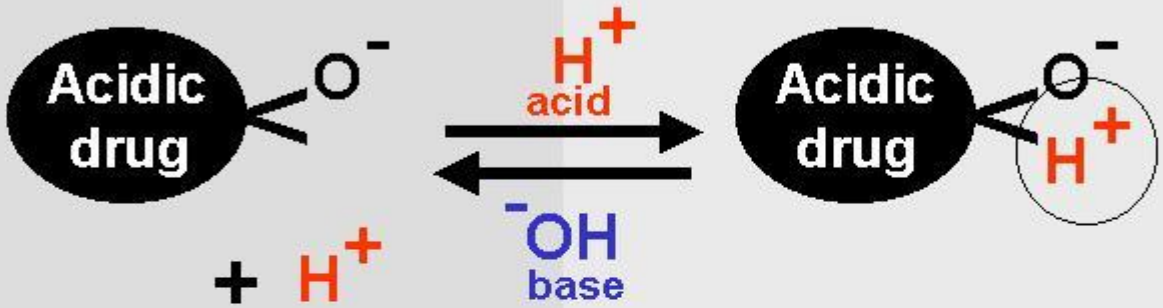
pKeq = pH + log [X]ionized/[X]non-ionized

This affects a drug's solubility, permeability, binding, and other characteristics.

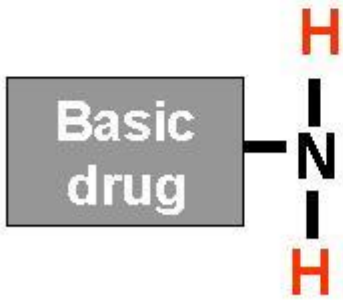
Uncharged drug	WATER SOLUBLE drug must be charged to be excreted in urine	LIPID SOLUBLE drug must be uncharged to cross a membrane

(hydroxyl group)

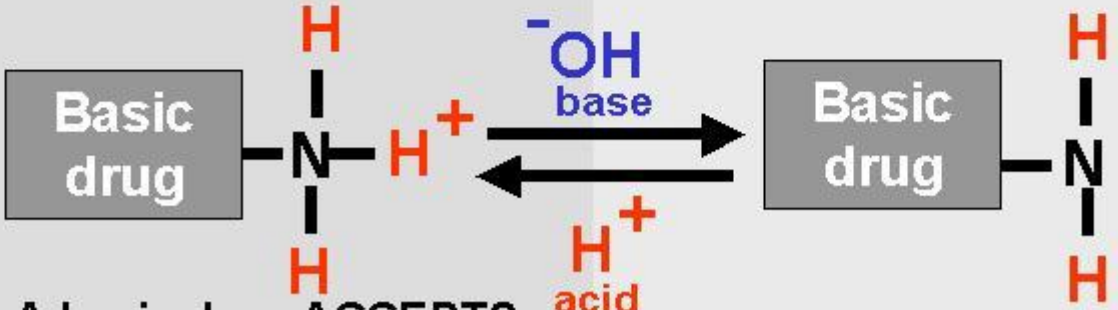
(water = H^+ + ^-OH)



An acidic drug DONATES a H^+ when dissolved in water



(amine group)



A basic drug ACCEPTS a H^+ when dissolved in water

DISTRIBUTION: DEPENDS ON BLOOD FLOW AND BLOOD BRAIN BARRIER

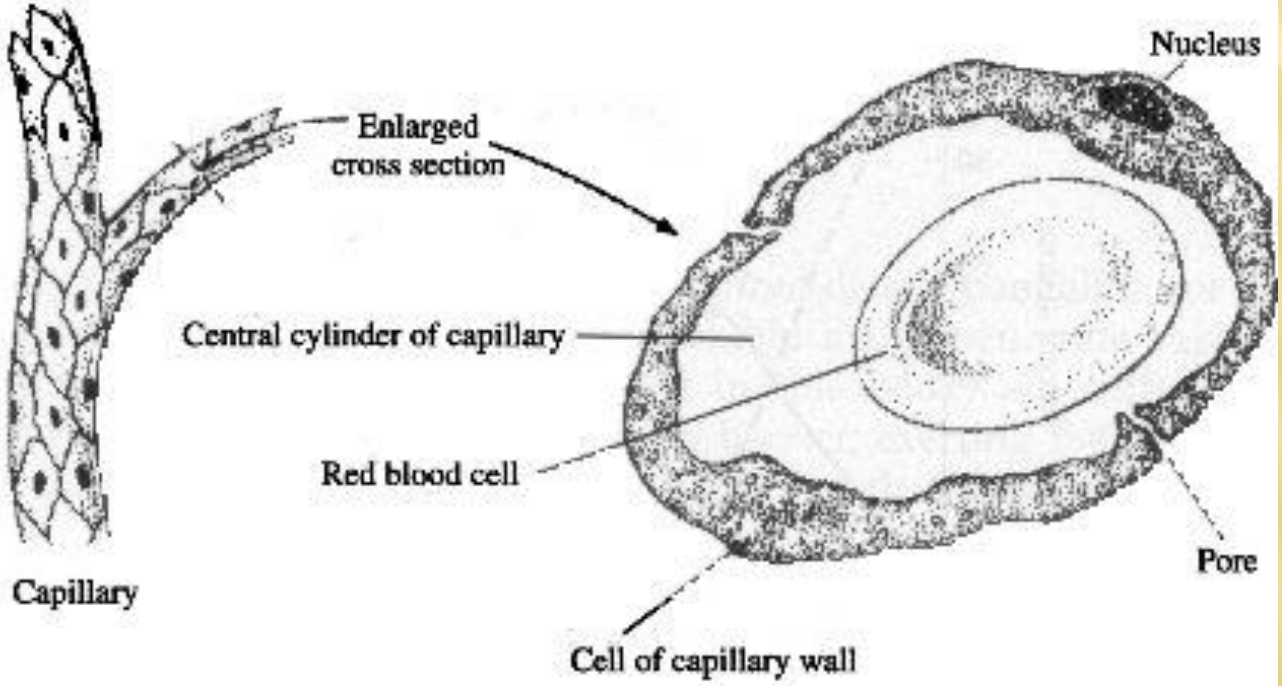


FIGURE 1.8 Cross section of a blood capillary. Within the capillary are the fluids, proteins, and cells of the blood, including the red blood cells. The capillary itself is made up of cells that completely surround and define the central cylinder (or lumen) of the capillary. Water-filled pores form channels, allowing free flow of blood plasma and extracellular fluid.

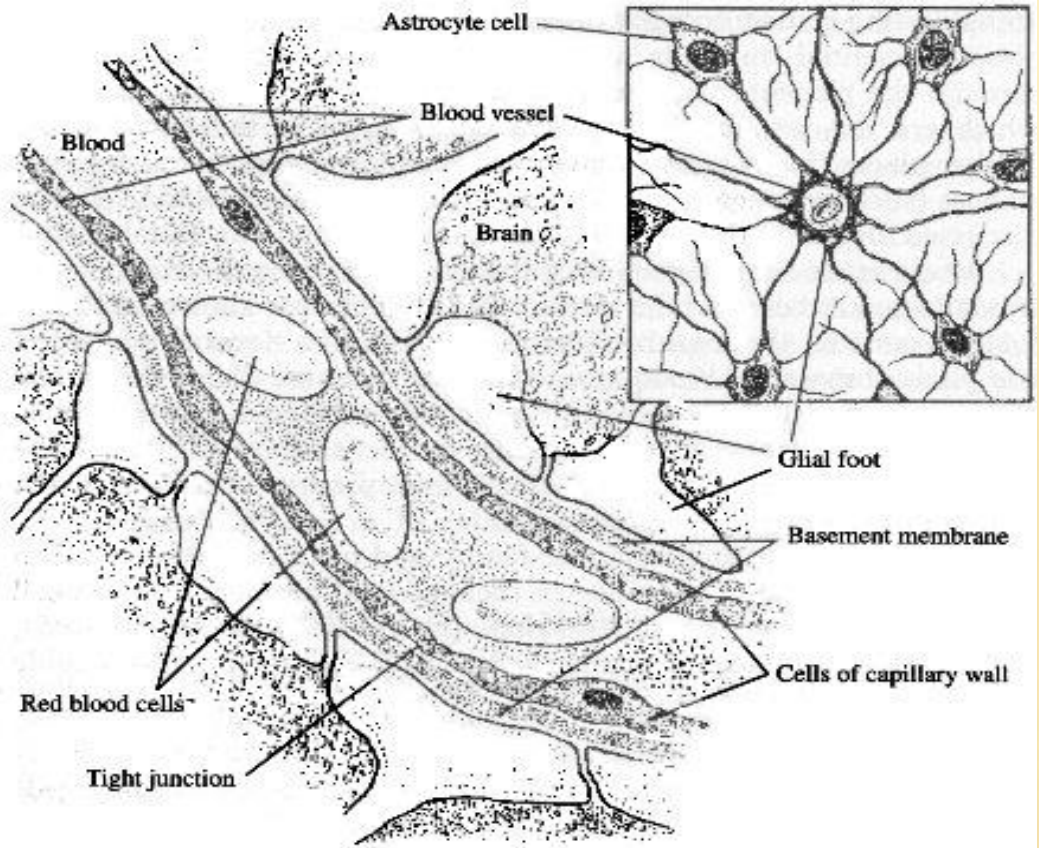


FIGURE 1.10 Blood-brain barrier. Blood and brain are separated by capillary cells packed tightly together and by a fatty barrier called the glial sheath, which is made up of extensions (glial feet) from nearby astrocyte cells (*inset*). A drug diffusing from blood to brain must move through the cells of the capillary wall because there are tight junctions rather than pores between the cells; the drug must then move through the fatty glial sheath.

- Excludes ionized substances;
- Active transport mechanisms;
- Not uniform – leaky (circumventricular areas)

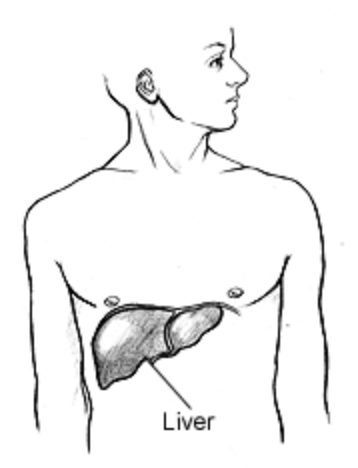
BIOAVAILABILITY

- The fraction of an administered dose of drug that reaches the blood stream.
- What determines bioavailability?
  - Physical properties of the drug (hydrophobicity, pKa, solubility)
  - The drug formulation (immediate release, delayed release, etc.)
  - If the drug is administered in a fed or fasted state
  - Gastric emptying rate
  - Circadian differences
  - Interactions with other drugs
  - Age
  - Diet
  - Gender
  - Disease state

DEPOT BINDING (ACCUMULATION IN FATTY TISSUE)

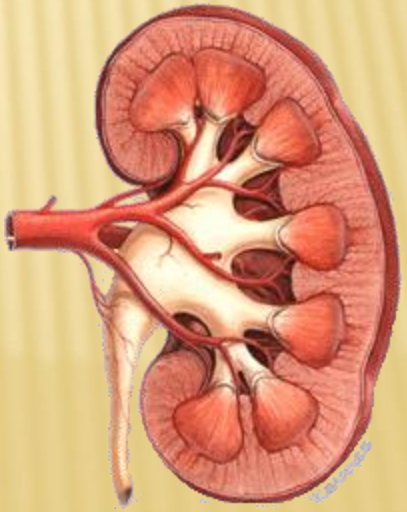
- Drugs bind to “depot sites” or “silent receptors” (fat, muscle, organs, bones, etc)
- Depot binding reduces bioavailability, slows elimination, can increase drug detection window
- Depot-bound drugs can be released during sudden weight loss – may account for flashback experiences?

Degradation & Excretion



- Liver
  - Enzymes(cytochrome P-450) transform drugs into more water-soluble metabolites
  - Repeated drug exposure increases efficiency → tolerance

- Kidneys
  - Traps water-soluble (ionized) compounds for elimination via urine (primarily), feces, air, sweat



EXCRETION: OTHER ROUTES

- Lungs
  - alcohol breath
- Breast milk
  - acidic ---> ion traps alkaloids
  - alcohol: same concentration as blood
  - antibiotics
- Also bile, skin, saliva ~~

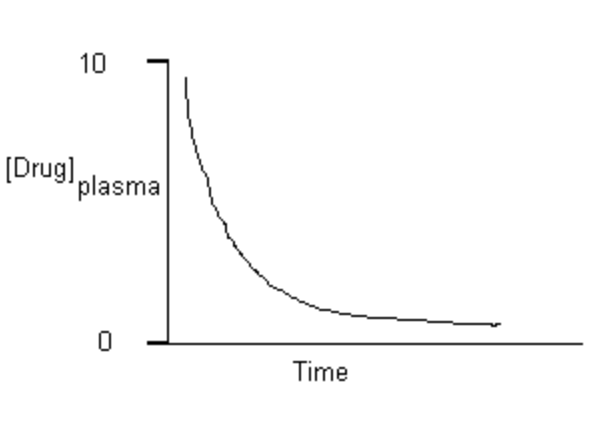
METABOLISM AND ELIMINATION (CONT.)

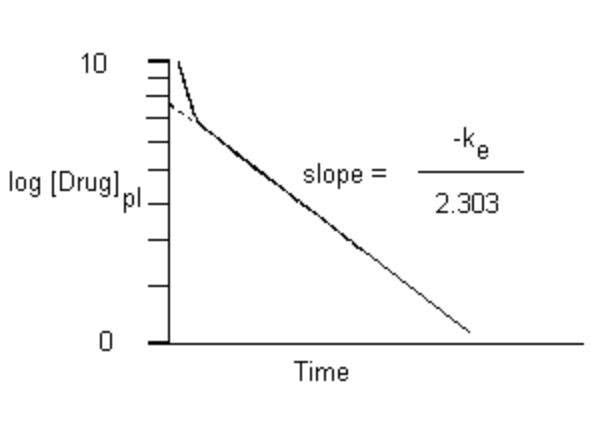
- Half-lives and Kinetics
  - Half-life:
    - Plasma half-life: Time it takes for plasma concentration of a drug to drop to 50% of initial level.
    - Whole body half-life: Time it takes to eliminate half of the body content of a drug.
  - Factors affecting half-life
    - age
    - renal excretion
    - liver metabolism
    - protein binding

First order kinetics

A constant *<u>fraction</u>* of drug is eliminated per unit of time.

When drug concentration is high, rate of disappearance is high.





Zero order kinetics

Rate of elimination is constant.

Rate of elimination is independent of drug concentration.

Constant *amount* eliminated per unit of time.

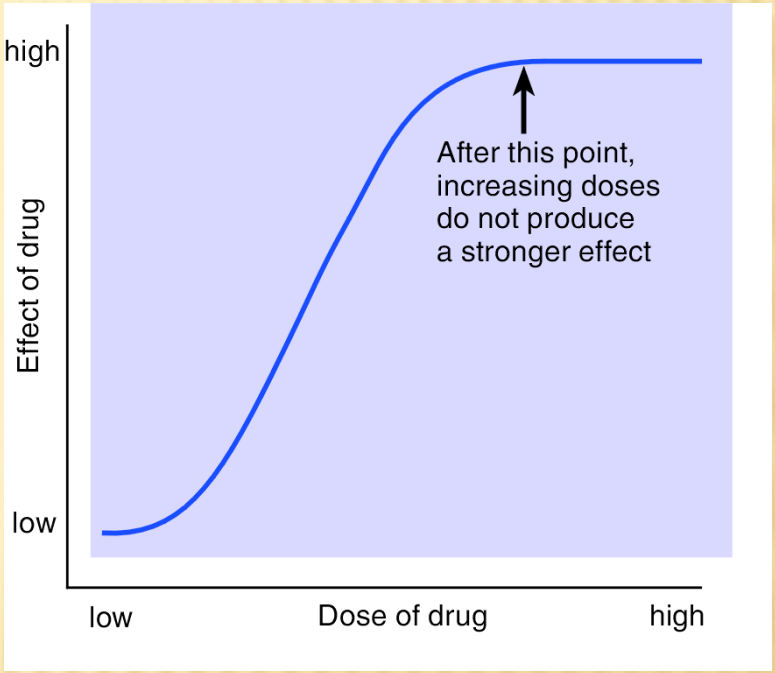
Example: Alcohol

COMPARISON

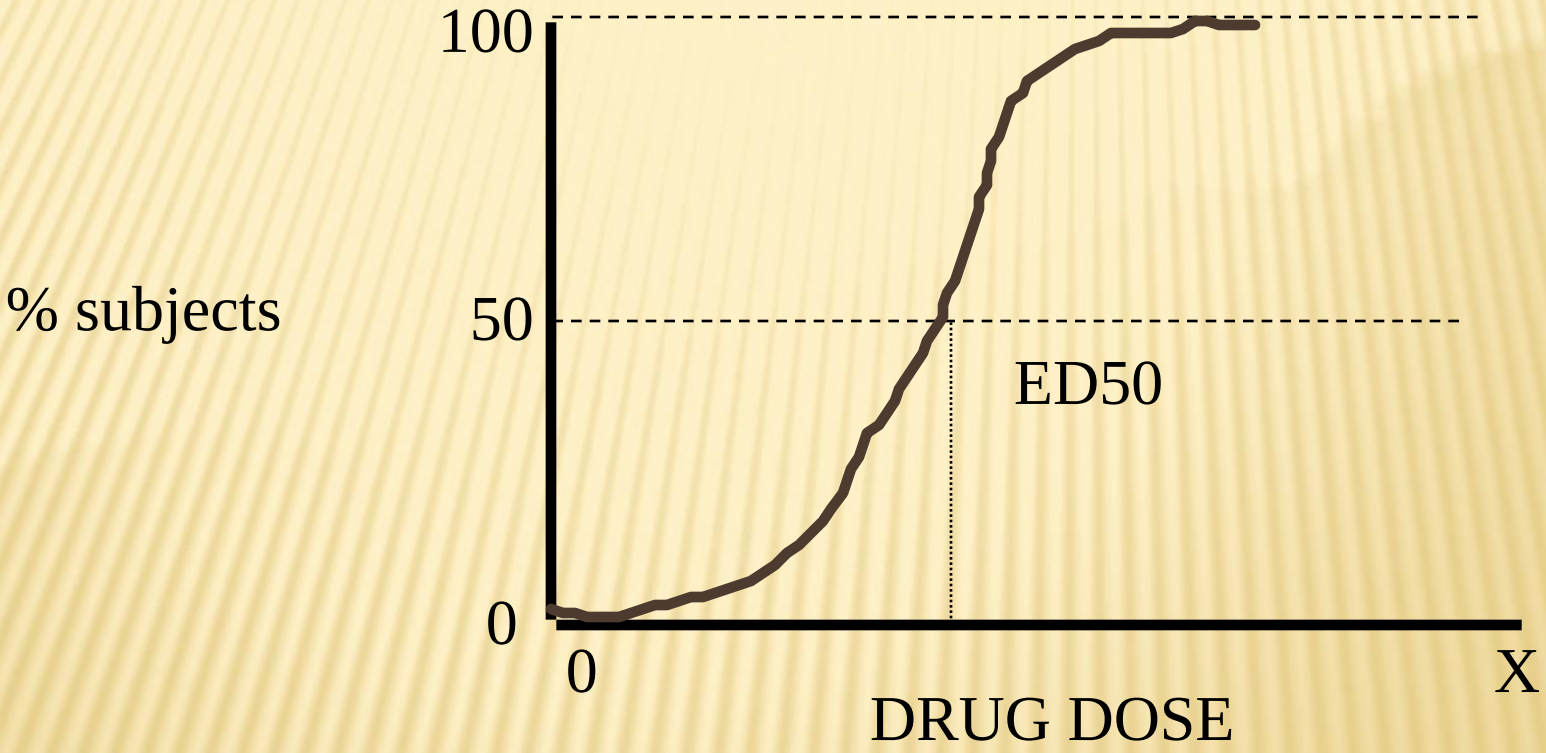
- First Order Elimination
  - [drug] decreases exponentially w/ time
  - Rate of elimination is proportional to [drug]
  - Plot of log [drug] or ln[drug] vs. time are linear
  - $t_{1/2}$ is constant regardless of [drug]
- Zero Order Elimination
  - [drug] decreases linearly with time
  - Rate of elimination is constant
  - Rate of elimination is independent of [drug]
  - No true $t_{1/2}$

DRUG EFFECTIVENESS

- Dose-response (DR) curve
  - 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
- The effectiveness of a drug is considered relative to its safety (therapeutic index)

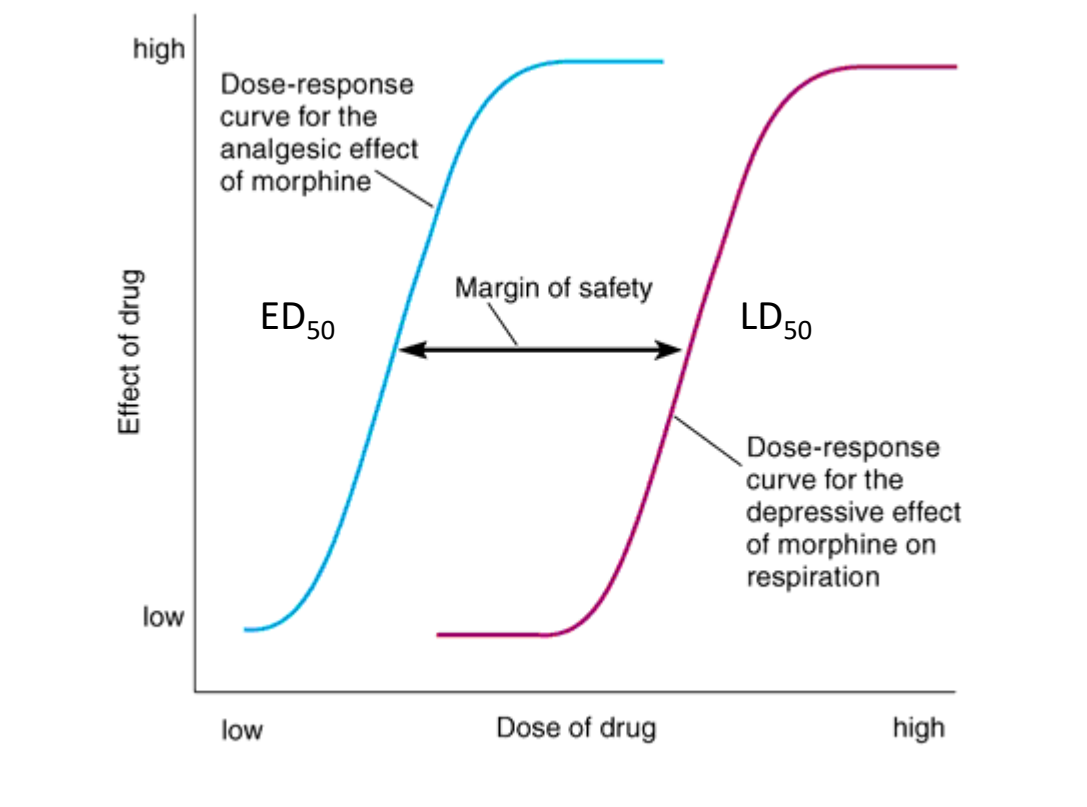


ED_{50} = effective dose in 50% of population



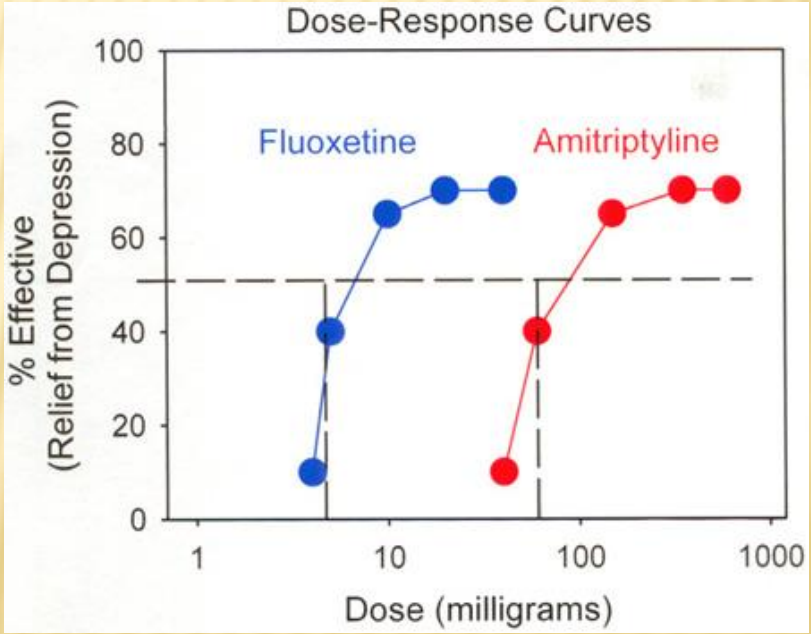
Therapeutic Index

- Effective dose (ED_{50}) = dose at which 50% population shows response
- Lethal dose (LD_{50}) =dose at which 50% population dies
- TI = LD_{50}/ED_{50}, an indication of safety of a drug (higher is better)

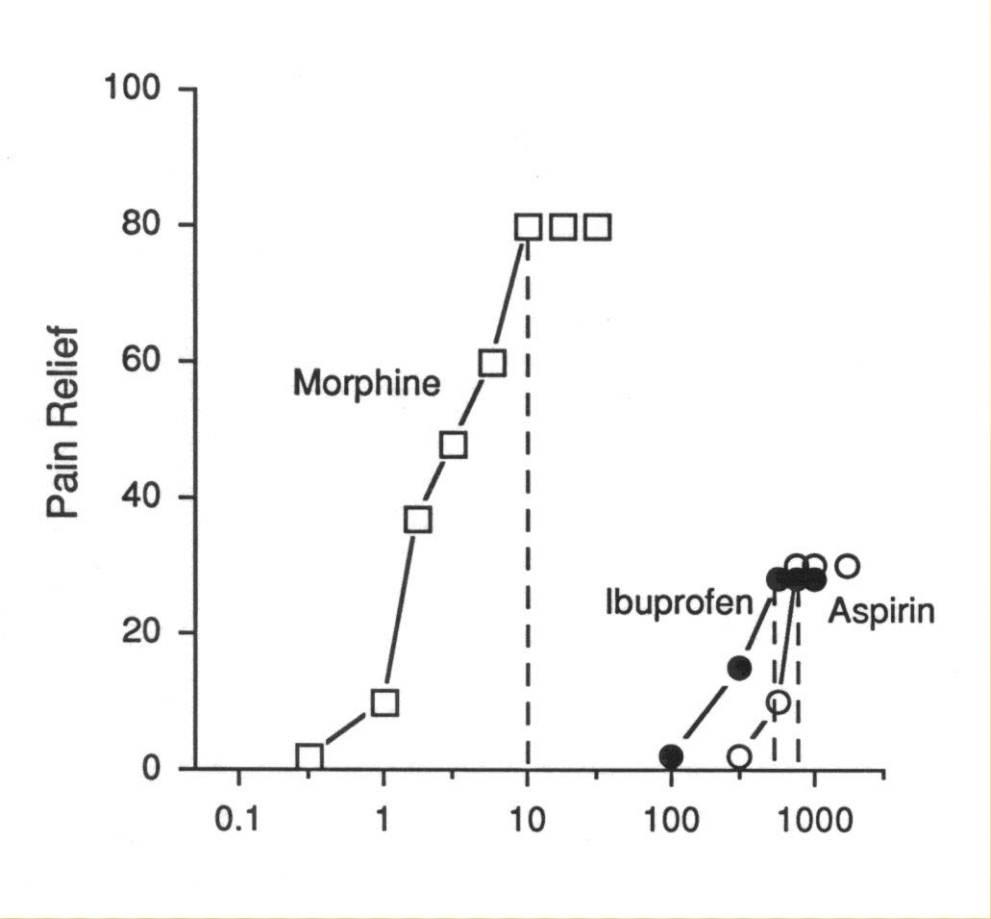


Potency

- Relative strength of response for a given dose
  - Effective concentration (EC_{50}) is the concentration of an agonist needed to elicit half of the maximum biological response of the agonist
  - The potency of an agonist is inversely related to its EC_{50} value
- D-R curve shifts left with greater potency

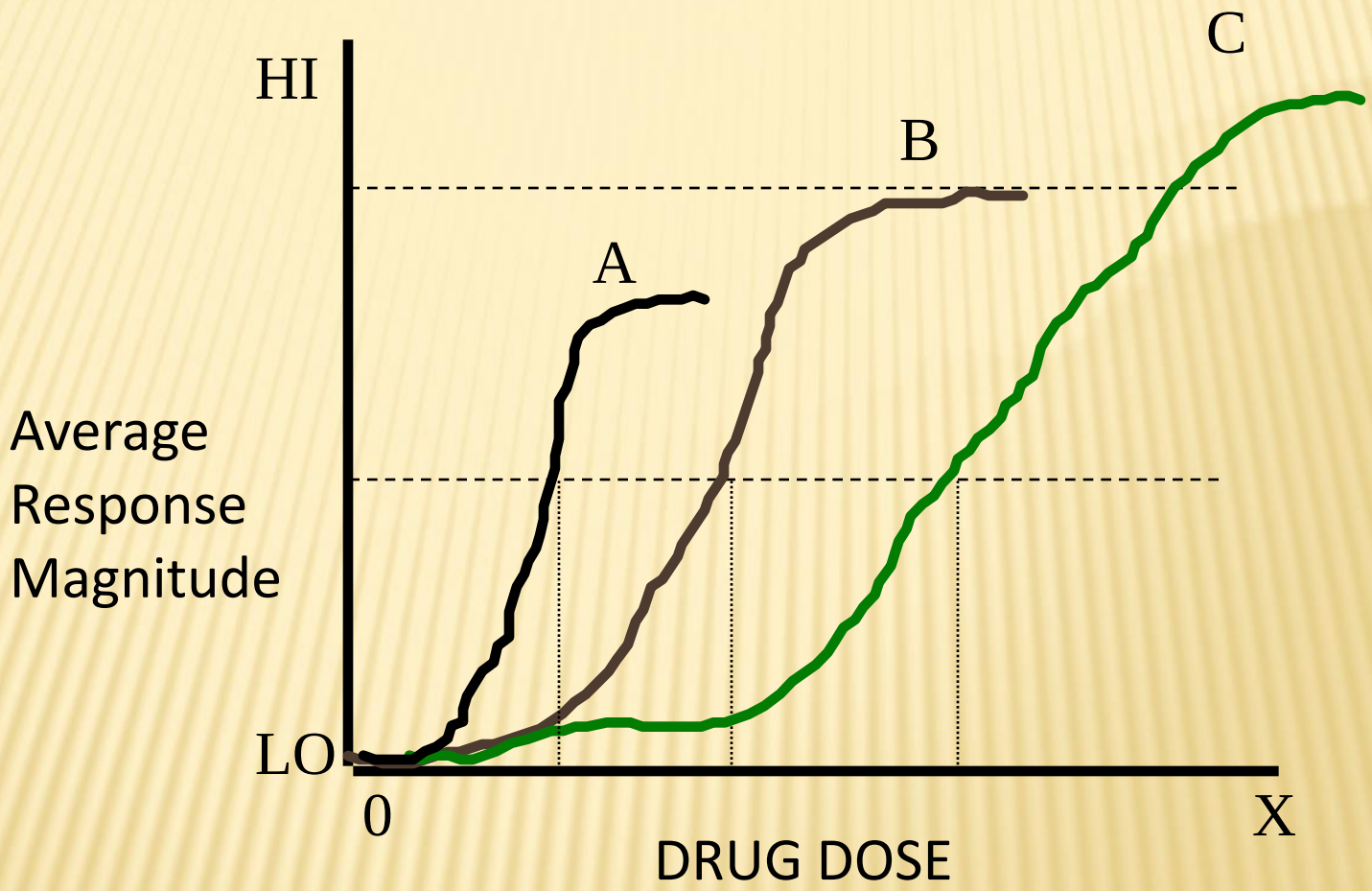


Efficacy



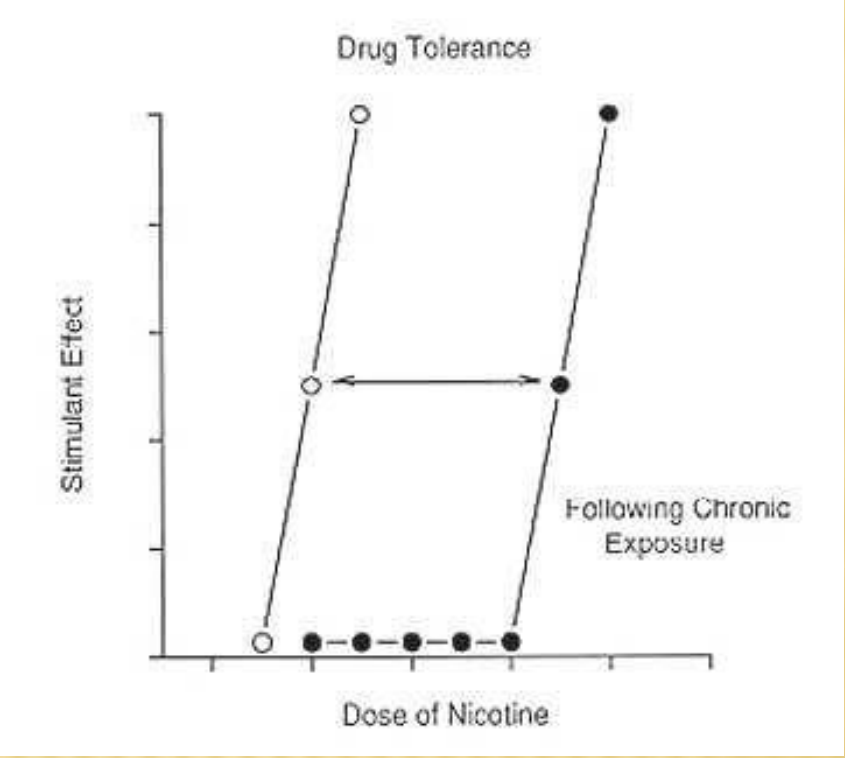
- Maximum possible effect relative to other agents
- Indicated by peak of D-R curve
- Full agonist = 100% efficacy
- Partial agonist = 50% efficacy
- Antagonist = 0% efficacy
- Inverse agonist = -100% efficacy

Comparisons

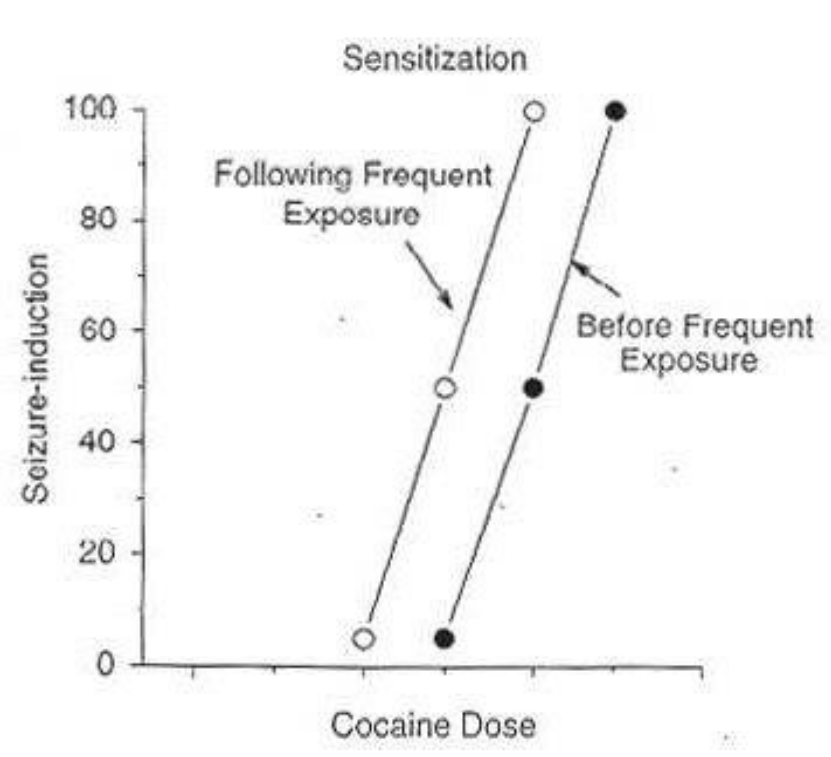


Tolerance
(desensitization)

- Decreased response to same dose with repeated (**constant)** exposure
- *or* more drug needed to achieve same effect
- Right-ward shift of D-R curve
- Sometimes occurs in an acute dose (e.g. alcohol)
- Can develop across drugs (cross-tolerance)
- Caused by compensatory mechanisms that oppose the effects of the drug



Sensitization



- Increased response to same dose with repeated (**binge-like**) exposure
- *or* less drug needed to achieve same effect
- Left-ward shift in D-R curve
- Sometimes occurs in an acute dose (e.g. amphetamine)
- Can develop across drugs (cross-sensitization)

It is possible to develop tolerance to some side effects AND sensitization to other side effects of the same drug

Mechanisms of Tolerance and Sensitization

- **Pharmacokinetic**
  - changes in drug availability at site of action (decreased bioavailability)
    - Decreased absorption
    - Increased binding to depot sites
- **Pharmacodynamic**
  - changes in drug-receptor interaction
    - G-protein uncoupling
    - Down regulation of receptors

Other Mechanisms of Tolerance and Sensitization

- **Psychological**

  As the user becomes familiar with the drug's effects, s/he learns tricks to hide or counteract the effects.

  Set (expectations) and setting (environment)
  Motivational
  Habituation
  Classical and instrumental conditioning (automatic physiological change in response to cues)

- **Metabolic**

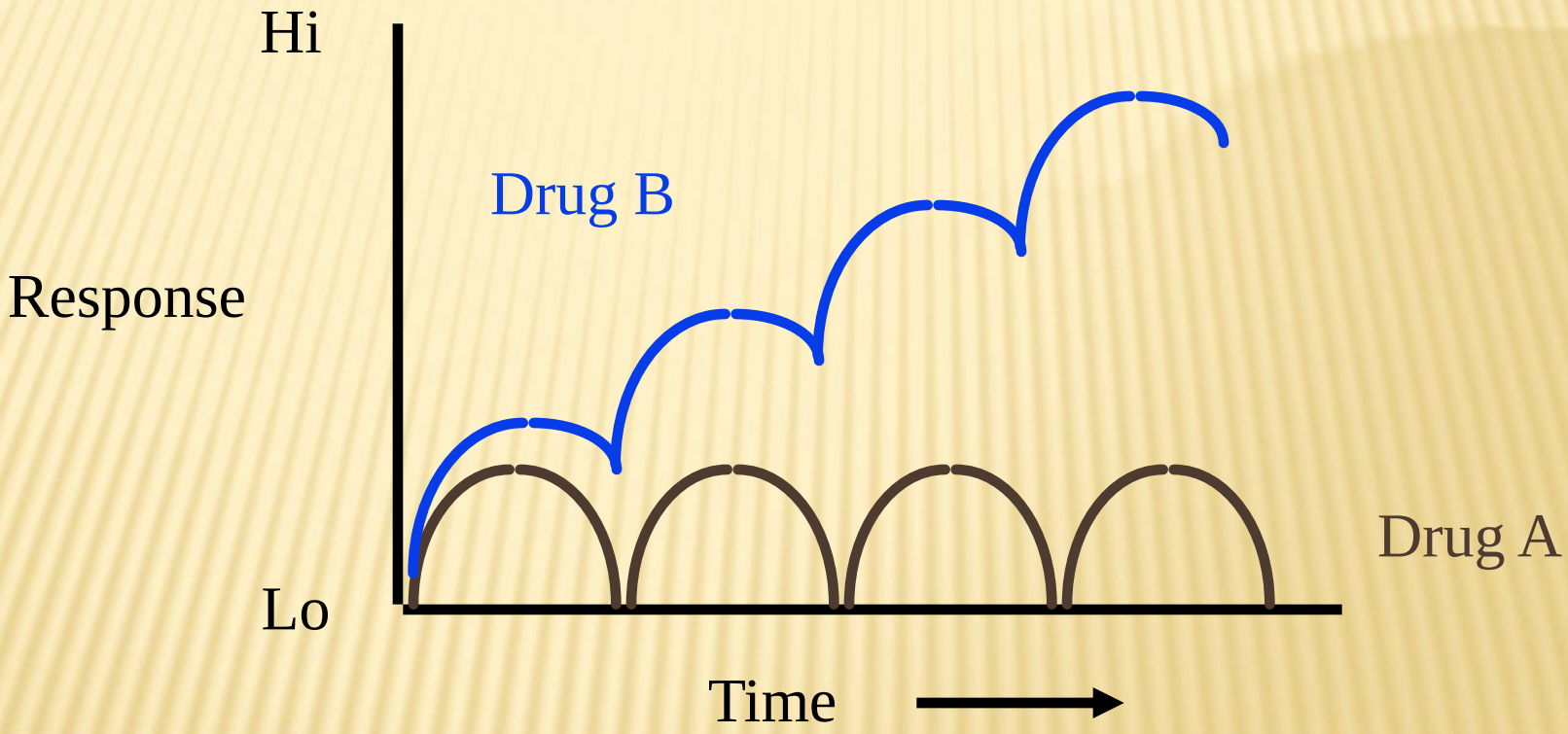
  The user is able to break down and/or excrete the drug more quickly due to repeated exposure.

  Increased excretion

DRUG-DRUG INTERACTIONS

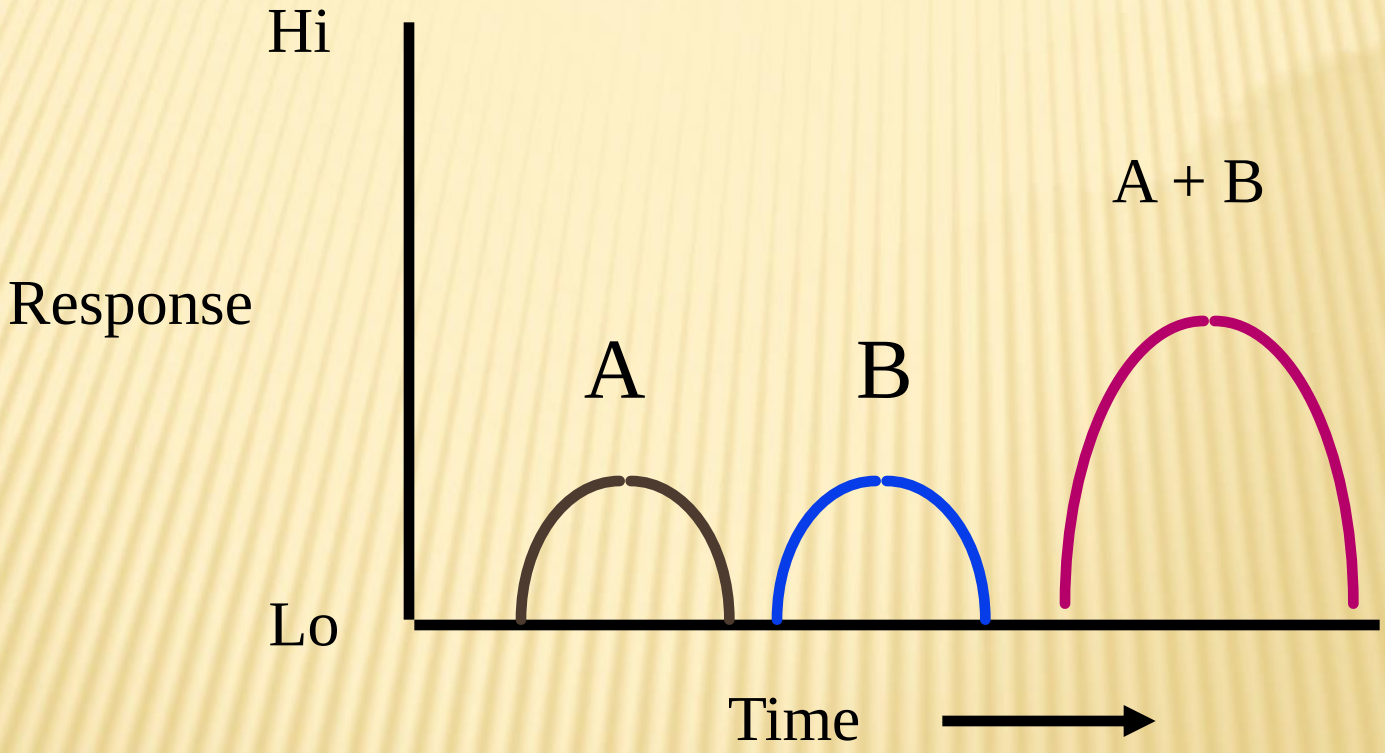
- Pharmacokinetic and pharmacodynamic
  - With pharmacokinetic drug interactions, one drug affects the absorption, distribution, metabolism, or excretion of another.
  - With pharmacodynamic drug interactions, two drugs have interactive effects in the brain.
  - Either type of drug interaction can result in adverse effects in some individuals.
  - In terms of efficacy, there can be several types of interactions between medications: cumulative, additive, synergistic, and antagonistic.

Cumulative Effects



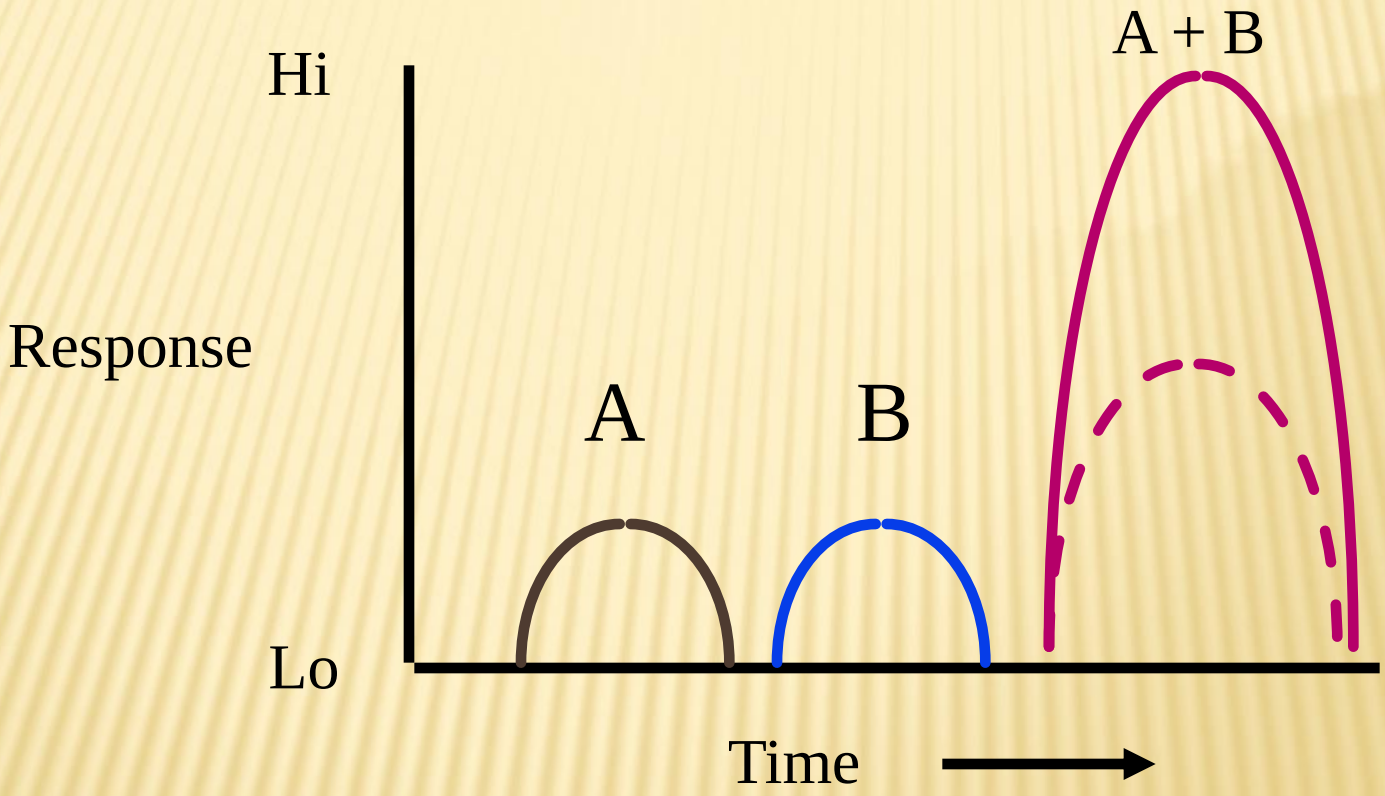
The condition in which repeated administration of a **drug may produce effects that are more pronounced than those produced by the first dose.**

Additive Effects



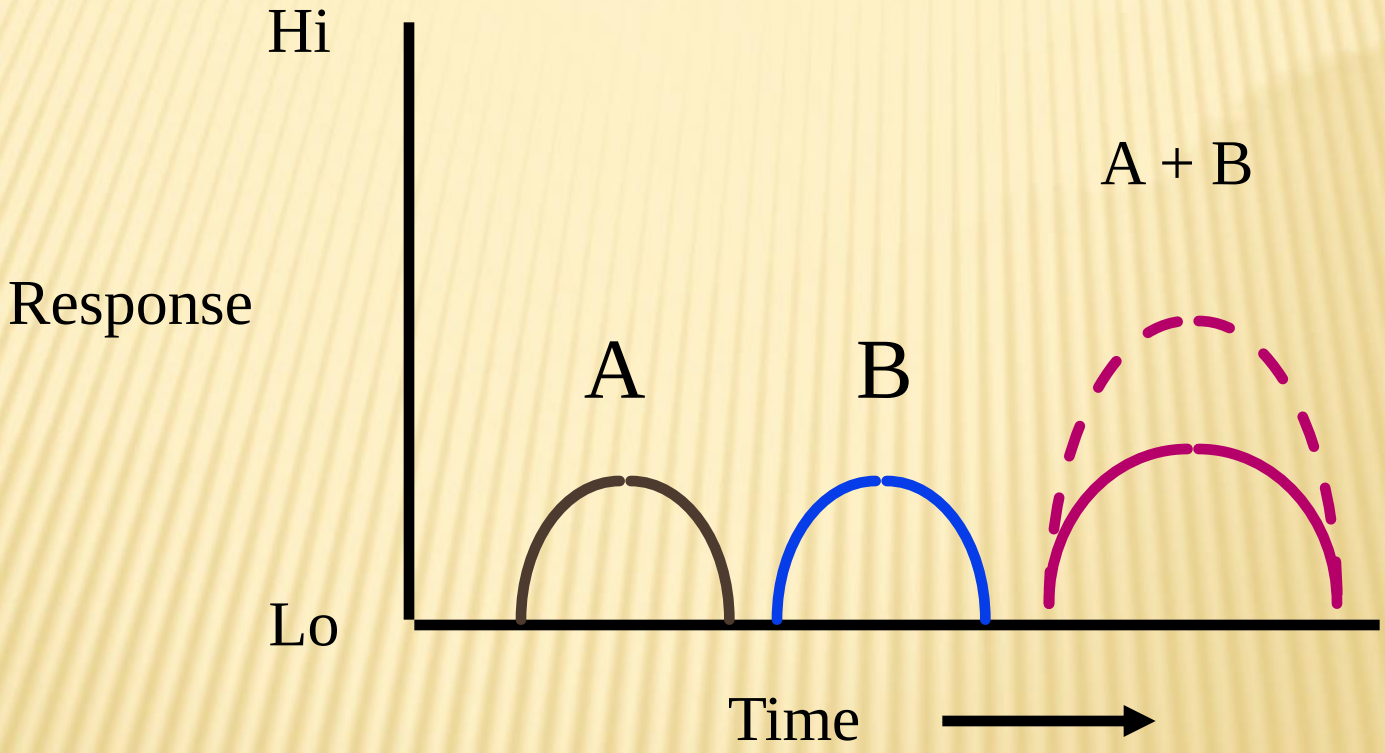
The effect of two chemicals is equal to the sum of the effect of the two chemicals taken separately, eg., aspirin and motrin.

Synergistic Effects



The effect of two chemicals taken together is greater than the sum of their separate effect at the same doses, e.g., alcohol and other drugs

Antagonistic Effects

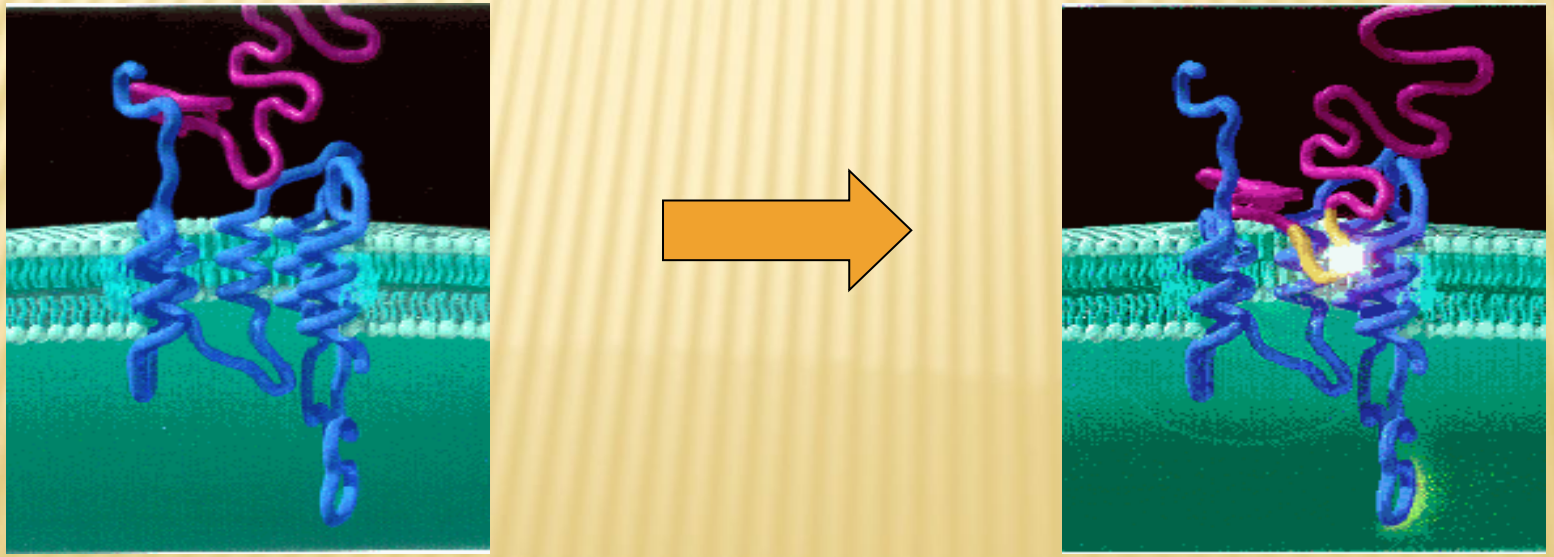


The effect of two chemicals taken together is less than the sum of their separate effect at the same doses

Pharmacodynamics

- Receptor
  - target/site of drug action (e.g. genetically-coded proteins embedded in neural membrane)

- Lock and key or induced-fit models
  - drug acts as key, receptor as lock, combination yields response
  - dynamic and flexible interaction



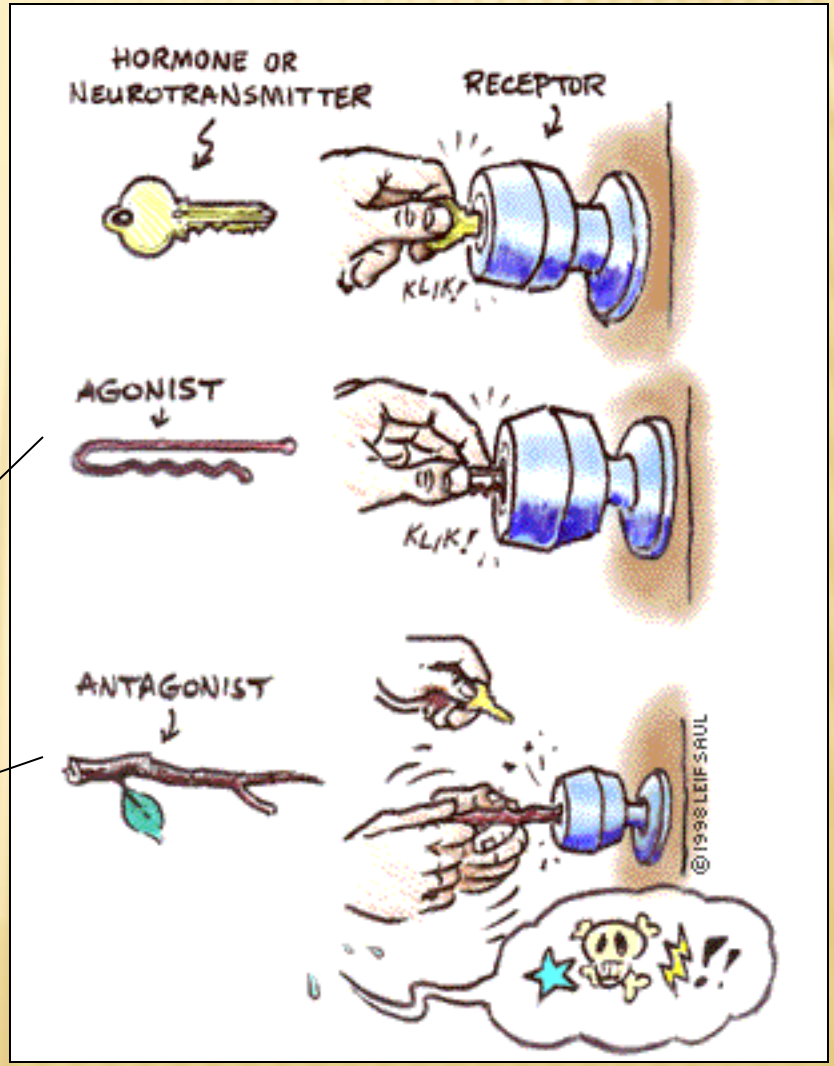
Pharmacodynamics (cont.)

- Affinity
  - propensity of a drug to bind with a receptor
- Selectivity
  - specific affinity for certain receptors (vs. others)

AGONISM AND ANTAGONISM

Agonists facilitate receptor response

Antagonists inhibit receptor response



(direct ant/agonists)

MODES OF ACTION

- Agonism
  - A compound that does the job of a natural substance.
  - Does not effect the rate of an enzyme catalyzed reaction.
- Up/down regulation
  - Tolerance/sensitivity at the cellular level may be due to a change in # of receptors (without the appropriate subunit) due to changes in stimulation
- Antagonism
  - A compound inhibits an enzyme from doing its job.
  - Slows down an enzymatically catalyzed reaction.

AGONISTS/ANTAGONISTS

- Full
- Partial
- Direct/Competitive
- Indirect/Noncompetitive
- Inverse

A single drug can bind to a single receptor and cause a mix of effects (agonist, partial agonist, inverse agonist, antagonist)

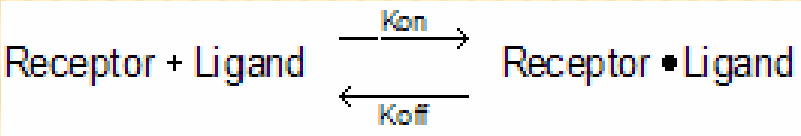
Functional Selectivity Hypothesis:
Conformational change induced by a ligand-receptor interaction may cause differential functional activation depending on the G-protein and other proteins associated with the target receptor

Important implications of drug-receptor interaction

- drugs can potentially alter rate of any bodily/brain function
- drugs cannot impart entirely new functions to cells
- drugs do not create effects, only modify ongoing ones
- drugs can allow for effects outside of normal physiological range

LAW OF MASS ACTION
(A MODEL TO EXPLAIN LIGAND-RECEPTOR BINDING)

- When a drug combines with a receptor, it does so at a rate which is dependent on the concentration of the drug and of the receptor
- Assumes it's a reversible reaction



- Equilibrium dissociation (Kd) and association/affinity (Ka) constants
  - K_d = Kon/Koff = [D][R]/[DR]
  - K_a = 1/Kd = Koff/Kon = [DR]/[D][R]