Pharmacology

Pharmacokinetics

Pharmacodynamics

Pharmacokinetics

- Time course of drug absorption, distribution, metabolism, excretion

How the drug comes and goes.

Pharmacokinetic Processes

"LADME" is key

Liberation

Metabolism

Absorption

Excretion

Distribution

Liberation

- Applies to drugs given orally
- Components
  - Release of drug from pill, tablet, capsule
  - Dissolving of active drug in GI fluids

Ex: Enteric coated aspirin slows absorption in stomach vs non-coated

Absorption

- Movement from administration site into circulation

Factors Affecting Liberation/Absorption

- Formulation factors
  - Tablet disintegration
  - Inert ingredient / solvent effects
  - Solubility
  - Drug pH
  - Concentration

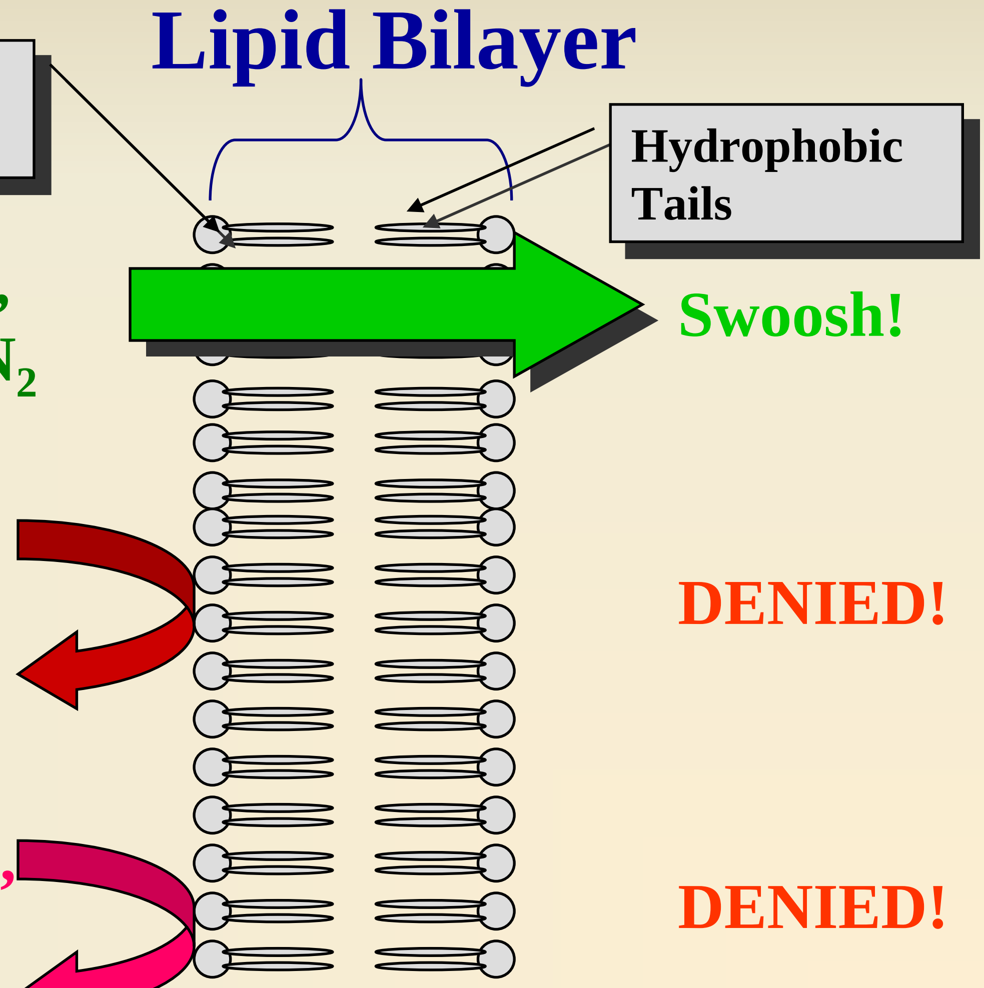
- Patient factors
  - Absorbing surface
  - Blood flow
  - Environmental pH
  - Disease states
  - Interactions with food, other drugs

Membranes and Absorption

Small, uncharged — **H_2O, urea, CO_2, O_2, N_2**

Large, uncharged — **Glucose, Sucrose**

Small charged ions — **H^+, Na^+, K^+, Ca^{2+}, Cl^-, HCO_3^-**



LaChatlier's Principle

a.k.a. Mass Action

A reaction at equilibrium responds to stress in a way to best return to equilibrium

System at Equilibrium

$$\overbrace{4\ Na^{+} + 4\ Cl^{-} \longleftrightarrow 4\ NaCl}$$

An example of LaChatlier’s Principle

Ionization

Acids — **Release/Donate H^+**

$$HA \rightleftharpoons H^+ + A^-$$

Ionized form

Bases — **Bind/Accept H^+**

$$H^+ + B^- \rightleftharpoons HB$$

Non-ionized form

Environmental pH and Ionization

If we put an acidic drug in an environment with a lot of H^+ (low pH) what will this equilibrium do?

$$HA \rightleftharpoons \uparrow H^+ + A^-$$

Non-ionized form predominates!

A real live, actual clinical question...

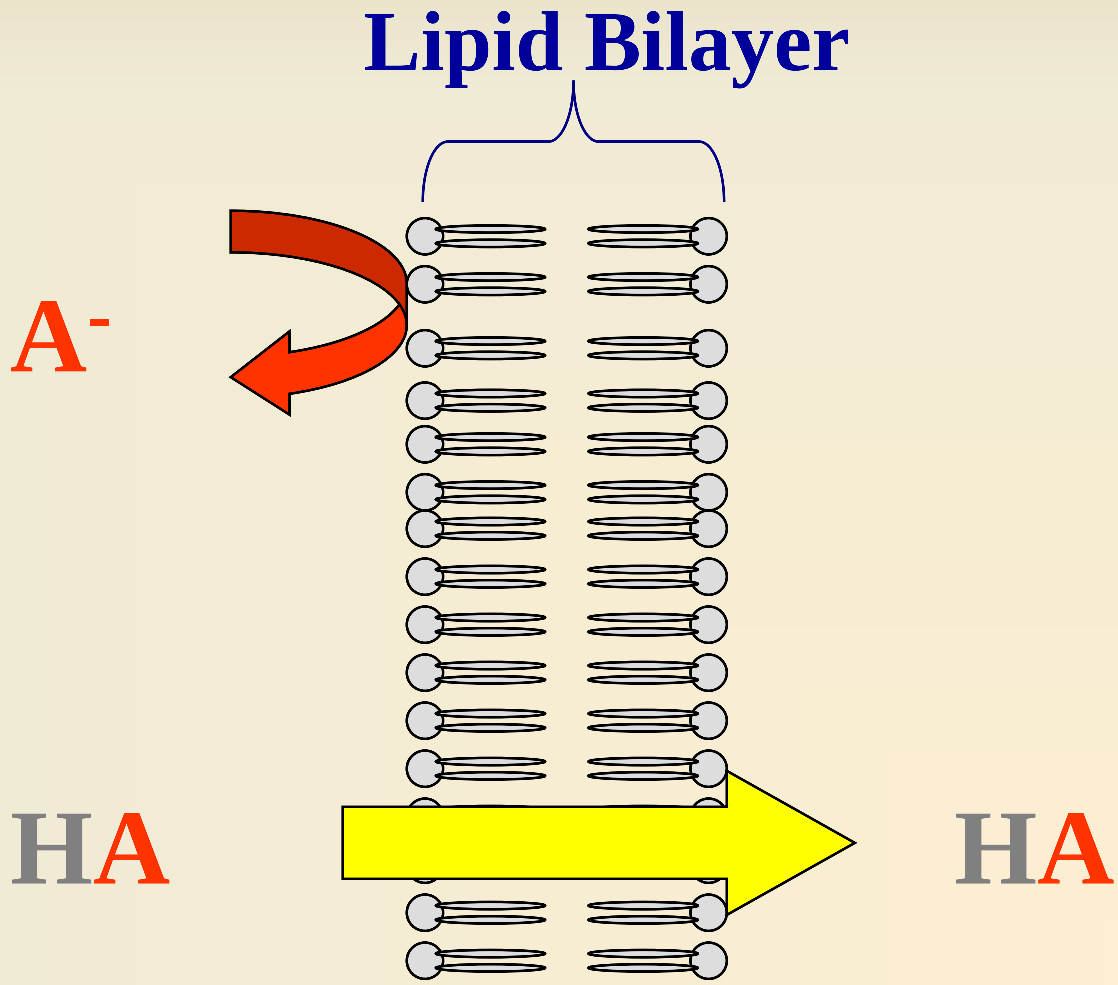
Aspirin is an acidic drug. In the stomach will it exist mostly in ionized or non-ionized form?

Why?

How will this affect aspirin absorption?

Ionized form (charged)

Ionized form (uncharged)



Moral of the story...

Acidic drugs are best absorbed from acidic environments

Basic drugs are best absorbed from basic environments

So...

To ⇑ absorption of an acidic drug…

acidify the environment

To ⇓ absorption of an acidic drug…

alkalanize the environment...

Distribution

- Rate of perfusion
- Plasma protein (albumin) binding
- Accumulation in tissues
- Ability to cross membranes
  - Blood-brain barrier
  - Placental barrier

Plasma Protein Binding

warfarin (Coumadin) is highly protein bound (99%). Aspirin binds to the same site on serum proteins as does Coumadin. If a patient on Coumadin also takes aspirin, what will happen?

1) Why?
2) Why do we care?

Blood-Brain Barrier

The blood brain barrier consists of cell tightly packed around the capillaries of the CNS. What characteristics must a drug possess to easily cross this barrier?

Why?

Metabolism (Biotransformation)

- Two effects
  - Transformation to less active metabolite
  - Enhancement of solubility
- Liver = primary site
- Liver disease
  - Slows metabolism
  - Prolongs effects

Hepatic ‘First-Pass’ Metabolism

- Affects orally administered drugs
- Metabolism of drug by liver before drug reaches systemic circulation
- Drug absorbed into portal circulation, must pass through liver to reach systemic circulation
- May reduce availability of drug

Elimination

- Kidneys = primary site
  - Mechanisms dependent upon:
    - Passive glomerular filtration
    - Active tubular transport
  - Partial reabsorption
  - Hemodialysis
- Renal disease
  - Slows excretion
  - Prolongs effects

Active Tubular Transport

Probenecid is moved into the urine by the same transport pump that moves many antibiotics. Why is probenecid sometimes given as an adjunct to antibiotic therapy?

It competes with the antibiotic at the pump and slows its excretion.

Urine pH and Elimination

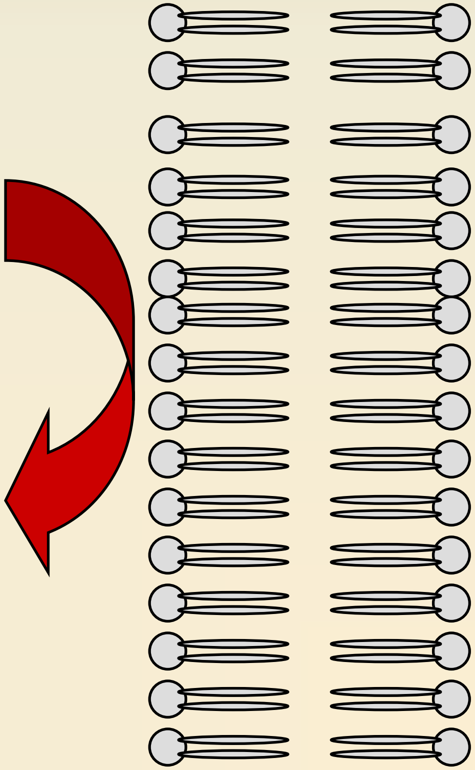
A patient has overdosed on phenobartital. Phenobarbital is an acid. If we 'alkalinalize' the urine by giving bicarbonate what will happen to the phenobarbital molecules as they are filtered through the renal tubules?

They will ionize...

How will this affect phenobarbital reabsorption by the kidney?

Non-ionized **Ionized**

$$\mathbf{HA \longrightarrow H^{+} + A^{-}}$$



Decreased reabsorption

Increased elimination

Elimination

- Other sources
  - Feces
  - Exhaled air
  - Breast milk
  - Sweat

Biological Half-life ($t_{1/2}$)

- Amount of time to eliminate 1/2 of total drug amount
- Shorter $t_{1/2}$ may need more frequent doses
- Hepatic disease may increase $t_{1/2}$

A drug has a half life of 10 seconds. You give a patient a dose of 6mg. After 30 seconds how much of the drug remains?

Time	Amount
0 sec	6 mg
10 sec	3 mg
20 sec	1.5 mg
30 sec	0.75 mg

Administration Routes

- Intravenous
  - Fastest, Most dangerous
- Endotracheal
  - Lidocaine, atropine, narcan, epinephrine
- Inhalation
  - Bronchodilators via nebulizers
- Transmucosal
  - Rectal or sublingual

Administration Routes

- Intramuscular
  - Depends on perfusion quality
- Subcutaneous
  - Depends on perfusion quality
- Oral
  - Slow, unpredictable
  - Little prehospital use

Pharmacodynamics

- The biochemical and physiologic mechanisms of drug action

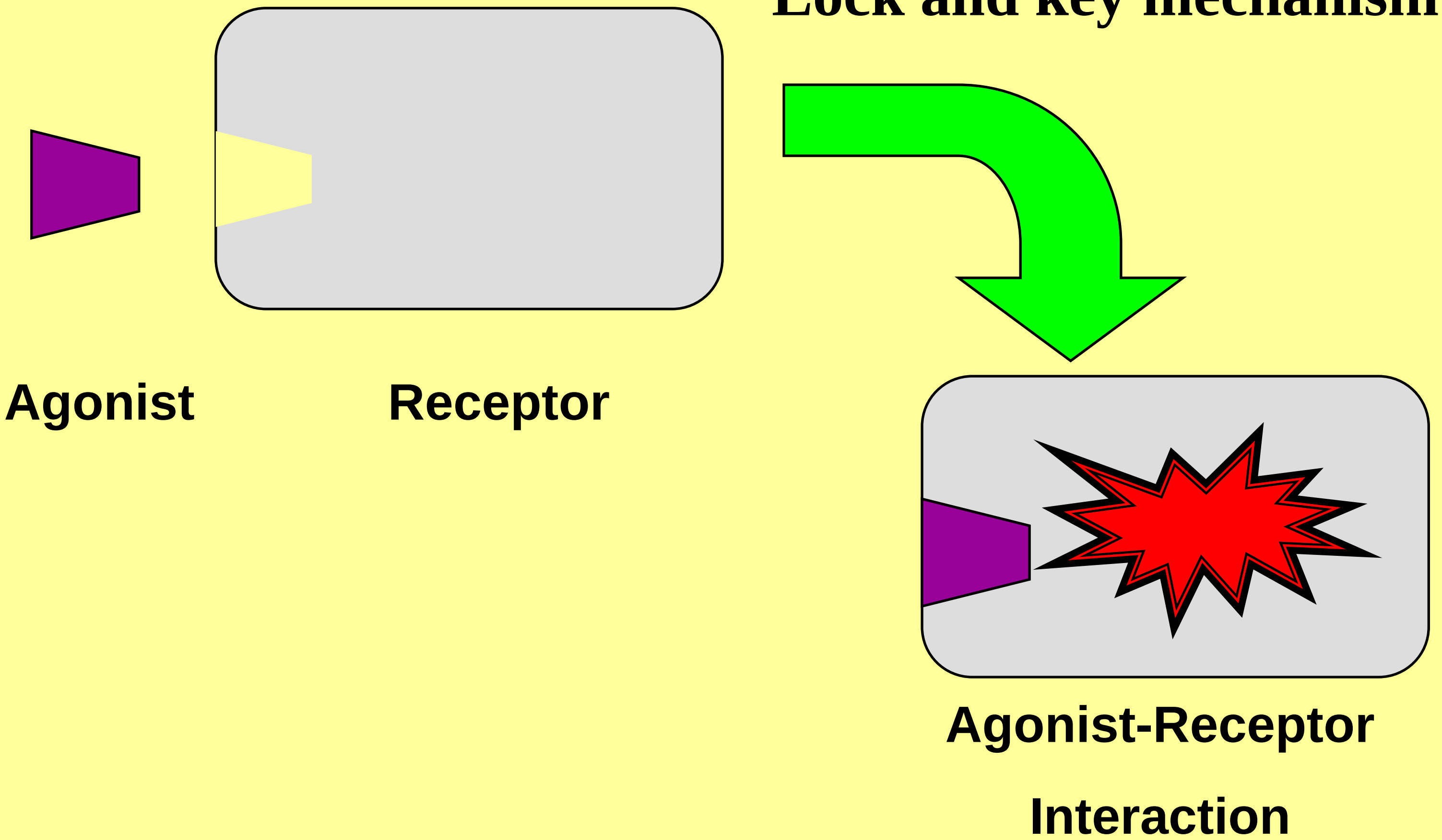
What the drug does when it gets there.

Drug Mechanisms

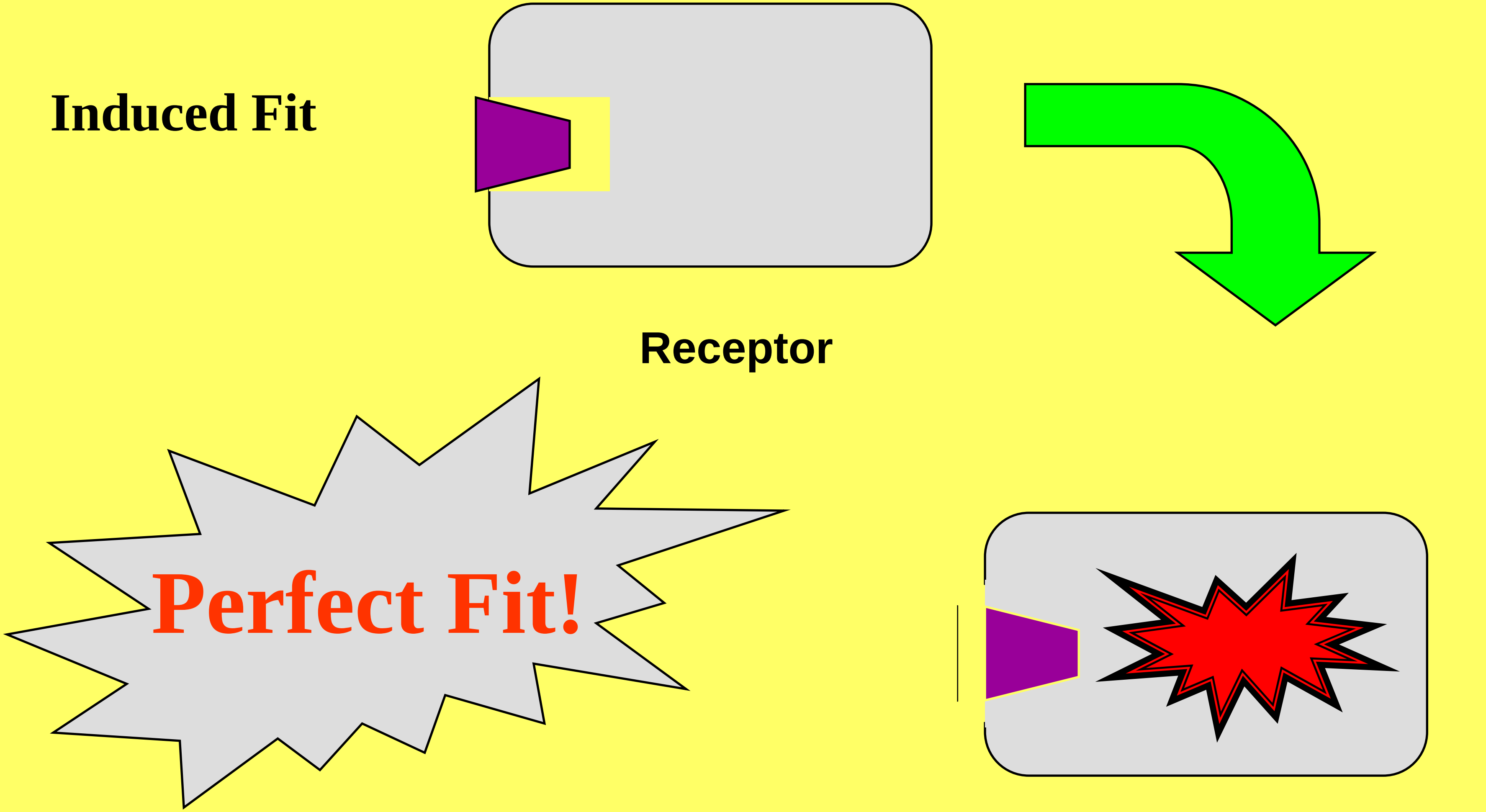
- Receptor interactions
- Non-receptor mechanisms

Receptor Interactions

Lock and key mechanism

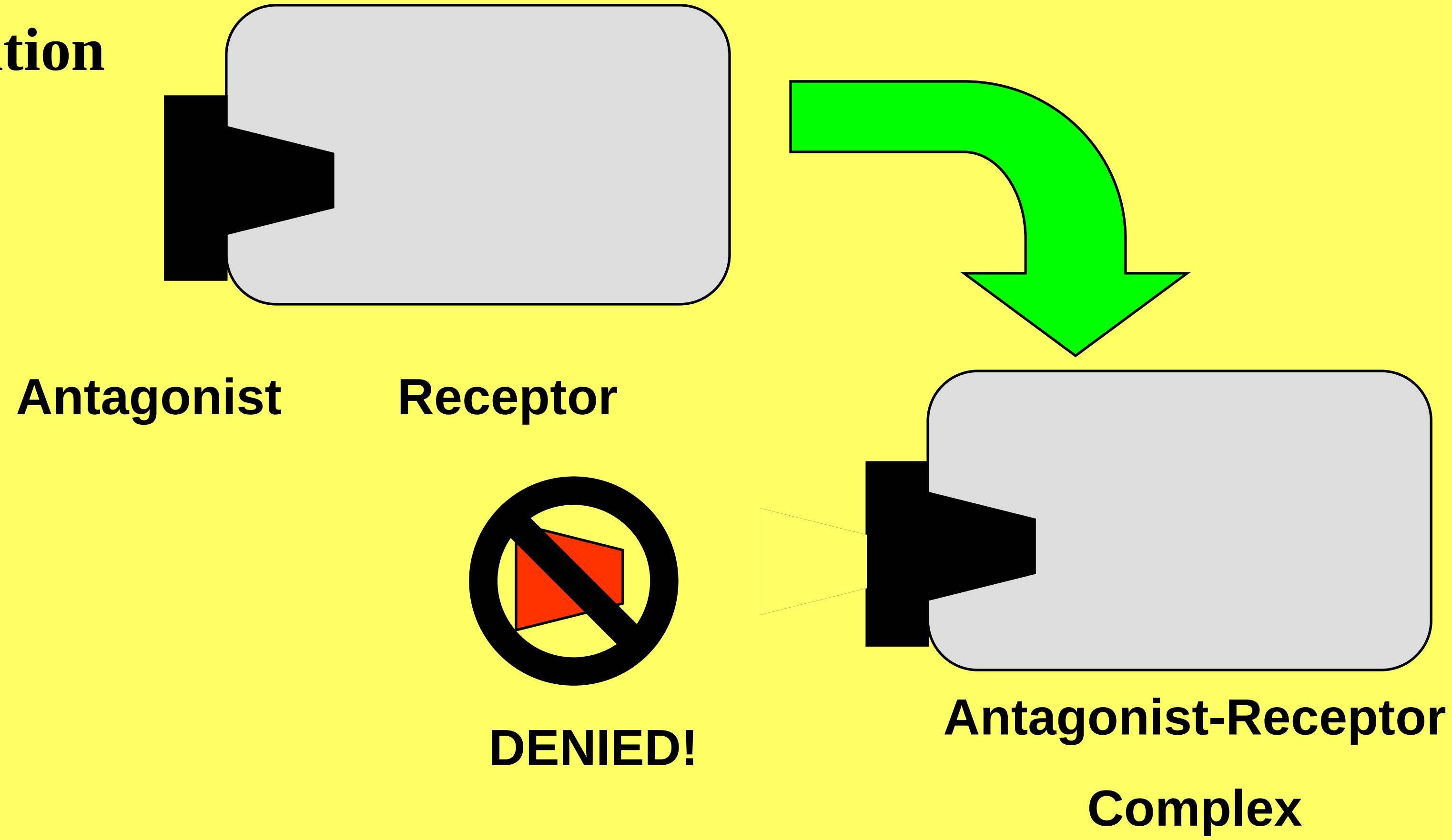


Receptor Interactions



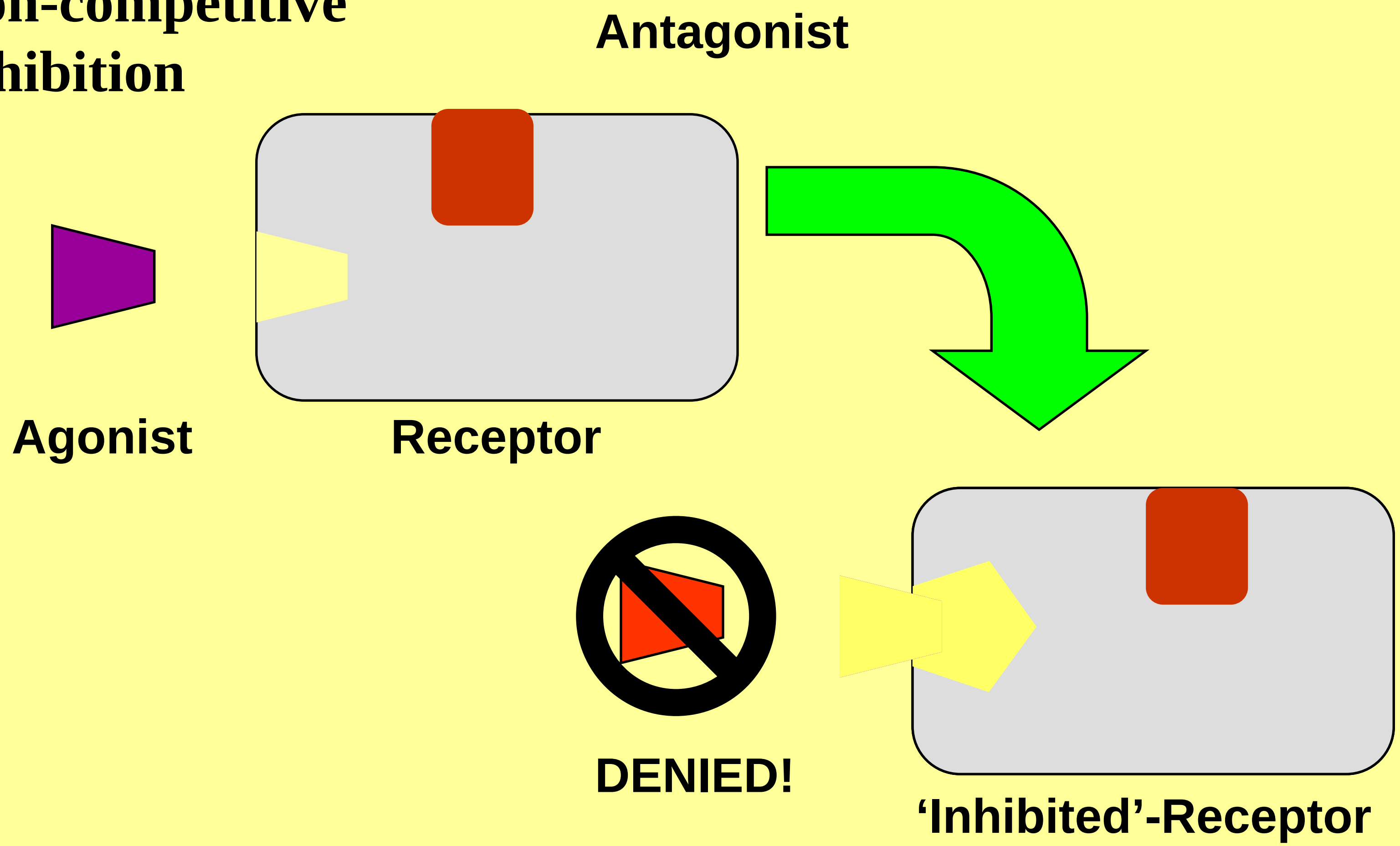
Receptor Interactions

Competitive Inhibition



Receptor Interactions

Non-competitive Inhibition



Non-receptor Mechanisms

- Actions on Enzymes
  - Enzymes = Biological catalysts
    - Speed chemical reactions
    - Are not changed themselves
  - Drugs altering enzyme activity alter processes catalyzed by the enzymes
  - Examples
    - Cholinesterase inhibitors
    - Monoamine oxidase inhibitors

Non-receptor Mechanisms

- Changing Physical Properties
  - Mannitol
  - Changes osmotic balance across membranes
  - Causes urine production (osmotic diuresis)

Non-receptor Mechanisms

- Changing Cell Membrane Permeability
  - Lidocaine
    - Blocks sodium channels
  - Verapamil, nefedipine
    - Block calcium channels
  - Bretylium
    - Blocks potassium channels
  - Adenosine
    - Opens potassium channels

Non-receptor Mechanisms

- Combining With Other Chemicals
  - Antacids
  - Antiseptic effects of alcohol, phenol
  - Chelation of heavy metals

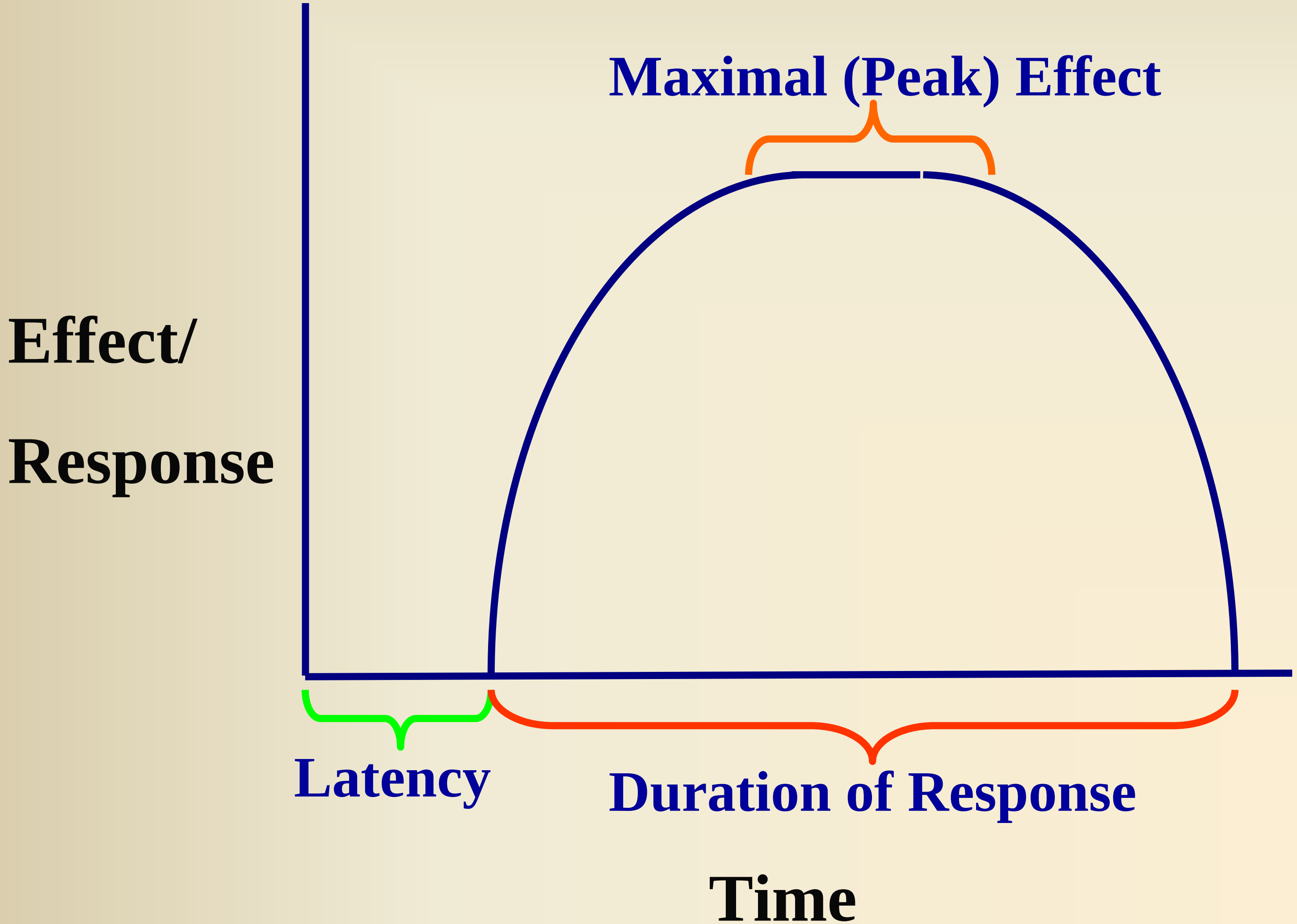
Non-receptor Mechanisms

- Anti-metabolites
  - Enter biochemical reactions in place of normal substrate "competitors"
  - Result in biologically inactive product
  - Examples
    - Some anti-neoplastics
    - Some anti-infectives

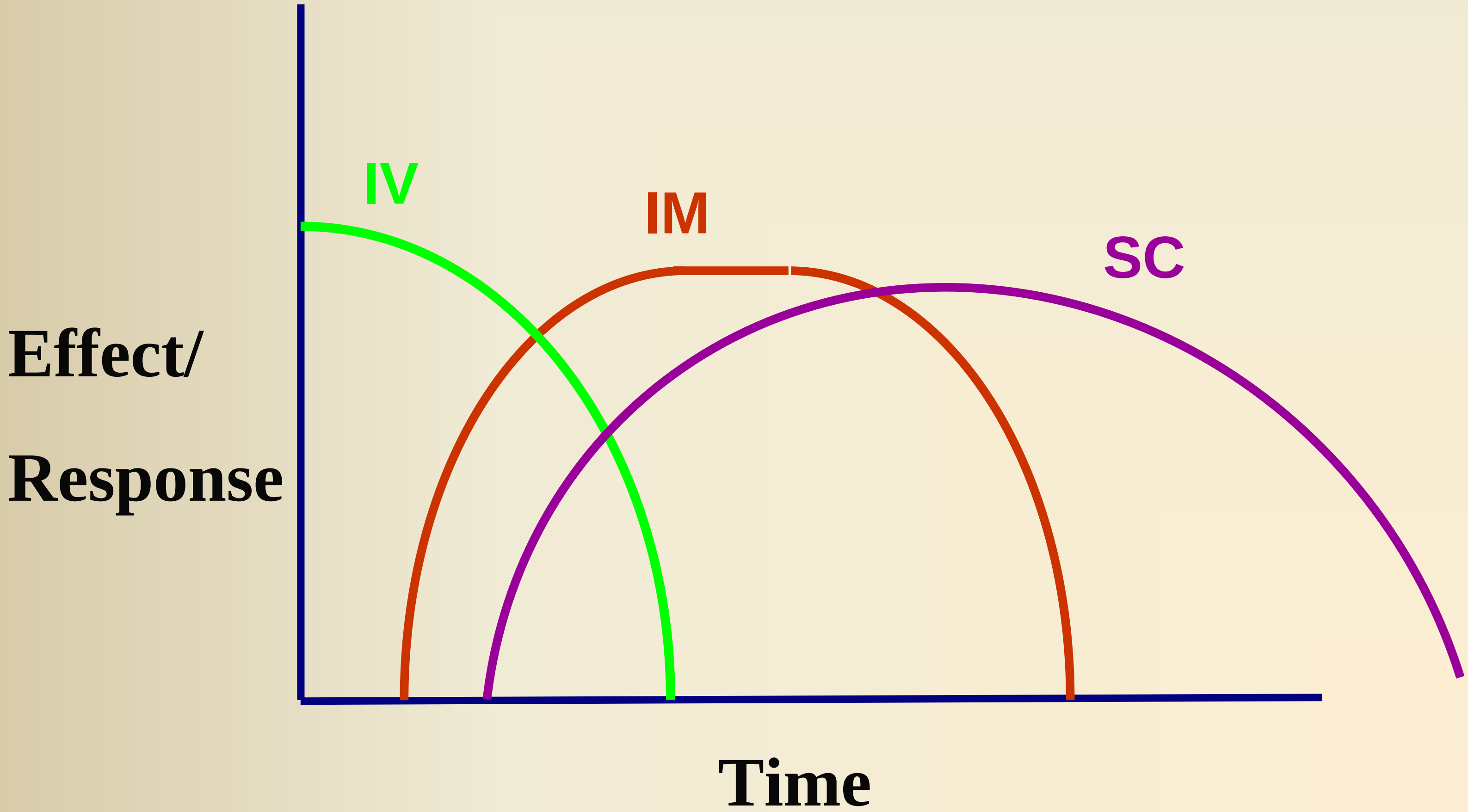
Drug Response Relationships

- Time Response
- Dose Response

Time Response Relationships



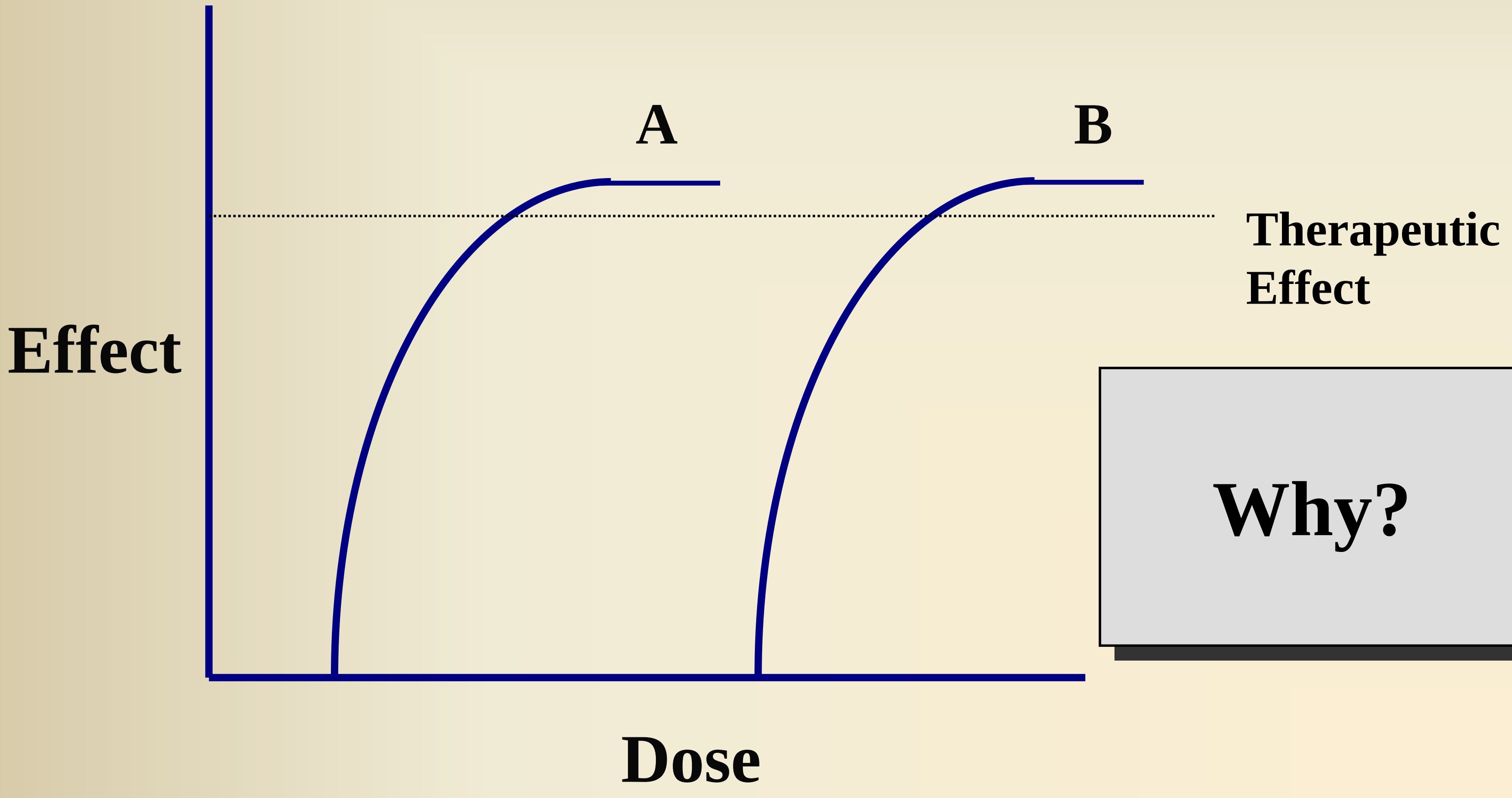
Time Response Relationships



Dose Response Relationships

- Potency
  - Absolute amount of drug required to produce an effect
  - More potent drug is the one that requires lower dose to cause same effect

Potency



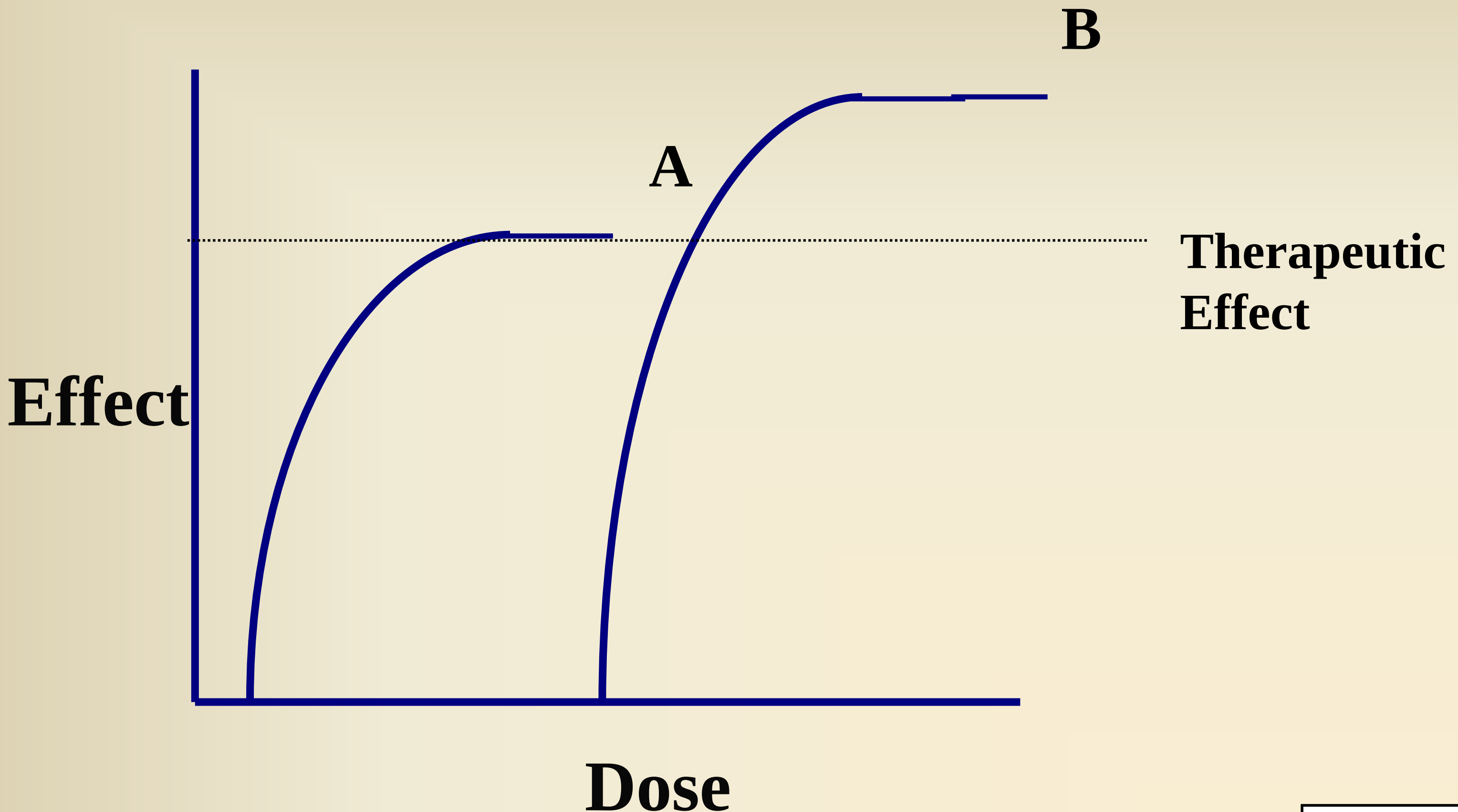
Why?

Which drug is more potent?

Dose Response Relationships

- Threshold (minimal) dose
  - Least amount needed to produce desired effects
- Maximum effect
  - Greatest response produced regardless of dose used

Dose Response Relationships



Which drug has the lower threshold dose?

Which has the greater maximum effect?

Dose Response Relationships

- Loading dose
  - Bolus of drug given initially to rapidly reach therapeutic levels
- Maintenance dose
  - Lower dose of drug given continuously or at regular intervals to maintain therapeutic levels

Therapeutic Index

- Drug's safety margin
- Must be >1 for drug to be usable
- Digitalis has a TI of 2
- Penicillin has TI of >100

$$TI = \frac{LD50}{ED50}$$

Therapeutic Index

Why don’t we use a drug with a TI <1?

ED50 < LD50 = Very Bad!

Factors Altering Drug Responses

- Age
  - Pediatric or geriatric
  - Immature or decreased hepatic, renal function
- Weight
  - Big patients “spread” drug over larger volume
- Gender
  - Difference in sizes
  - Difference in fat/water distribution

Factors Altering Drug Responses

- Environment
  - Heat or cold
  - Presence or real or perceived threats
- Fever
- Shock

Factors Altering Drug Responses

- Pathology
  - Drug may aggravate underlying pathology
  - Hepatic disease may slow drug metabolism
  - Renal disease may slow drug elimination
  - Acid/base abnormalities may change drug absorption or elimination

Influencing factors

- Genetic effects
  - Lack of specific enzymes
  - Lower metabolic rate
- Psychological factors
  - Placebo effect

Pediatric Patients

- Higher proportion of water
- Lower plasma protein levels
  - More available drug
- Immature liver/kidneys
  - Liver often metabolizes more slowly
  - Kidneys may excrete more slowly

Geriatric Patients

- Chronic disease states
- Decreased plasma protein binding
- Slower metabolism
- Slower excretion

- Dietary deficiencies
- Use of multiple medications
- Lack of compliance

Web Resources

- Basic Pharmacokinetics on the Web
  - http://pharmacy.creighton.edu/pha443/pdf/Default.asp
- Merk Manual: Overview of Drugs
  - http://www.merck.com/pubs/mmanual_home/sec2/5.htm

Web Resources

- Merk Manual: Factors Affecting Drug Response
  - http://www.merck.com/pubs/mmanual_home/sec2/8.htm
- Merk Manual: Pharmacodynamics
  - http://www.merck.com/pubs/mmanual_home/sec2/7.htm

Thank You!

- To Temple College EMS Professions for permission to use their materials