Pharmacokinetics and Pharmacodynamics

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Adapted from slides by Stephanie Hsia, PharmD and Ryan Beechinor, PharmD
Reviewed by: Tina Brock, EdD

- **What you (should) already know**
  - Renal, hepatic, exercise, and endocrine physiology
  - Drug actions at the receptor level
- **What we will discuss today**
  - Difference between pharmacokinetics (PK) and pharmacodynamics (PD)
  - ADME (absorption, distribution, metabolism, elimination)
  - Effects of physical therapy (PT) on ADME
  - Types of PD effects
  - PK- and PD-based drug-drug interactions (DDIs)
  - How PK and PD concepts inform pharmacists' clinical practice
  - Implications of PK and PD concepts for physical therapy (PT) clinical practice
- **What you should be able to do after this lecture**
  - Recognize abbreviations of common routes of administration
  - List and describe the important PK parameters (ADME)
  - Explain the concept of steady state
  - Predict effects of various PT treatments on a patient's PK and a medication's PD effects based on available data
  - Distinguish between PK- and PD-based DDIs
  - Describe how pharmacists use PK and PD concepts in clinical practice
  - Propose an example of how a PK and/or PD principle could be useful for patient care in your clinicals

Why Should I Care?

Physical Therapy
Journal of the American Physical Therapy Association

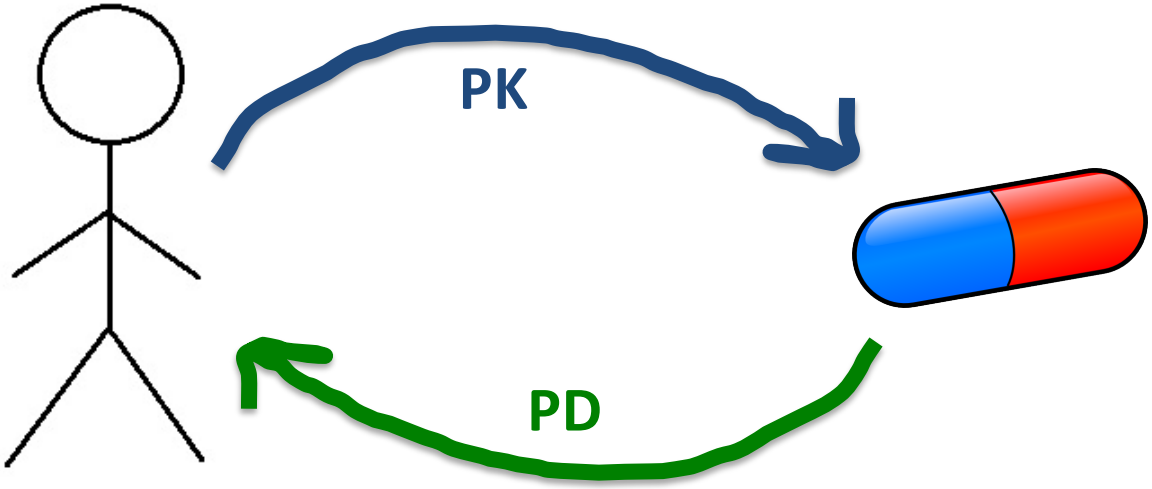
Basic Pharmacokinetics and the Potential Effect of Physical Therapy Interventions on Pharmacokinetic Variables

Charles D Ciccone

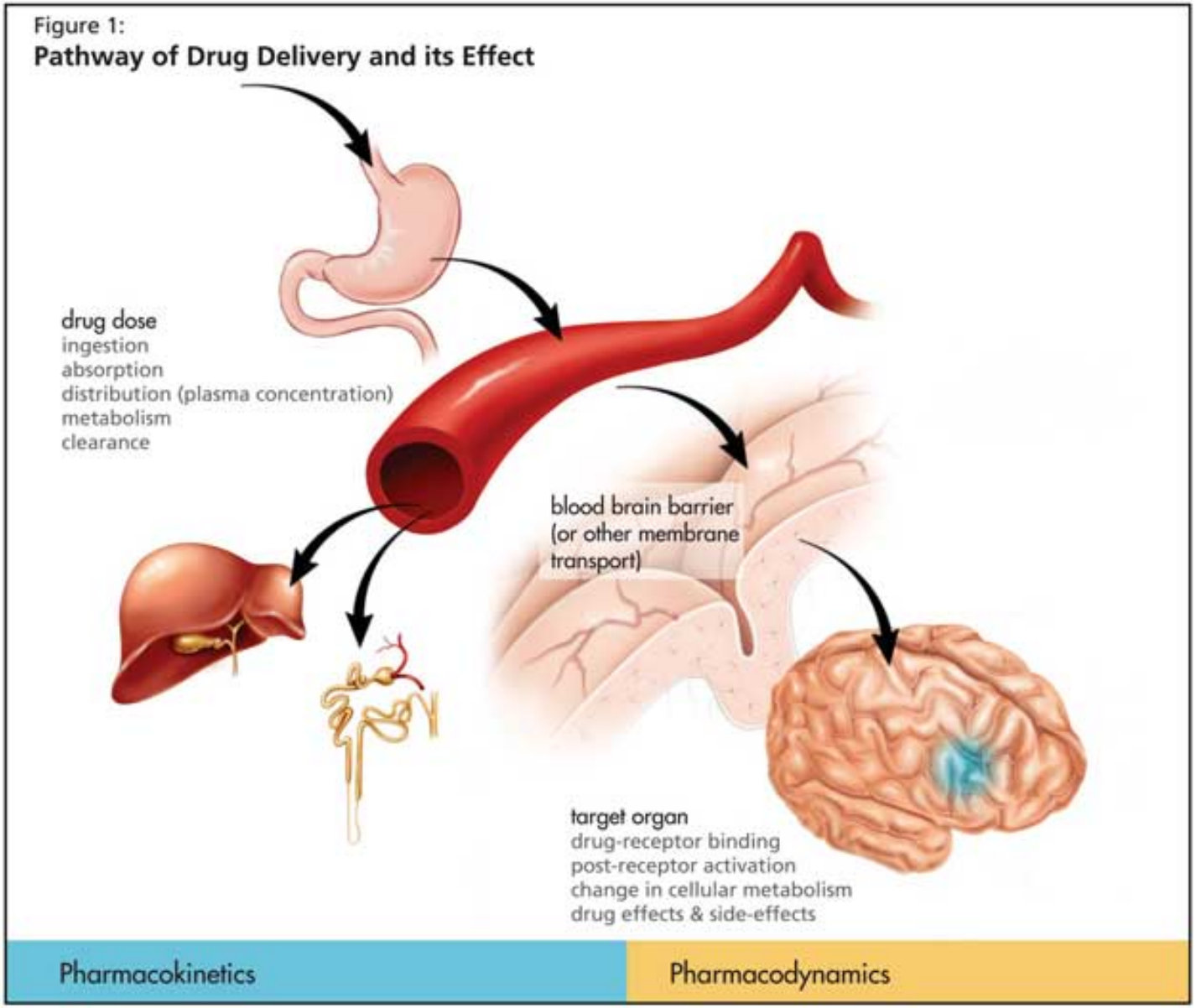
PHYS THER. 1995; 75:343-351.

Pharmacokinetics (PK) vs. Pharmacodynamics (PD)

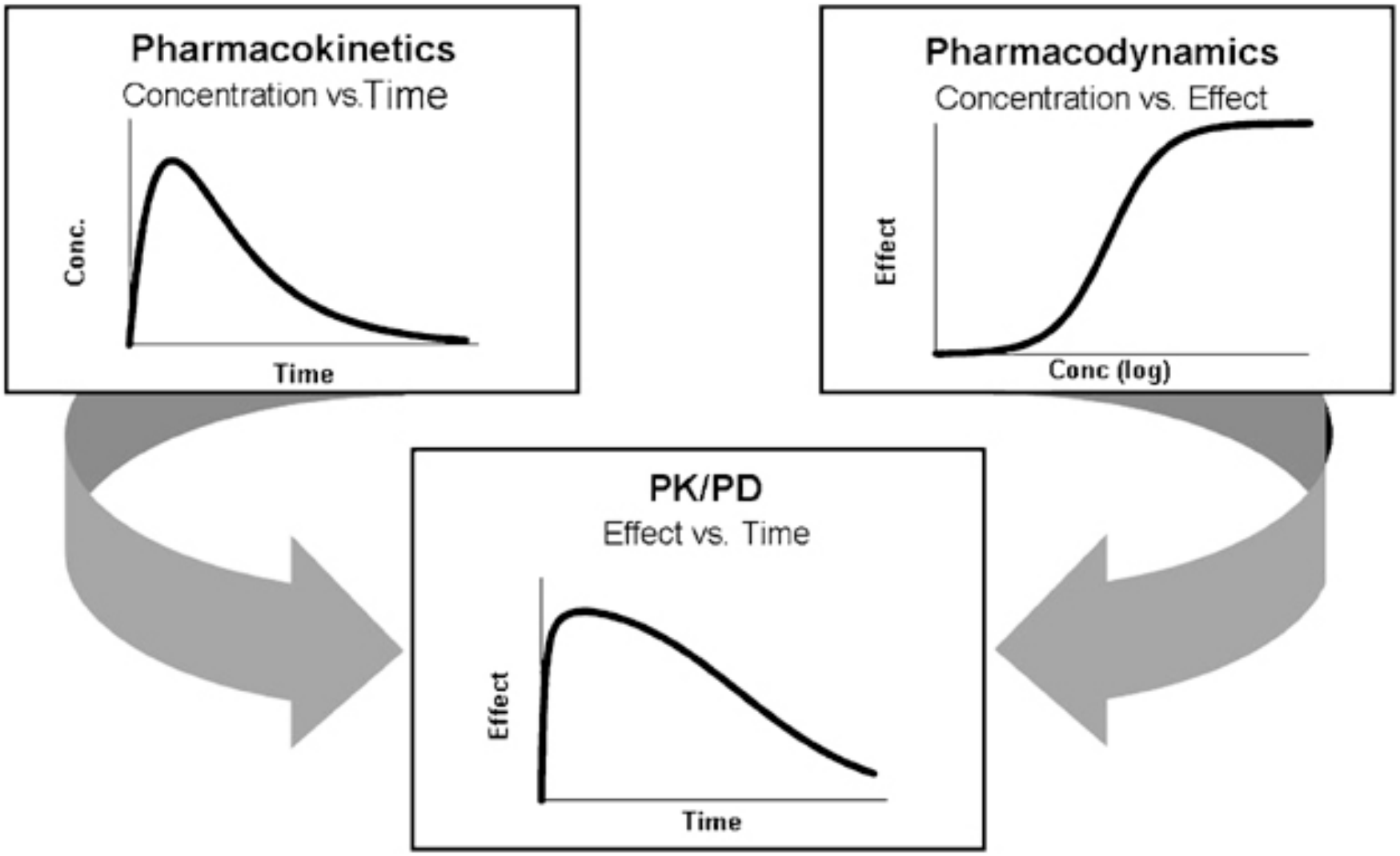
- PK: What your **body** does to the **drug**
  - ADME
  - Example: The liver breaks down acetaminophen
- PD: What the **drug** does to your **body**
  - Example: Acetaminophen relieves pain



Pharmacokinetics vs. Pharmacodynamics



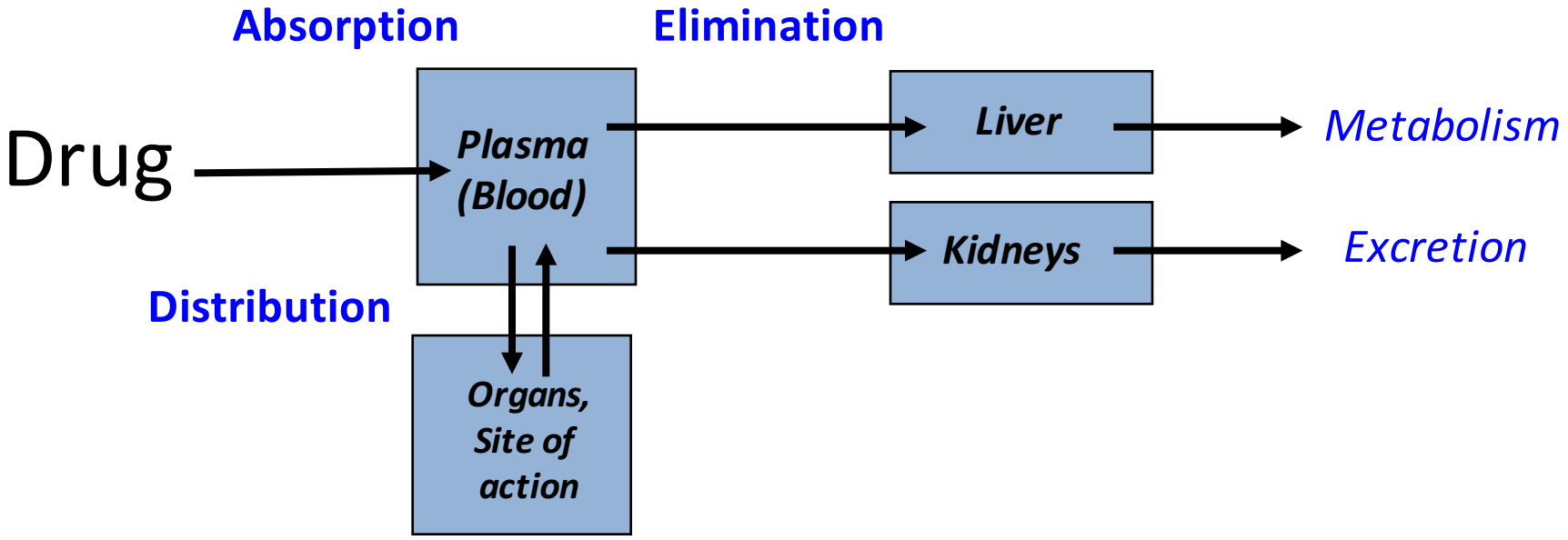
Pharmacokinetics vs. Pharmacodynamics



Pharmacokinetics

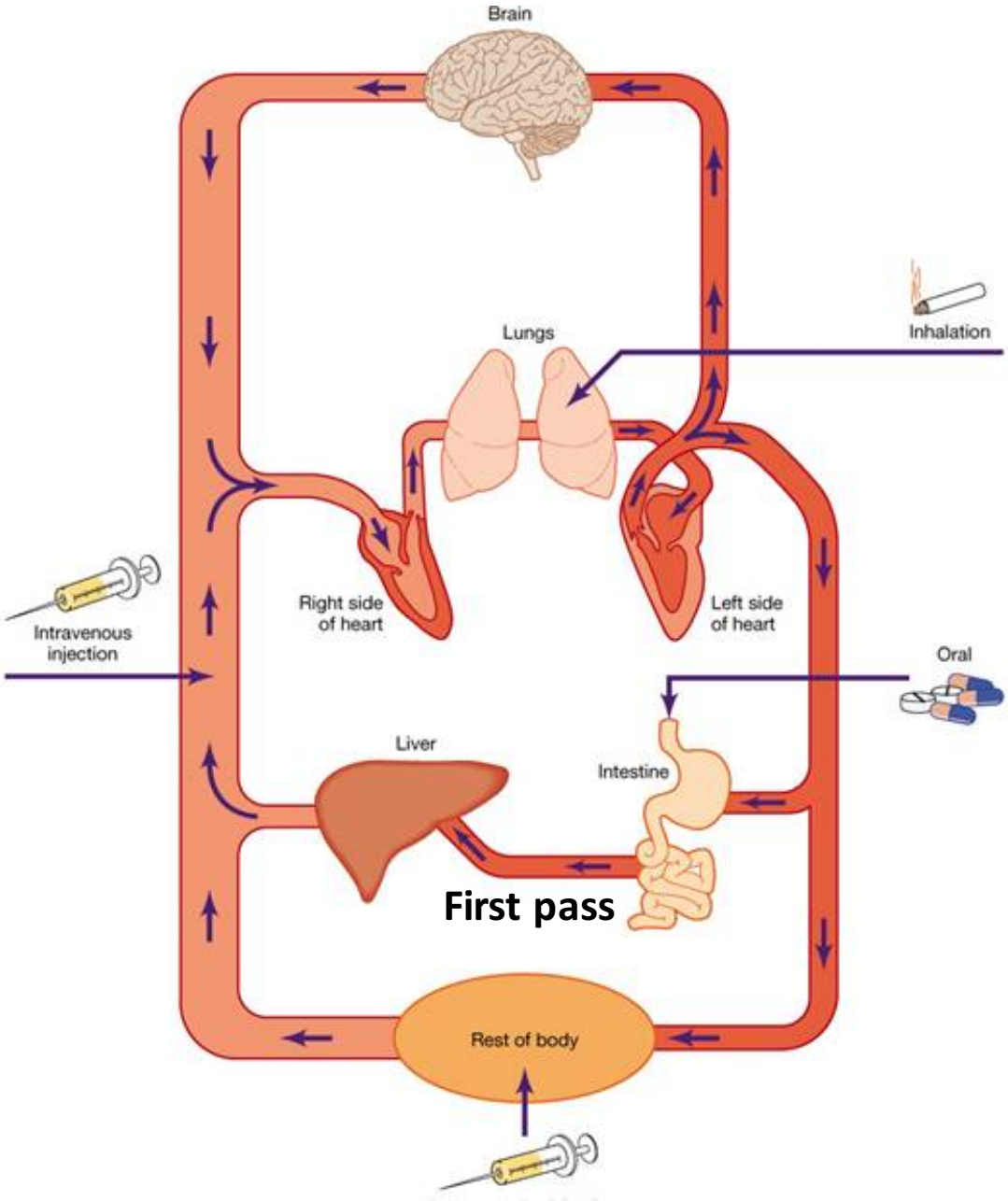
What the **body** does to the **drug**

Pharmacokinetics



- **A**bsorption: Passage of drug from site of administration into the blood
- **D**istribution: Movement of drug from blood into tissues, other compartments, or site of action
- **M**etabolism: Breakdown of drug into metabolites
- **E**xcretion: Drugs and their metabolites are removed from the body

Routes of Administration



Vocab Lesson!

- Parenteral
  - *Para* = “beside”
  - *enteron* = “intestine”
  - Parenteral = beside intestine (a.k.a. bypasses the intestine)
  - Means any route that doesn’t pass through the intestine

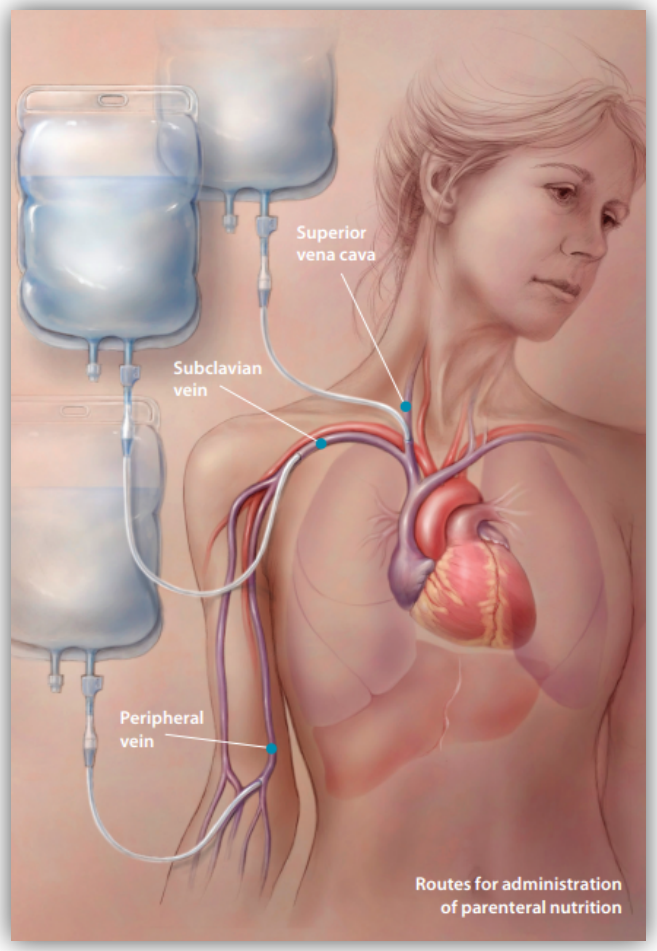


Image: Tilton J. Oncology Nurse Advisor. July/August 2011.

Routes of Administration

- Enteral
  - Oral (PO)
  - Rectal (PR)
  - Through feeding tube
- Transdermal
- Topical

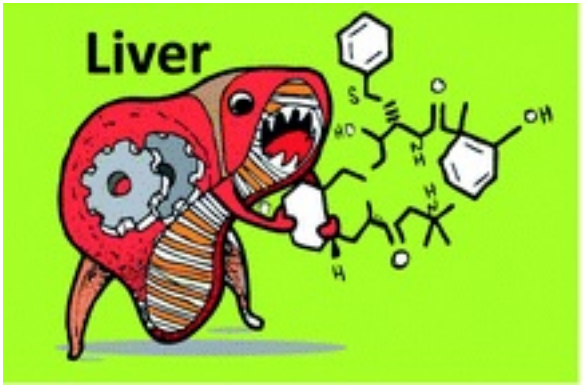
SC, SQ, and sub q are on the ISMP's Error-Prone Abbreviation list

- Parenteral
  - Inhaled
  - Intravenous (IV)
  - Sublingual (SL)
  - Buccal
  - Intramuscular (IM)
  - Subcutaneous (subcut)
  - Intrathecal (IT)

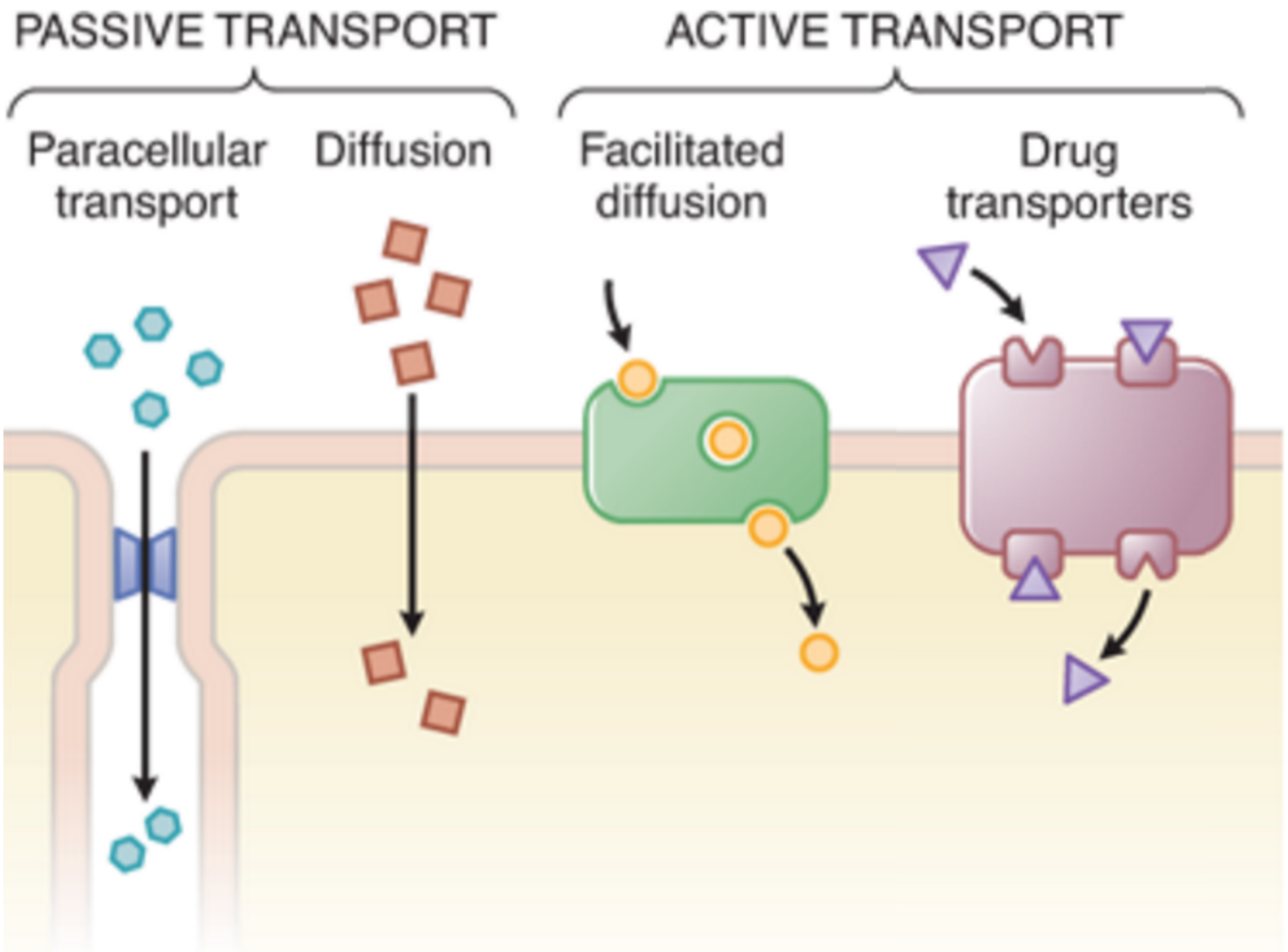
https://www.ismp.org/tools/errorproneabbreviations.pdf

Absorption

- Many factors affect absorption
- Solubility: aqueous vs. lipophilic
- Acid: stable vs. labile
- Molecular size: large vs. small
- Proteins
- First pass metabolism



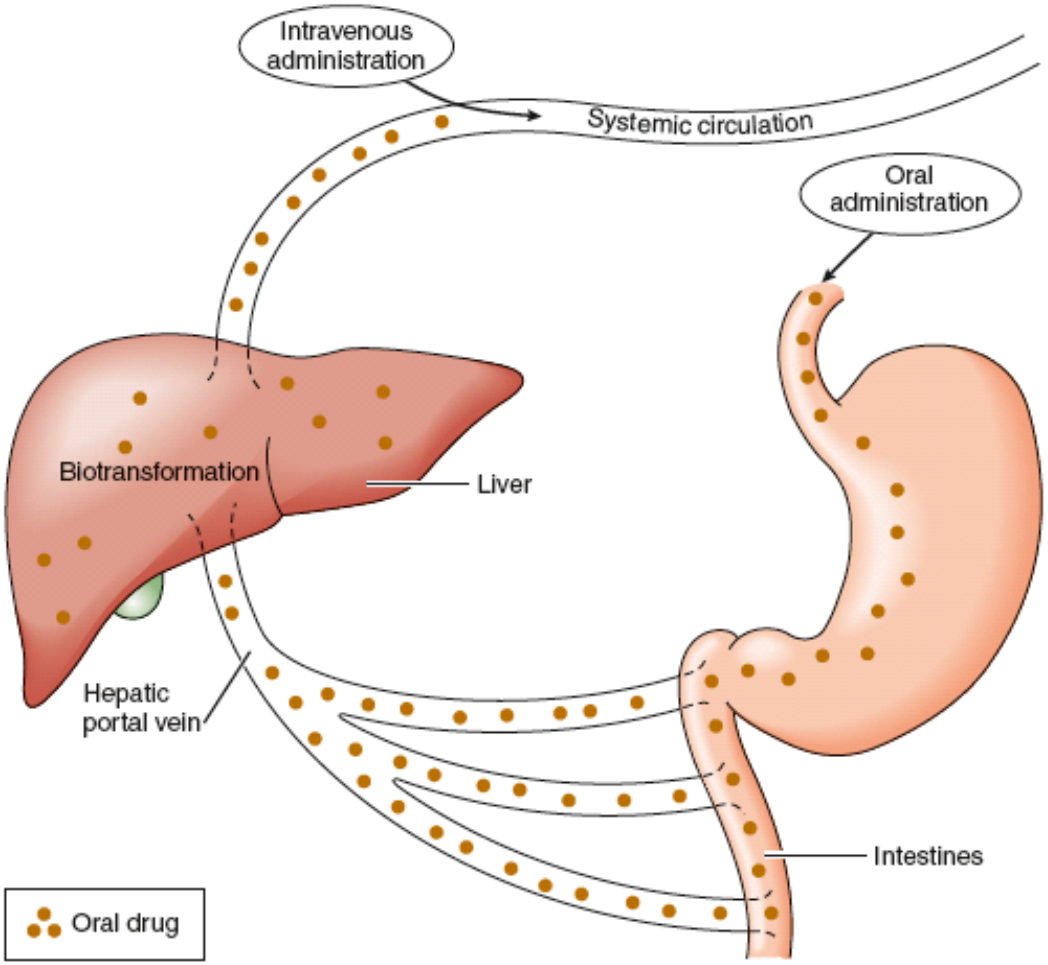
Absorption



Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 12ed. Figure 2-2.

Bioavailability (F)

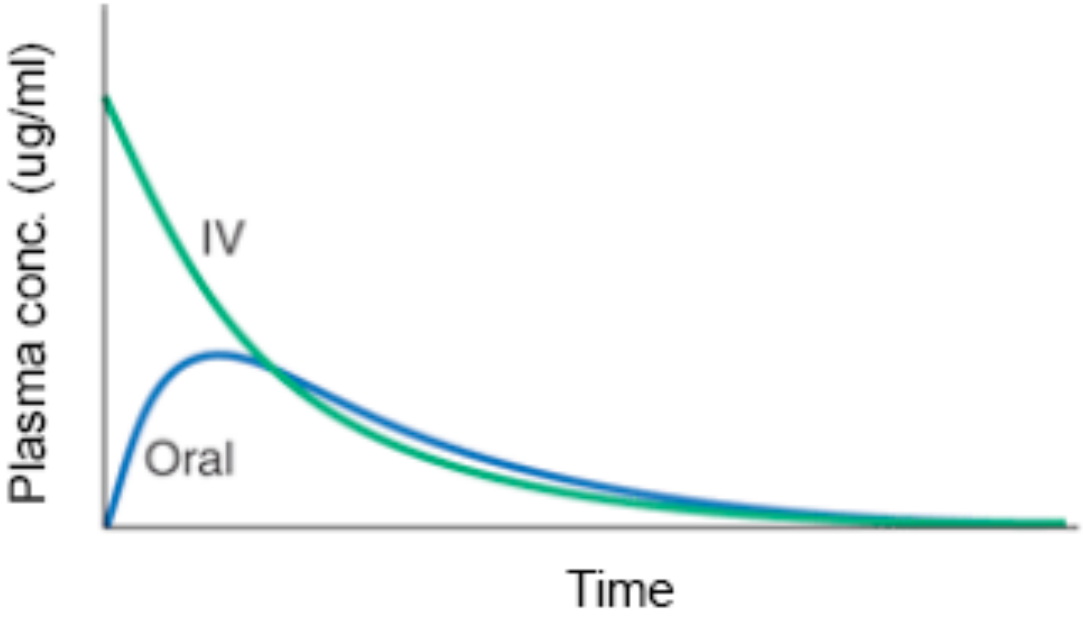
"The fraction or percentage of active medication that reaches the **systemic circulation** following administration from any route"



A DME

Bioavailability (F)

- Number between 0-1 (represents a percentage)
- IV medications: F = 1
- $F = \frac{AUC\ Oral}{AUC\ IV}$
- AUC = Area Under the Curve



Example: PO Vancomycin

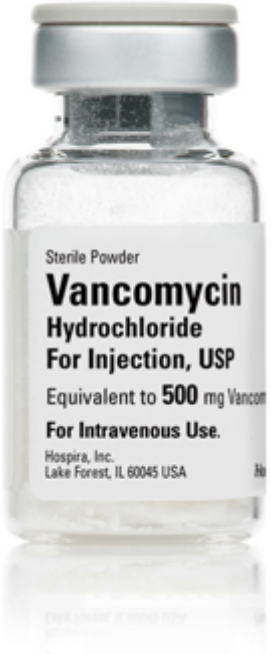


Image: Hospira website

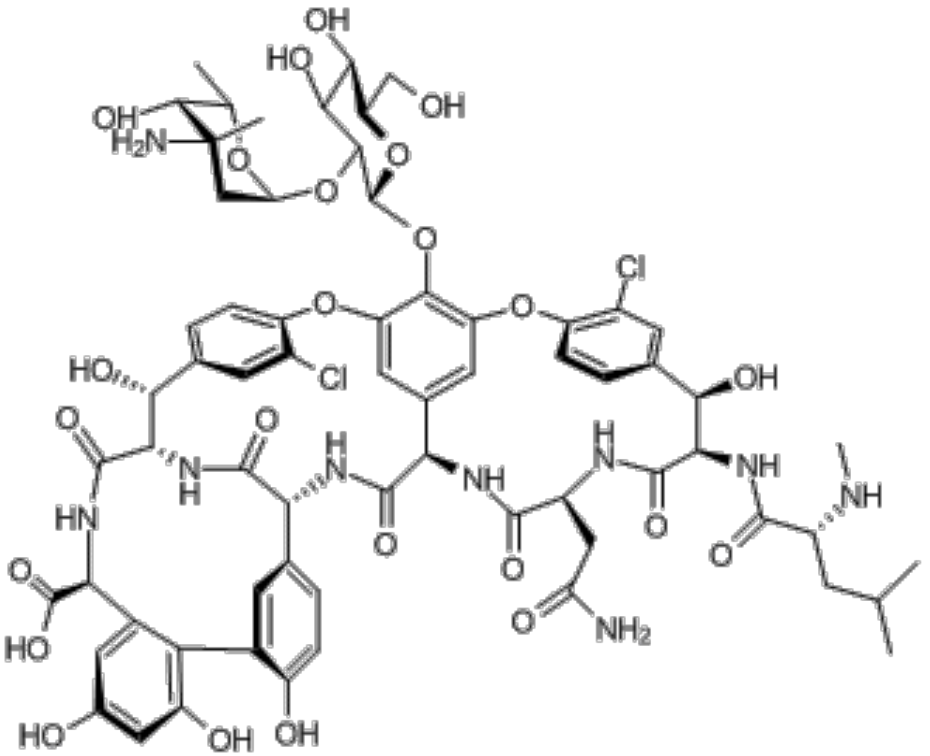


Image: Koteva K et al. Nature Chemical Biology. 2010;6:327-329.

If F<0.05, what's the rationale for PO vancomycin?

A DME

Test Your Understanding

If F of oral oxycodone is 0.70 how many mg of an oxycodone 10 mg tablet would you expect to reach the patient's blood?

What about generic drugs?

- Must demonstrate **bioequivalence** to the original, brand-name drug
- Ensures that the generic version delivers the same active ingredient by the same route of administration at the same rate and to the same extent

Image: Forbes website

Image: ABC News website

Effects of Physical Therapy on Absorption

- PO medications
  - Variable (can increase or decrease plasma levels)
  - During exercise, blood is directed away from the gut which can **decrease** absorption
  - Exercise can also increase blood flow which can **increase** absorption
- SQ or IM medications
  - Exercise can **increase** absorption of drug injected **near** actively exercising muscles by increasing diffusion and blood flow
  - Massaging the injection site can also **increase** absorption
  - Exercise can **decrease** absorption if drug is injected into **non-exercising** tissues by decreasing blood flow
  - Example: insulin

Lenz TL. Expert opinion on drug metabolism & toxicology. 2011;7(3):257-266.

Effects of Physical Therapy on Absorption

- Transdermal medications
  - Exercise usually **increases** absorption by increasing skin temperature and sweating
  - Certain physical therapy treatments (whirlpool, heating pad) involving heat could **increase** absorption
- Inhaled medications
  - Exercise can **increase** absorption by increasing pulmonary blood flow

Lenz TL. Expert opinion on drug metabolism & toxicology. 2011;7(3):257-266. A DME

Example: Prednisolone 5 mg PO

Hypotheses:
- Exercise shunted blood flow away from viscera towards muscles
- Exercise reduced stomach-emptying rate

Non-Exercise Arm: Remained seated for duration of experiment

Exercise Arm: Cycled at 70% VO_{2max} intensity until exhaustion;
Gave rise to a significantly lower C_{max} ($p<0.05$)

PK blood sampling pre-dose

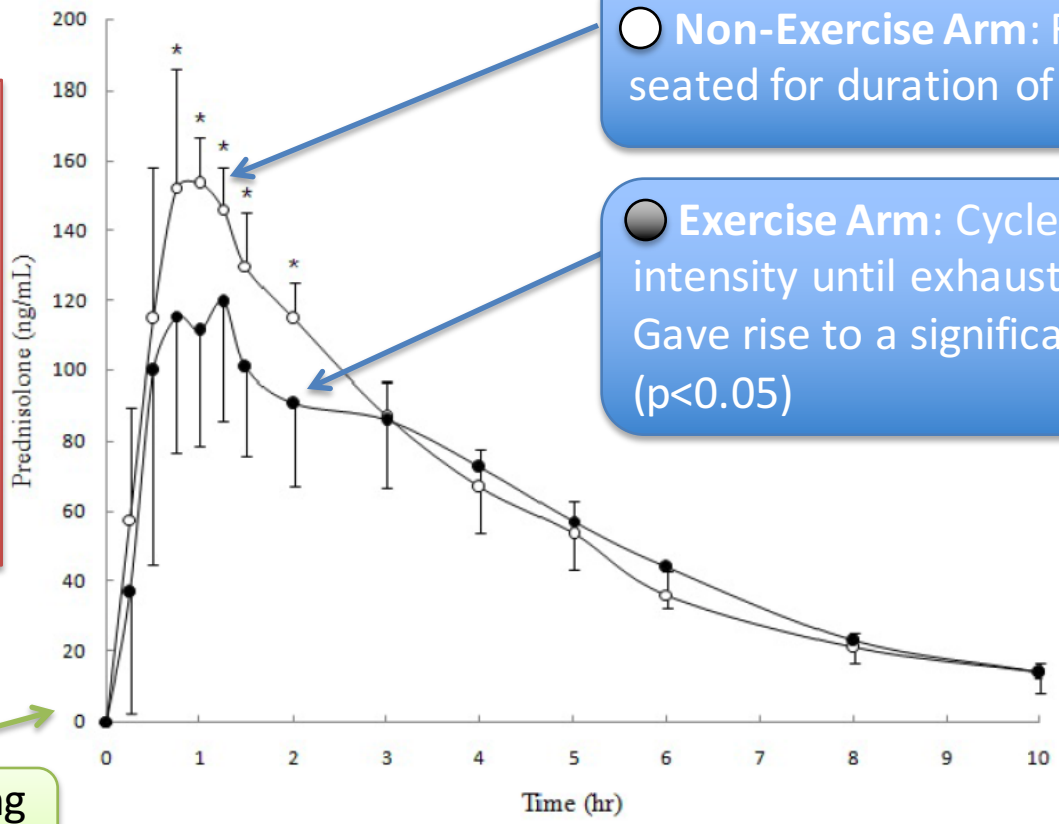


Figure 2. Mean plasma prednisolone concentration-time profile after oral administration of 5mg of prednisolone. Data are shown as the mean ± SD. *Significantly different from the other group ($p<.05$)

Chien KY et al. J Pharm Pharmaceut Sci. 2010;13(1):58-66.

A DME

Example: Fentanyl Patch

Exposing the patch to heat, either from an external source, increased exertion, or possibly high fever, could increase release of the drug, which might lead to an overdose and fatal respiratory depression

Image: Kaiser Permanente>Drugs & natural medicines website

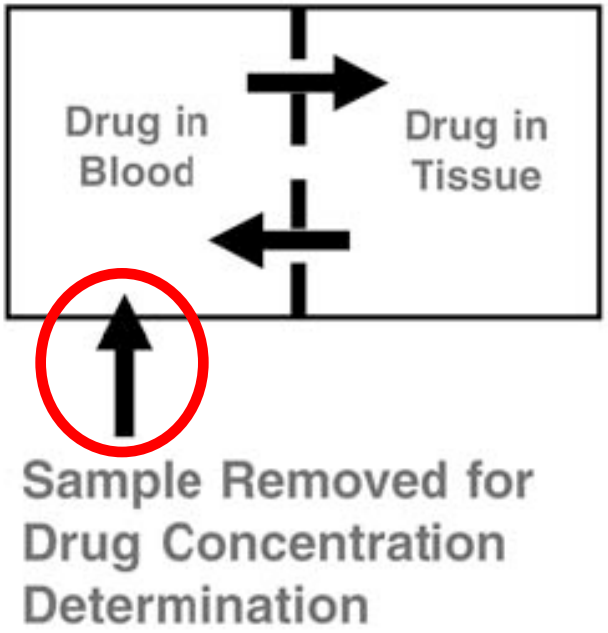
In brief: heat and transdermal fentanyl. Med Lett Drugs Ther. 2009;51(1318):64.

New York Times Story – Doctors and Nurses, Still Learning. April 29, 2009.

A DME

Distribution

- How much of the drug **distributes** into the tissues
- Factors that affect distribution
  - Water/lipid solubility
  - Drug size
  - Protein binding
- Equilibrium between circulation and tissue



Volume of Distribution

- Has no physiological meaning
- Apparent volume of the drug in the body
- $V_d = \frac{Total\ Amount\ of\ Drug\ in\ Body}{Concentration\ of\ Drug\ in\ Plasma}$
- Plasma volume = 7 L
- Whole body volume = 42 L
- If V_d is **large**, most of the drug is in the **tissues**
- If V_d if **small**, most of the drug is in the **blood**

Test Your Understanding

Phenytoin has a volume of distribution ~49 L.
Where is most of the drug?

Test Your Understanding

Chloroquine has a volume of distribution ~100 L/kg. Where is most of the drug?

Effects of Physical Therapy on Distribution

- Exercise can **decrease** the V_d of certain medications (verapamil, propranolol, caffeine)
  - **Less** of the drug reaches the target tissues
  - Can lead to **decreased** effect
- Exercise can **increase** the V_d of certain medications (digoxin)
  - Digoxin binds to cell membrane of skeletal muscle
  - Can **increase** effect and lead to possible toxicity
- Clinical effects are unclear

Lenz TL. Expert opinion on drug metabolism & toxicology. 2011;7(3):257-266.

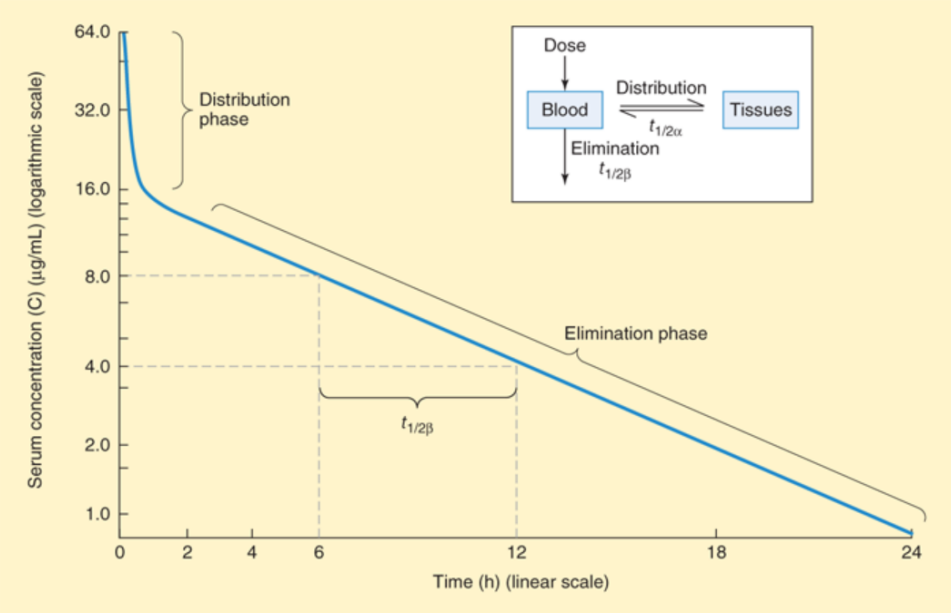
Clearance

- The process by which drug is eliminated from the systemic circulation by **metabolism** and **excretion**
- Units are volume per time (ex: mL/min)
- Drugs can be cleared through many pathways
  - **Liver metabolism (biotransformation)**
  - **Renal excretion into urine**
  - Other pathways
- $CL_{Total} = CL_{Renal} + CL_{Non-renal}$

AD ME

Half-life

- The amount of time it takes to go from one concentration to half of that concentration
- Depends on the clearance and V_d
- Longer half-life = drug stays in body longer



Katzung and Trevor's Pharmacology, 11e. Figure 1-4.

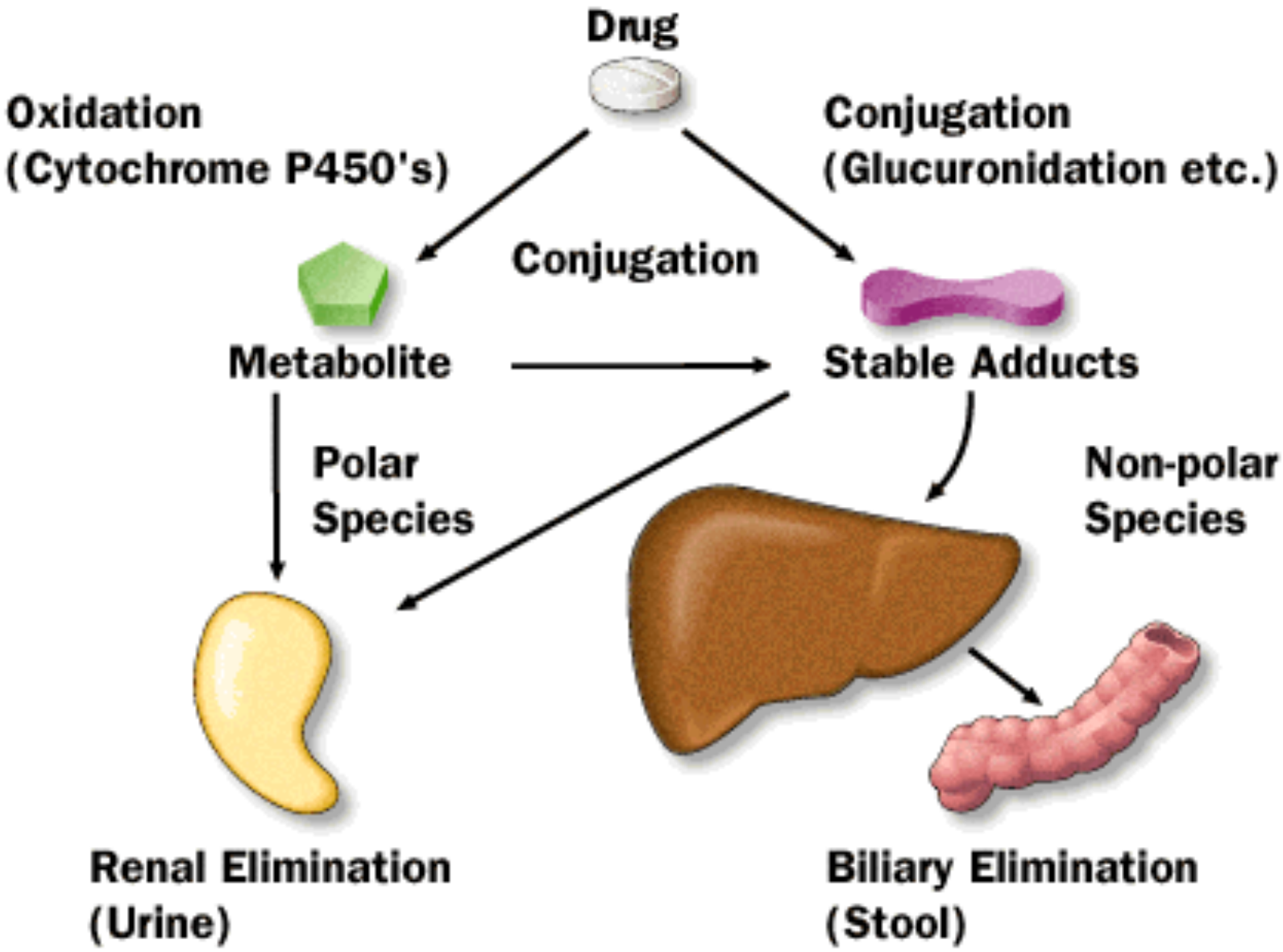
AD ME

Metabolism

- Process of increasing the water solubility of a drug to **increase renal excretion** in the urine
- Often happens in the **liver**
- Not all drugs are metabolized
- May result in active or inactive metabolites
- CYP450 enzymes (CYPs) metabolize drugs
  - Many different enzymes metabolize different drugs
- Patient with liver failure have **decreased** metabolism, typically leading to **decreased** clearance

Lenz TL. Expert opinion on drug metabolism & toxicology. 2011;7(3):257-266.

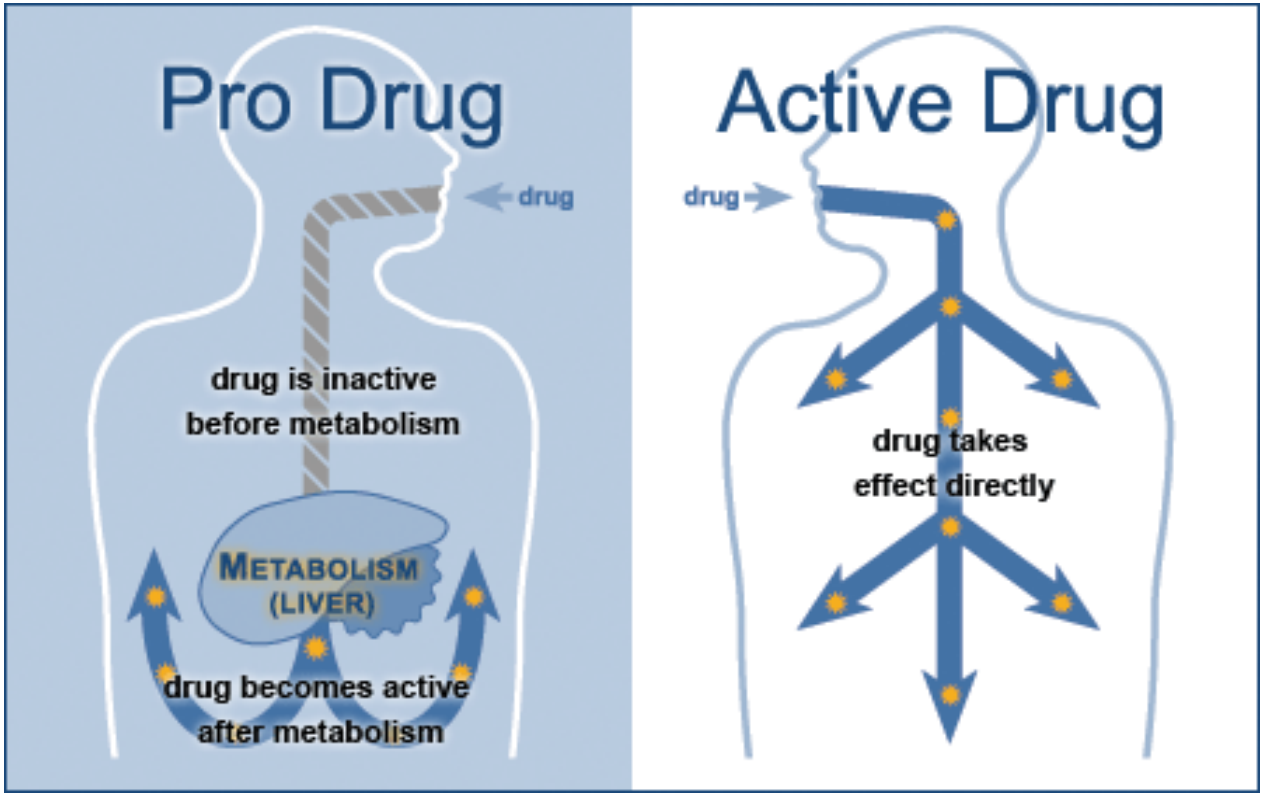
Metabolism



AD M E

Pro-drugs

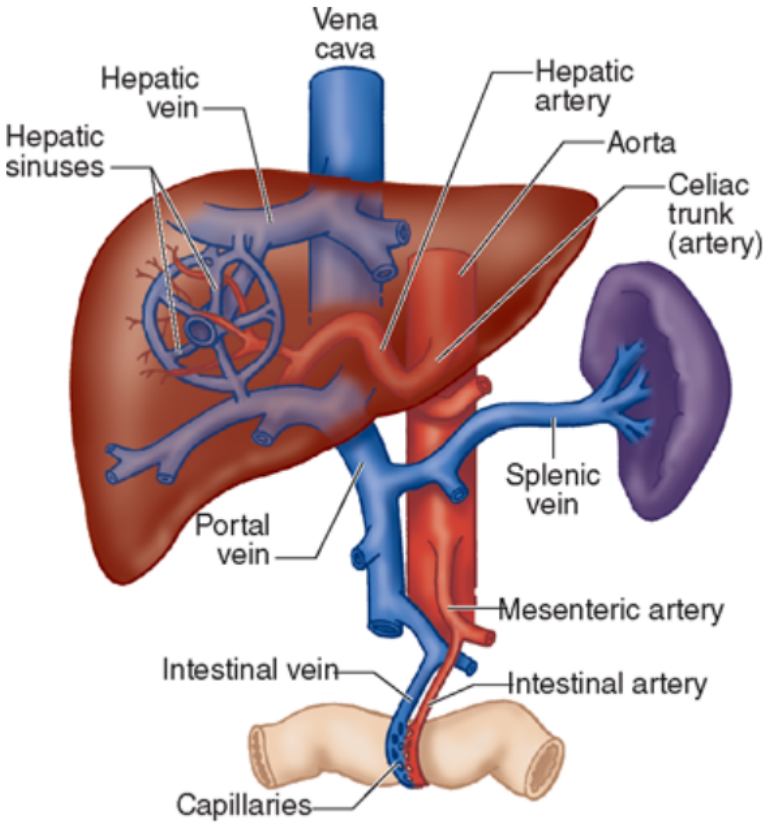
- Drugs that need to be metabolized by the liver to their **active** form
- Example: clopidogrel (Plavix)



AD M E

Effects of Physical Therapy on Metabolism

- Exercise **decreases** blood flow to the liver, which decreases the amount of drug that can reach the liver and **decreases** clearance
- Clinical effects are unclear



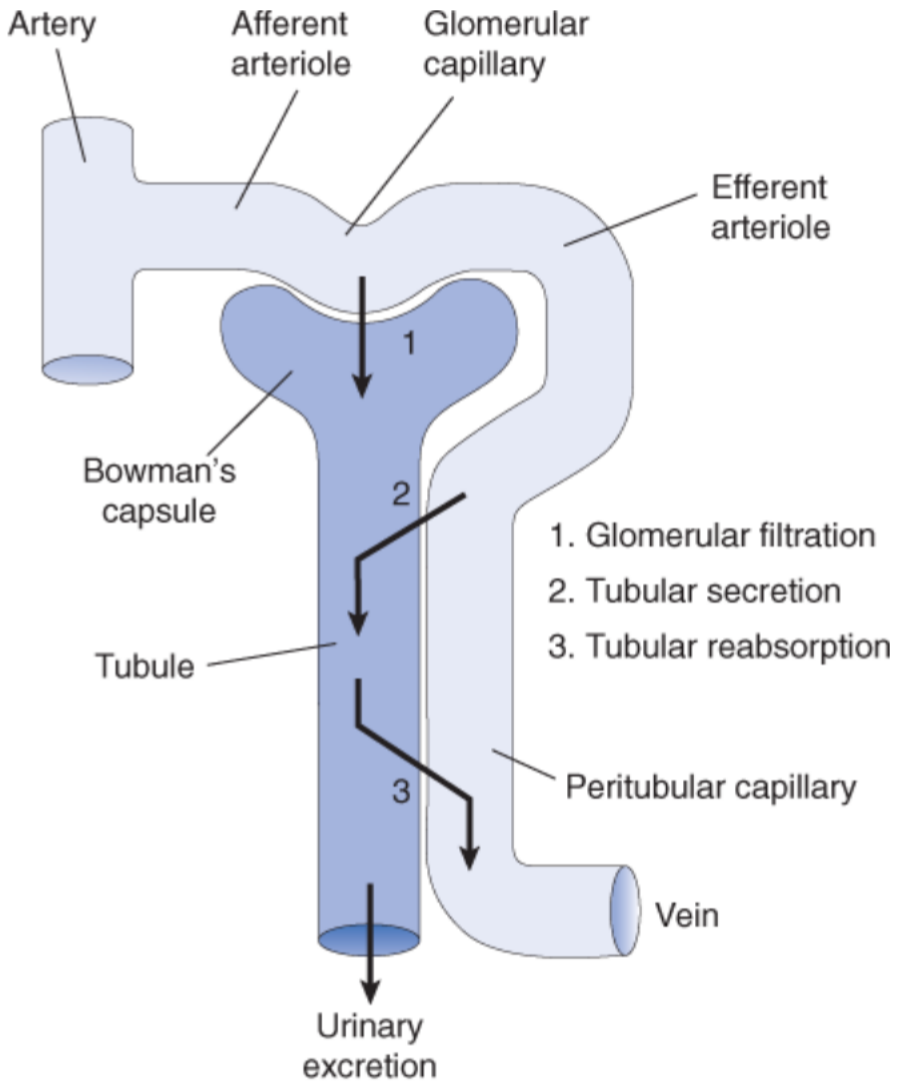
Morgan & Mikhail's Clinical Anesthesiology, 5e. Figure 32-2.

Lenz TL. Expert opinion on drug metabolism & toxicology. 2011;7(3):257-266. **AD M E**

Excretion

- Removal of drug from the body mostly through **urine**
- Can also be removed through bile, sweat, tears, feces, breast milk, and exhaled air
- Many drugs are excreted **renally**
- Dose must be adjusted based on the patient's kidney function
- Example: gentamicin

Renal Excretion



Vander's Renal Physiology, 8e. Figure 1-7.

ADM E

Effects of Physical Therapy on Excretion

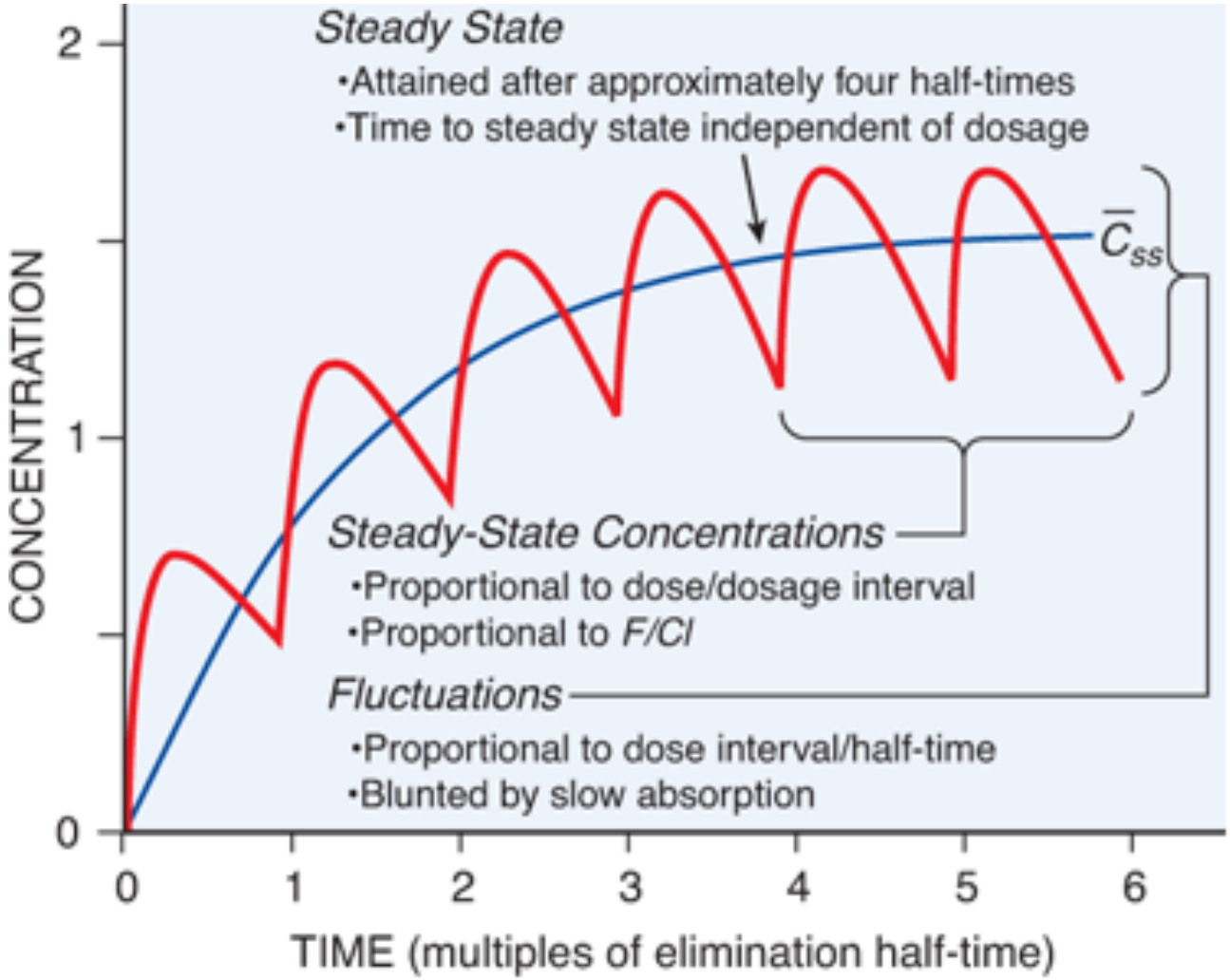
- Exercise can **decrease** renal blood flow, which **decreases** renal excretion and clearance
- Clinical effects are unclear

Table 2. Blood distribution during physical activity and rest (%) [9,10].

	Muscle	Liver	Kidney	Skin	Heart	Other
Rest	20	27	22	6	4	21
Exercise						
Light	47	12	10	15	4	12
Moderate	71	3	3	12	4	7
Maximum	88	1	1	2	4	4

Lenz TL. Expert opinion on drug metabolism & toxicology. 2011;7(3):257-266.

Steady State



Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 12ed. Figure 2-5.

Pharmacokinetics Summary

- What the **body** does to the **drug**
- **Absorption**: Drugs can be administered many different ways and have varying degrees of absorption (bioavailability)
- **Distribution**: Drugs can distribute into tissues, depending on their volume of distribution (high V_d means the drug goes into tissues)
- Clearance depends on the **metabolism** of the drug by the **liver** and the **excretion** of the drug by the **kidney**
- Exercise can have different effects on ADME; however, effects of PT on **absorption** are the only one that have demonstrated clinical effect

Pharmacodynamics

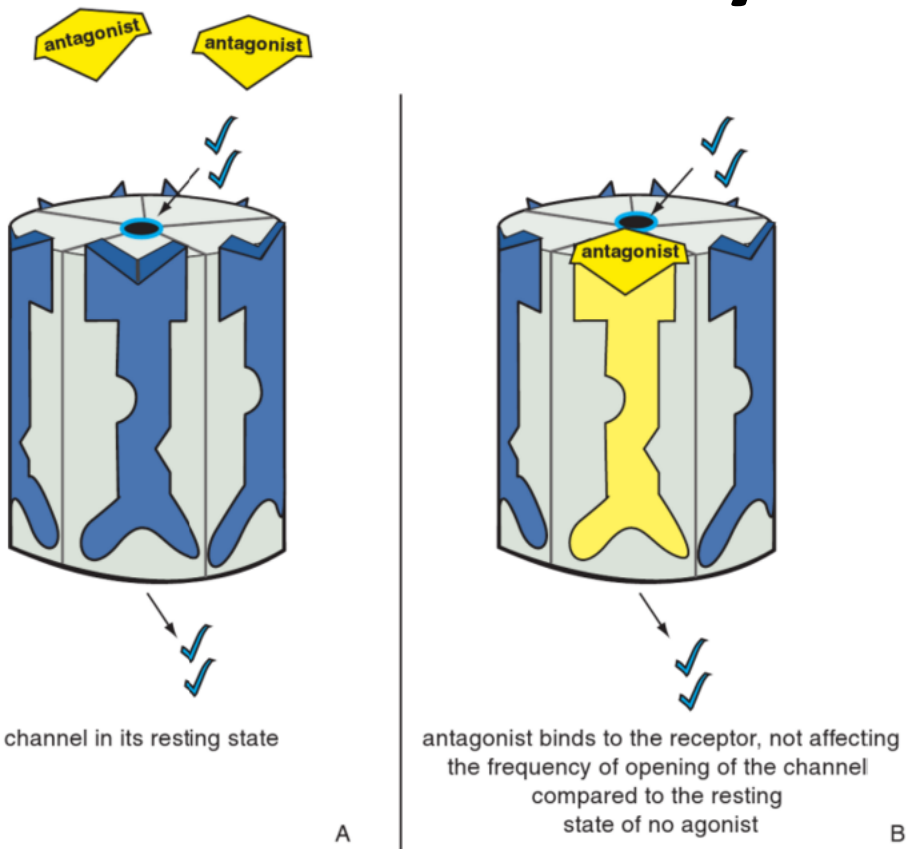
What the **drug** does to the **body**

Pharmacodynamics

- Two main types of effects
  - Agonist
    - Drug activates the receptor and elicits the normal physiologic response
    - Full vs. partial agonist
    - Example: albuterol is a short acting beta-2 **agonist**
  - Antagonist
    - Antagonize = against
    - Drug binds the receptor and prevents receptor activation
    - Competitive vs. irreversible (non-competitive) inhibitor
    - Example: propranolol is a beta-1 **antagonist**

Trevor AJ, Katzung BG, and Masters SB. Katzung and Trevor's Pharmacology, 7e.

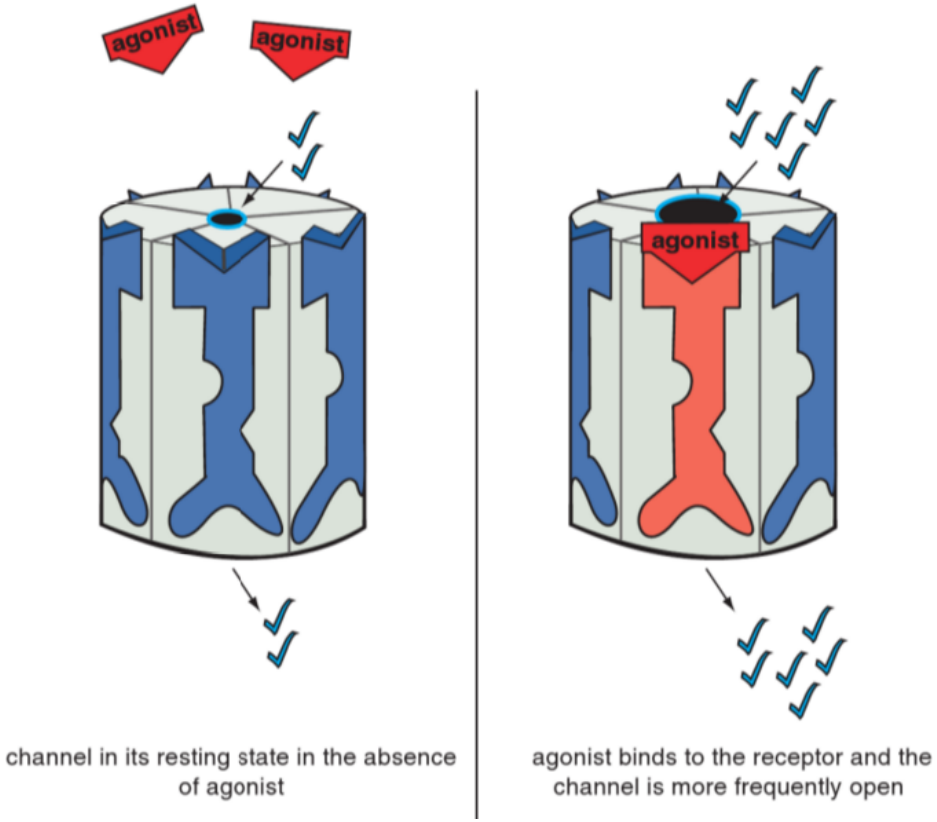
Antagonist: Constitutive activity only



When the antagonist occupies the site normally occupied by the agonist on the ligand-gated ion channel, there is no consequence to this. There is no effect on the degree or frequency of opening of the channel compared to the resting state.

Stahl SM. Stahl's Essential Psychopharmacology, 4e. Figure 3-5.

Agonist:
Increased channel opening frequency

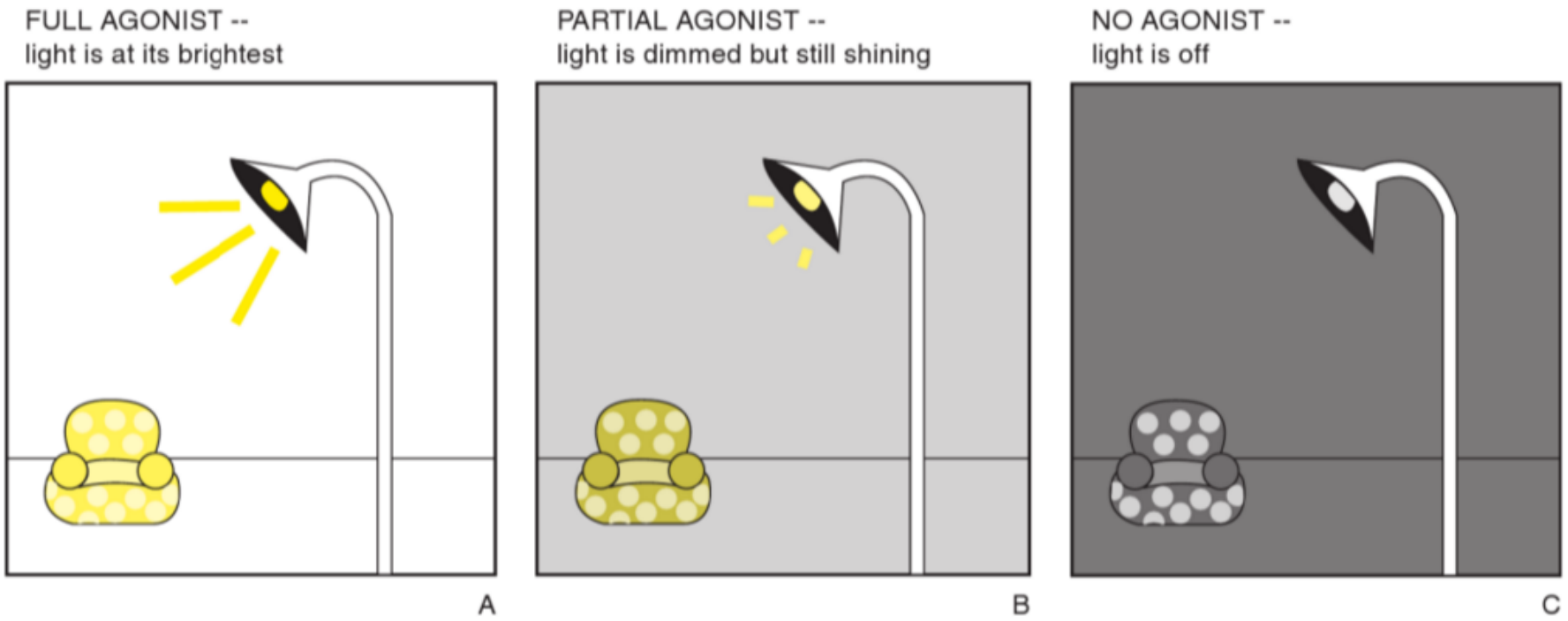


In its resting state, the ion channel opens infrequently (constitutive activity). When the agonist occupies its binding site on the ligand-gated ion channel, it increases the frequency at which the channel opens.

Stahl SM. Stahl's Essential Psychopharmacology, 4e. Figure 3-5.

Agonist Spectrum Analogy

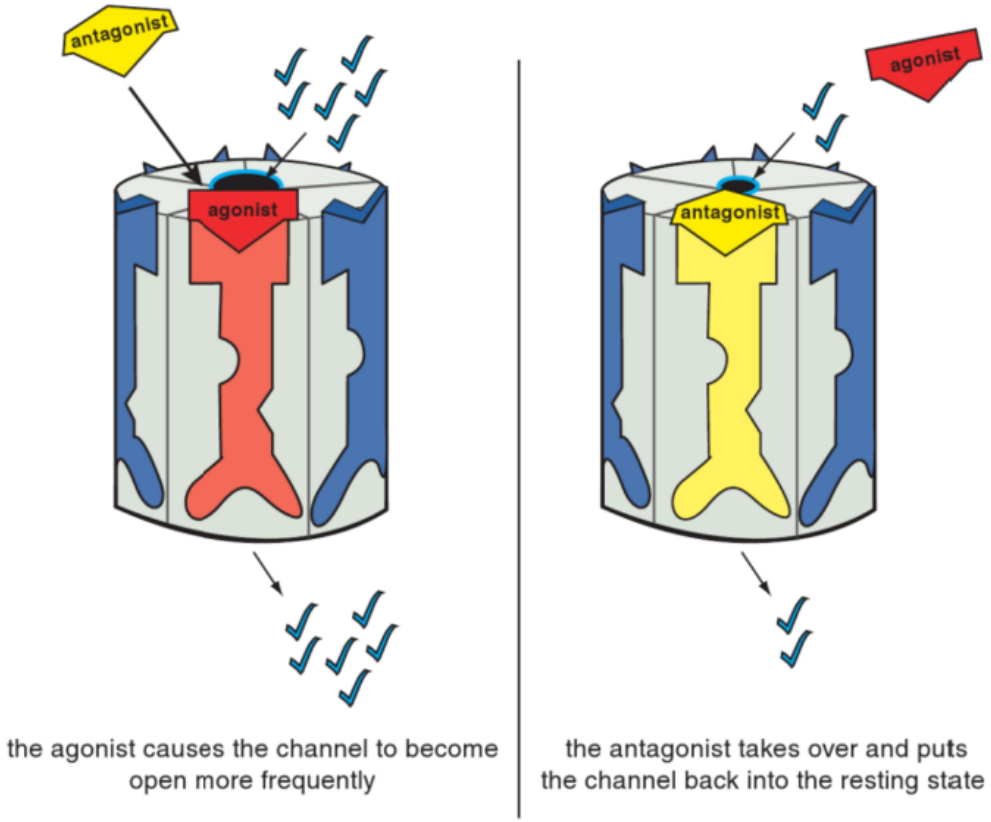
A useful analogy for the agonist spectrum is a light controlled by a rheostat ("dimmer"):



If the light is already on, a partial agonist will "dim" the lights, thus acting as a net antagonist.

Stahl SM. Stahl's Essential Psychopharmacology, 4e. Figure 2-8.

Antagonist in presence of Agonist: Constitutive activity only



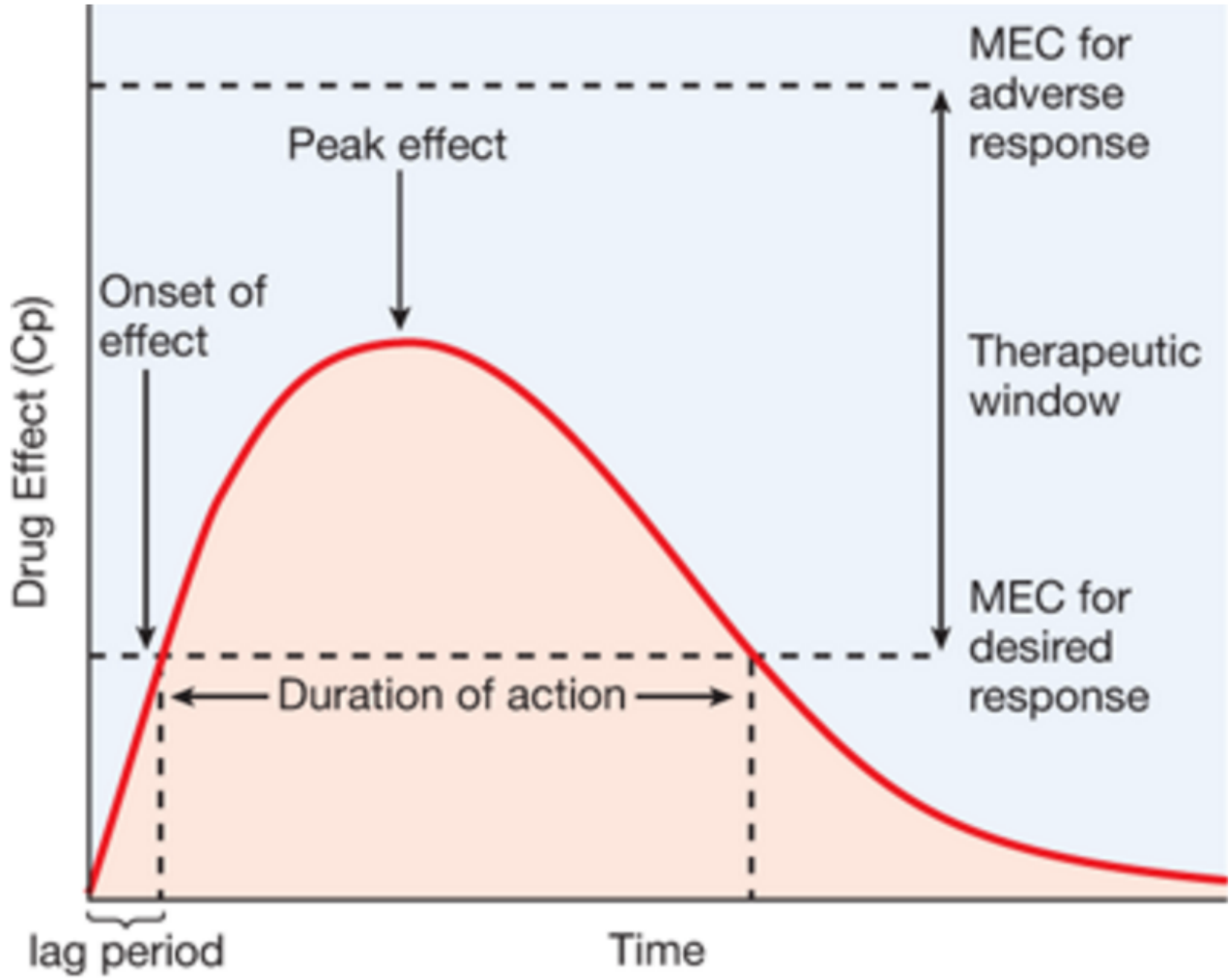
In the presence of an agonist, the antagonist shoves the agonist off the binding site, reversing the agonist's actions and restoring the resting state. Thus, the ion channel has returned to its status before the agonist acted.

Stahl SM. Stahl's Essential Psychopharmacology, 4e. Figure 3-5.

Pharmacodynamic Effects

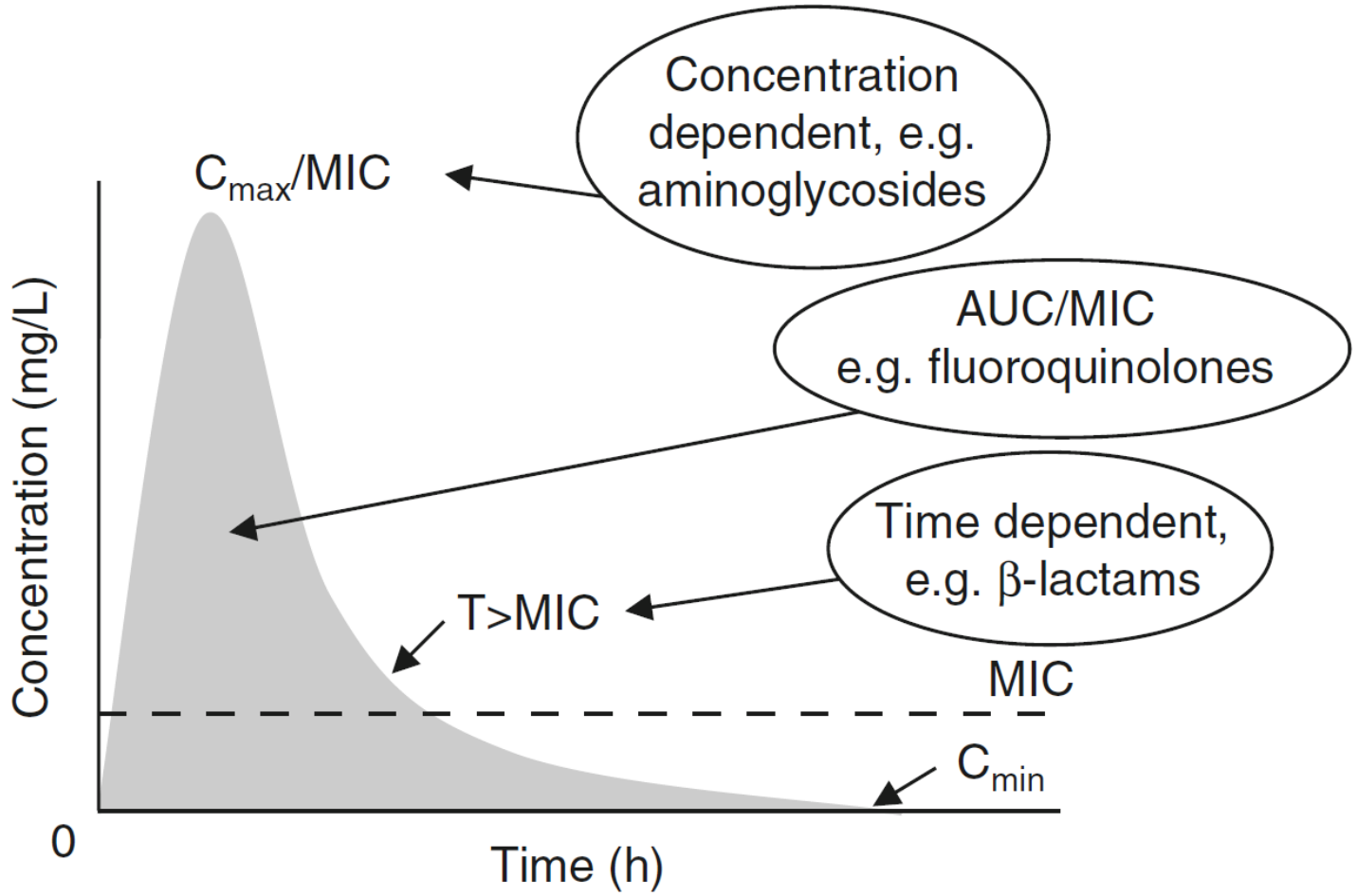
- Therapeutic effect
  - What you want the drug to do
  - Example: morphine relieves pain
- Side effects
  - "Off-target" effects (can range from mild to severe)
  - Idiosyncratic: unpredictable
    - Ex: Steven-Johnsons Syndrome
  - Paradoxical: opposite of what you'd expect
    - Ex: Benzodiazepines
  - Iatrogenic: caused by medical treatment
    - Ex: Chemotherapy drugs

How Do We Relate Pharmacokinetics to Pharmacodynamics?



Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 12e. Figure 2-6.

How Do We Relate Pharmacokinetics to Pharmacodynamics?



MIC=minimum inhibitory concentration

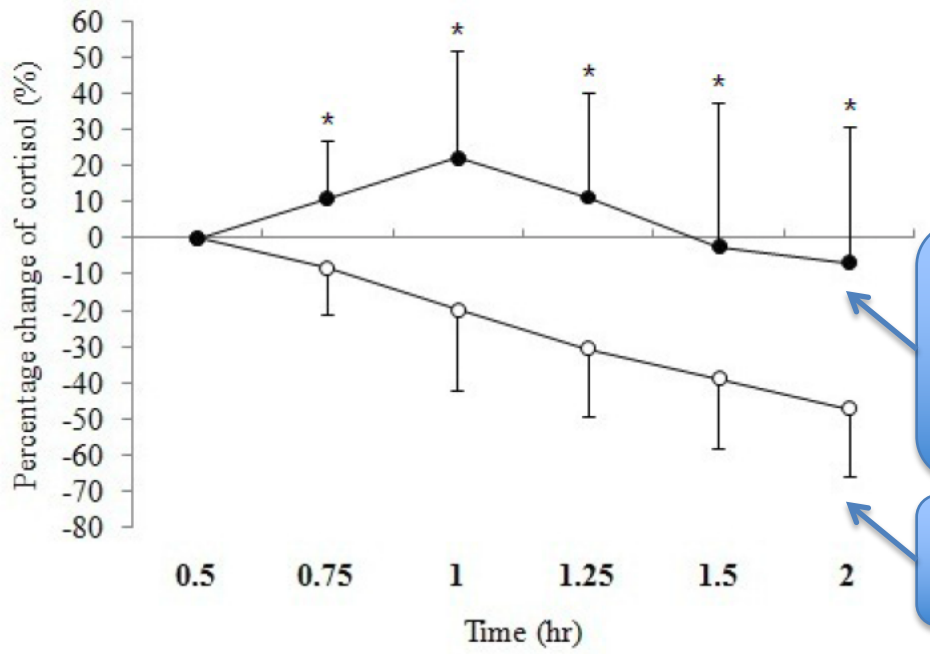
Roberts JA and Lipman J. Clin Pharmacokinet. 2006;45(8):755-773.

Effects of Physical Therapy on Pharmacodynamics

- Physical therapy sessions can work in conjunction with pharmacodynamics of medications
- Example: Patient who has shoulder tendonitis can take ibuprofen to reduce his shoulder pain while also attending physical therapy to increase his range of motion and further decrease his pain

Lenz TL. Expert opinion on drug metabolism & toxicology. 2011;7(3):257-266.

Back to our Prednisolone Example



- Exercise of appropriate intensity is a potent stimulus for GH and cortisol secretion.
- Diurnal cortisol variation

Exercise Arm: Cycled at 70% VO_{2max} intensity until exhaustion; significantly lower C_{max} ($p<0.05$)

Non-Exercise Arm: Remained seated for duration of experiment

Figure 3. Mean percentage change of cortisol after prednisolone administration. Data are shown as the mean ± SD.
*Significantly different from the other group ($p<.05$)

Chien KY et al. J Pharm Pharmaceut Sci. 2010;13(1):58-66.
Kanaley JA. The Journal of Clinical Endocrinology & Metabolism. 2001;86(6):2881-2889.

Pharmacodynamics Summary

- What the **drug** does to the **body**
- Drugs can either act as **agonists** (stimulate receptors) or **antagonists** (block receptors)
- Drugs can exert their therapeutic effect, but may also cause side effects
- Scientists relate PK to PD through curves, which help to determine doses and dosing intervals

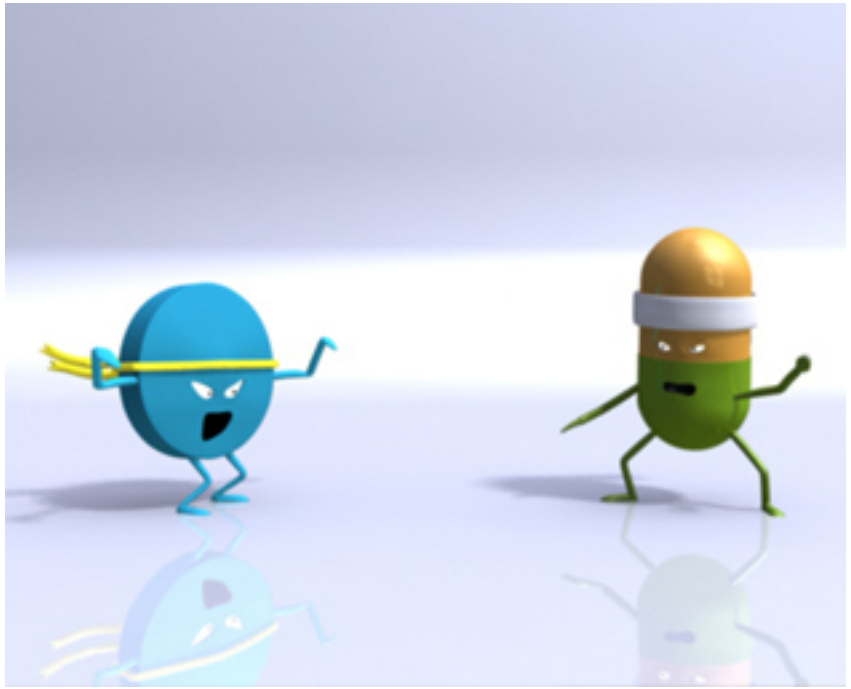
Time to put on your pharmacist hat (or coat!)

How Pharmacists Use PK & PD

- Drug-drug interactions
- Therapeutic Drug Monitoring
- Calculate doses
- Adjust doses for special populations
- Renal dose adjustments
- Clinical research
- Preclinical research

Drug-Drug Interactions (DDIs)

- Big part of a pharmacist's job
- Some drugs notorious for having DDIs (HIV drugs, warfarin)
- Can be PK or PD in nature
- Some are only theoretical whereas others have clinical effects
- DDI databases exist to provide guidance on how to manage DDIs (you'll learn about these next week!)



DDI Example #1

Propofol and Lorazepam

Both of these medications work by activating GABA receptors and causing CNS depression. The administration of these two together can result in decreased respiratory drive, bradycardia, and death.

PK or PD?

Lexicomp Online® , Lexi-Drugs® , Hudson, Ohio: Lexi-Comp, Inc.; February 21, 2016.

DDI Example #2

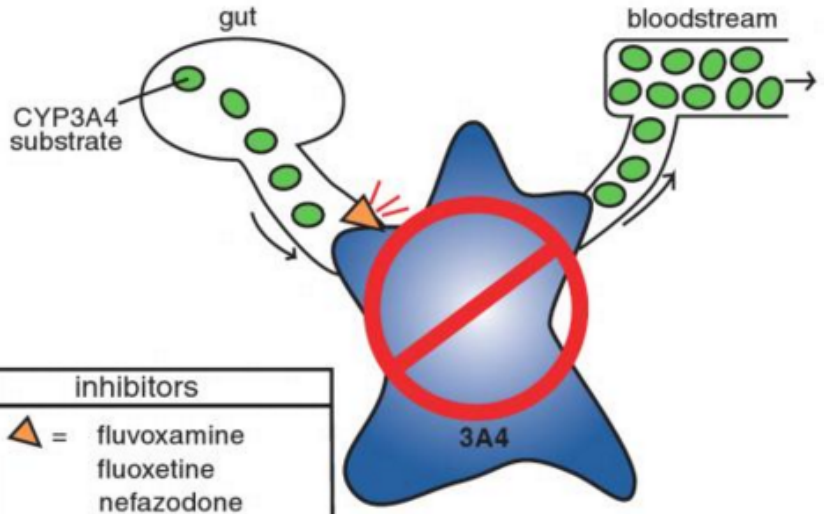
Ketoconazole and Quetiapine

Quetiapine is an antipsychotic that can cause QT prolongation. Ketoconazole is an inhibitor of the CYP450 enyzmes responsible for metabolizing quetiapine. Administration of the two together can cause prolonged QT interval and death.

PK or PD?

Lexicomp Online® , Lexi-Drugs® , Hudson, Ohio: Lexi-Comp, Inc.; February 21, 2016.

DDI Example #2



substrates	inhibitors
= pimozide alprazolam triazolam buspirone HMG-CoA reductase inhibitors (simvastatin, atorvastatin, lovastatin, cerevastatin) clozapine quetiapine sertindole aripiprazole zotepine lurasidone iloperidone	= fluvoxamine fluoxetine nefazodone erythromycin ketoconazole protease inhibitors verapamil diltiazem

Stahl SM. Stahl's Essential Psychopharmacology. 4th ed. Figure 2-20.

DDI Example #3

Fluoxetine and Tramadol

Fluoxetine is a Selective Serotonin Reuptake Inhibitor (SSRI) and works by increasing serotonin levels in the CNS. Tramadol is a pain medication which binds to opiate receptors and inhibits reuptake of serotonin and norepinephrine. Administration of the two together can lead to "serotonin syndrome," resulting in mental status changes, diaphoresis, tachycardia, and death.

PK or PD?

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DDI Example #4

Clopidogrel and Omeprazole

Clopidogrel is a pro-drug that prevents platelets from aggregating and reduces thrombosis risk in cardiac stent patients. Omeprazole inhibits the P450 enzyme that metabolizes clopidogrel. Administration of the two together can lead to reduced anti-platelet effect and stent thrombosis.

PK or PD?

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Therapeutic Drug Monitoring

- Very important for drugs with narrow therapeutic window and certain antibiotics (vancomycin)
- Measuring concentration of drug in the blood
- Making dose adjustments based on the level and the patient's pharmacokinetics (clearance and volume)
- Ensuring the concentration stays in the therapeutic range

Therapeutic Ranges for Commonly Used Drugs

Drug	Range
Digoxin	0.5–2.0 ng/mL
Lidocaine	1.5–5.0 mg/L
Lithium	0.6–1.4 mEq/L
Phenobarbital	15–40 mg/L
Phenytoin	10–20 mg/L
Quinidine	2–5 mg/L
Cyclosporin	150–400 ng/mL
Valproic acid	50–100 mg/L
Carbamazepine	4–12 mcg/mL
Ethosuxamide	40–100 mg/L
Primidone	5–12 mg/L

PK in Critically Ill Patients

- Leaky capillaries can lead to **increased V_d** for water-soluble drugs
  - Fluid shifts from intravascular compartment to interstitial space
- Increased cardiac index can lead to **increased CL**
  - Inotropic agents often prescribed for hypotension
- End-organ dysfunction can lead to **decreased CL**

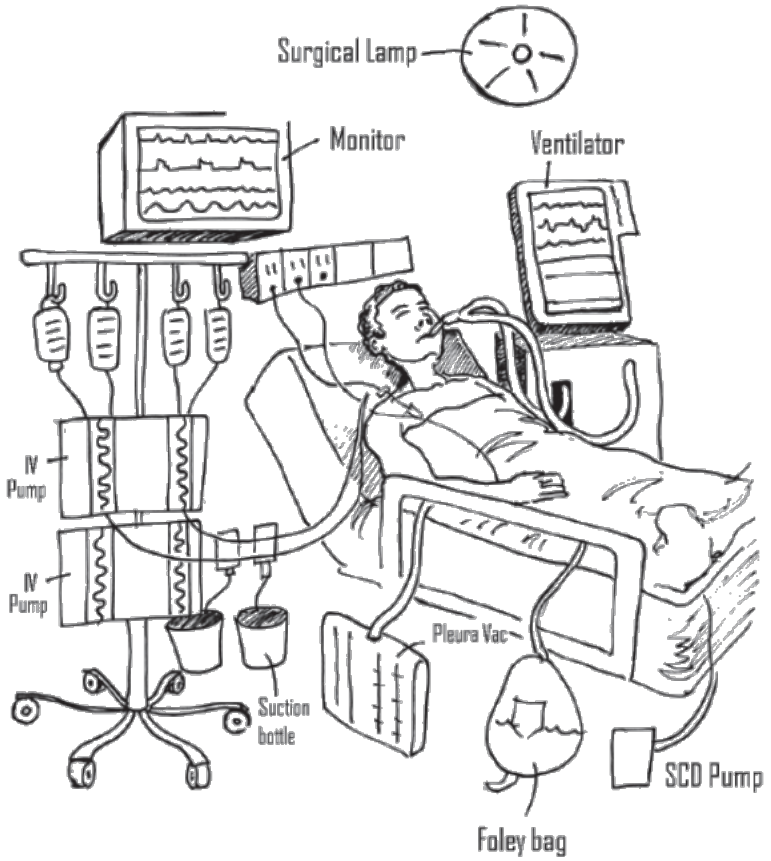
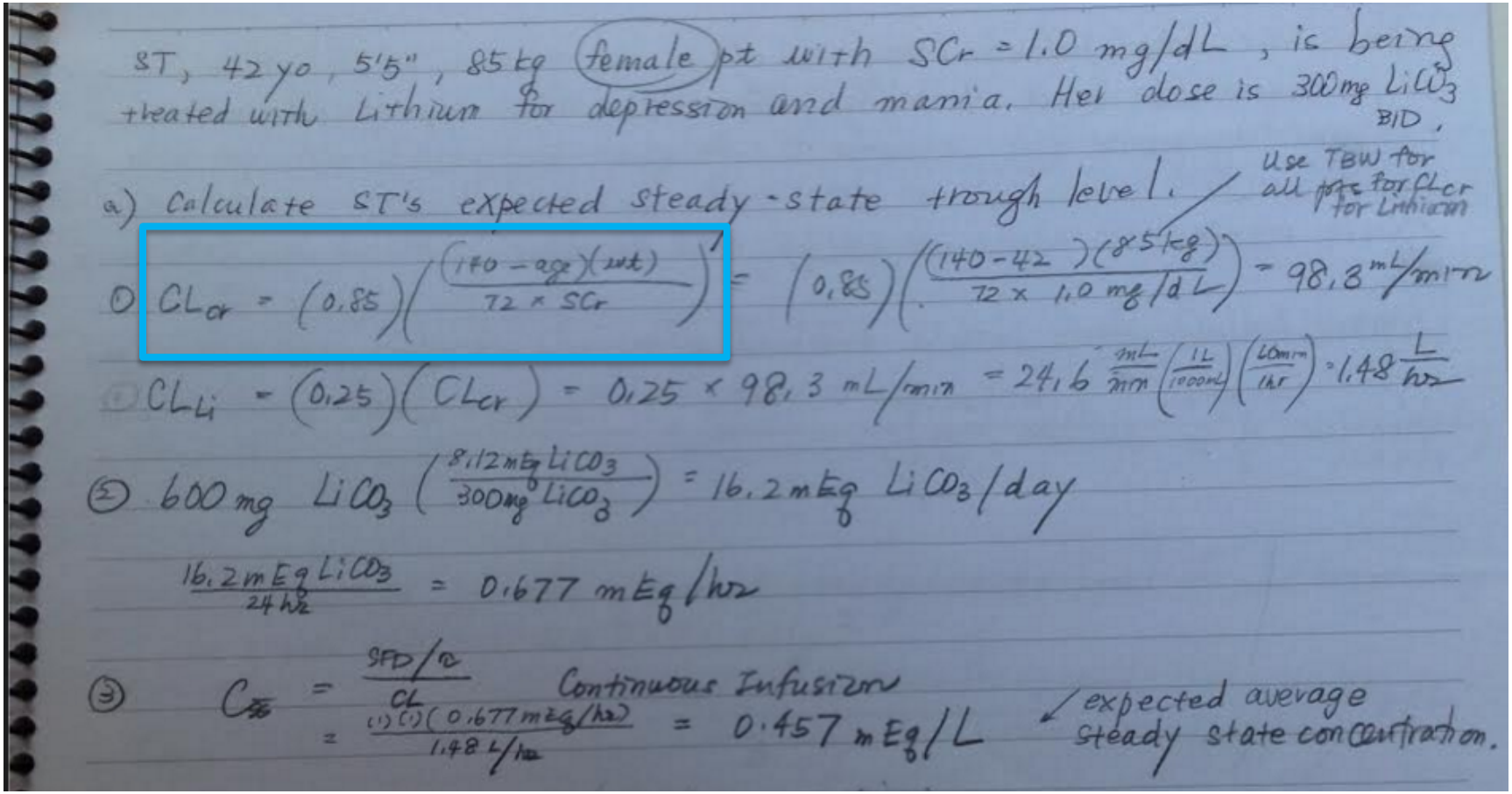


Image: UCSF Medical Center. A Family Guide to the ICU.

Roberts JA and Lipman J. Clin Pharmacokinet. 2006;45(8):755-773.

PK Calculations!



Cockcroft and Gault equation: estimates a patient's renal function

In Summary…

- PK and PD concepts are important for designing an optimally safe and efficacious therapeutic regimen
- Physical therapy treatments can affect how the body handles the drug (PK) and the patient's treatment outcome (PD)
- PK and PK/PD relationships can involve a lot of math, but understanding the underlying fundamental concepts is most important!

Questions?

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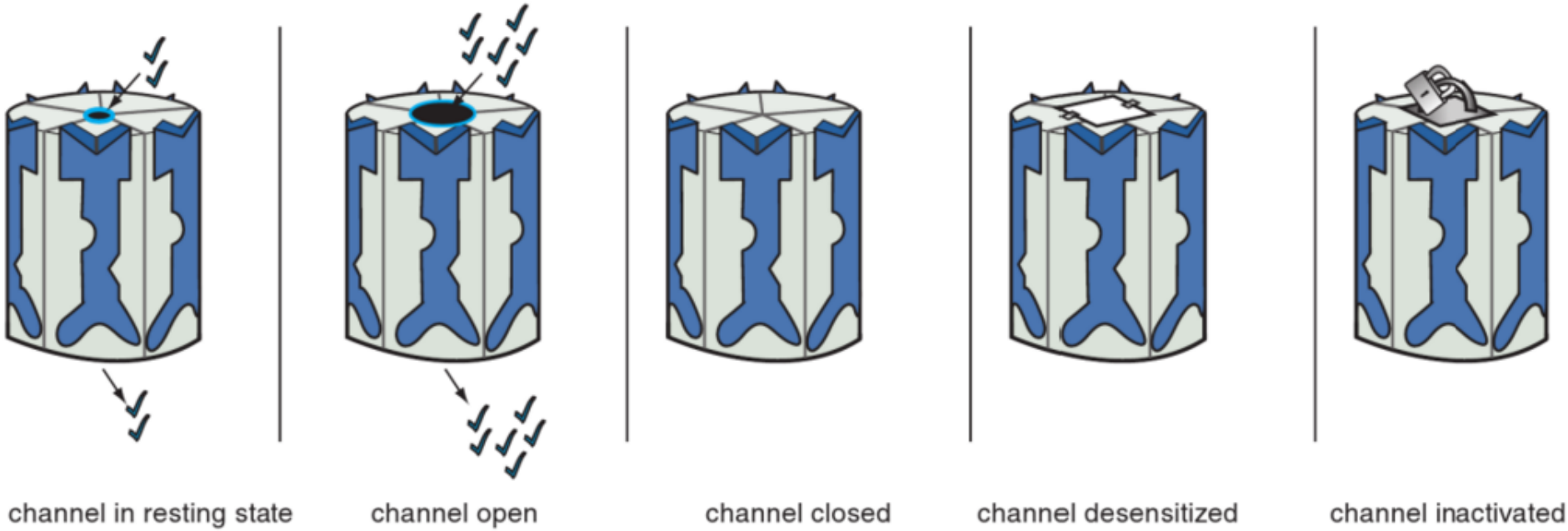
Ion Channels: Full Agonists, Partial Agonists, Antagonists

APPENDIX I: PD CONCEPTS

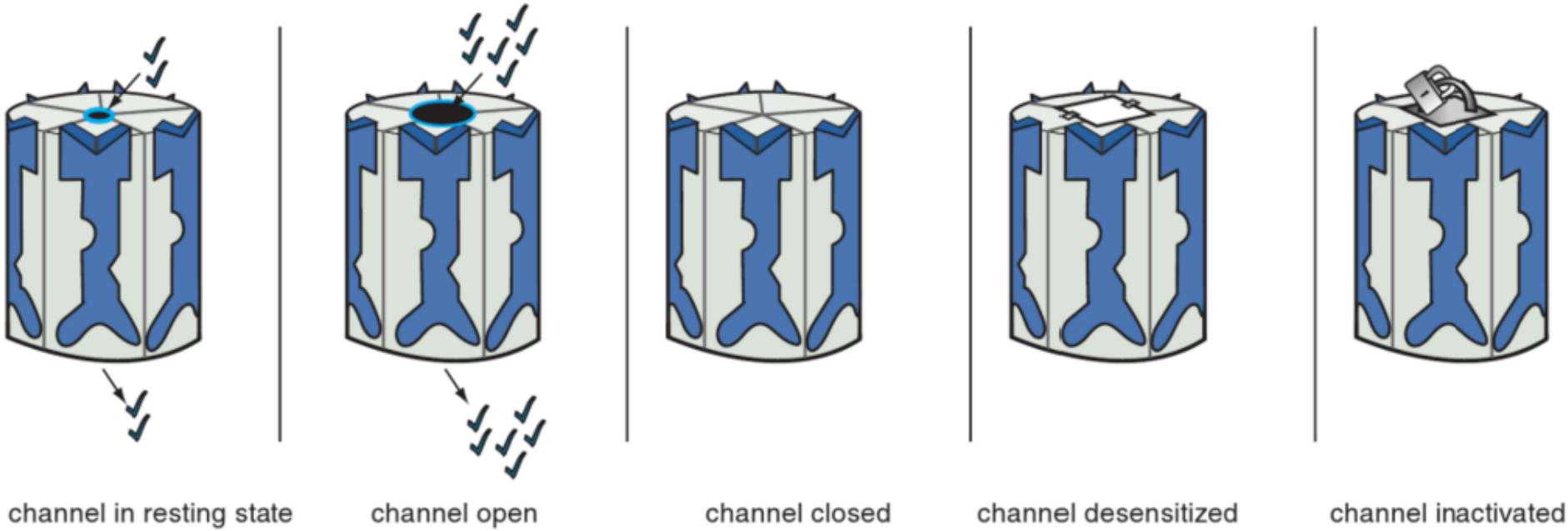
Five States of Ligand-Gated Ion Channels



- **Resting state**: channel opens infrequently; constitutive activity that may or may not lead to detectable signal transduction
- **Open state**: channel opens to allow ion conductance through the channel, leading to signal transduction
- **Closed state**: no ion flow, signal transduction is reduced to even less than is produced in the resting state

Stahl SM. Stahl's Essential Psychopharmacology. 4th ed. Figure 3-14.

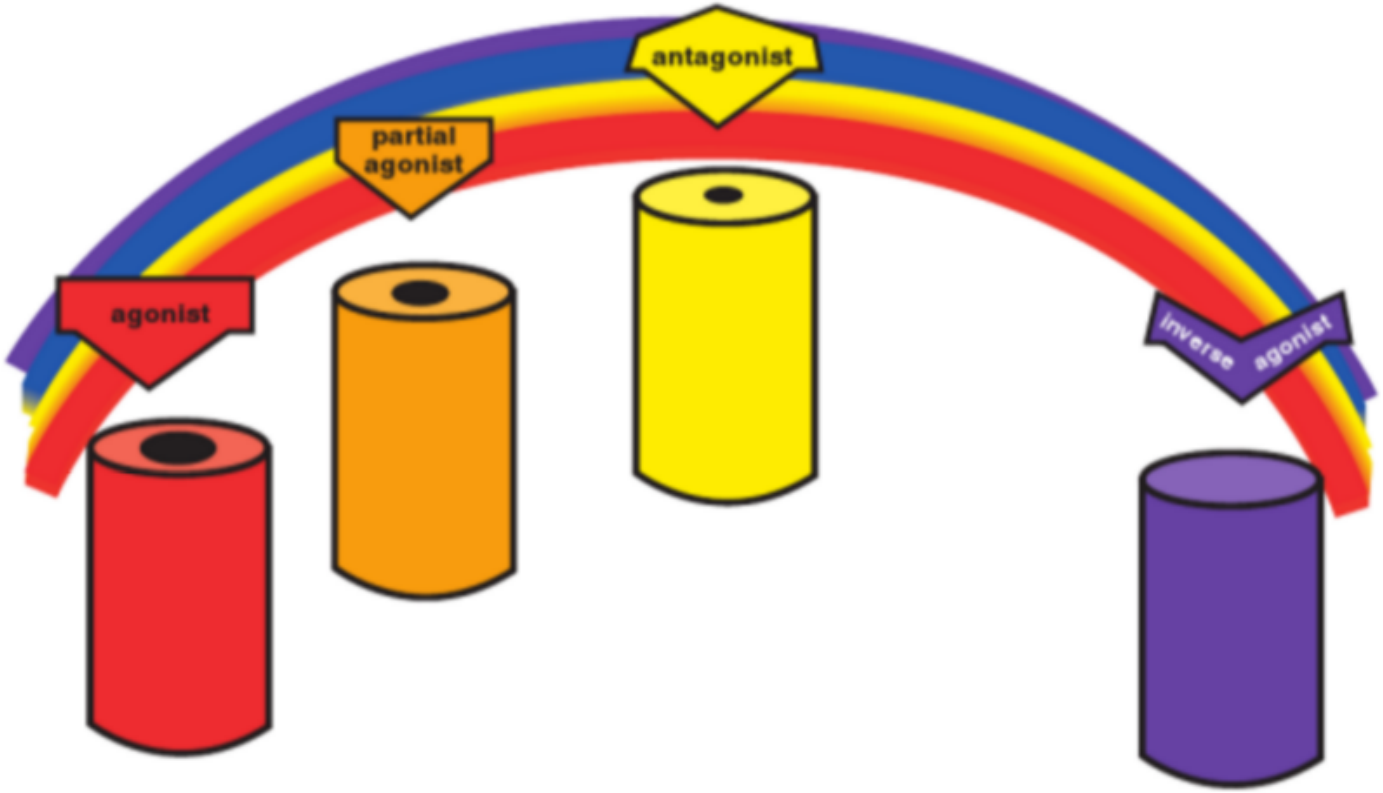
Five States of Ligand-Gated Ion Channels, continued



- **Channel desensitization:** an adaptive state in which the receptor stops responding to agonist even if it is still bound
- **Channel inactivation:** state in which a closed ion channel over time becomes stabilized in an inactive conformation

Stahl SM. Stahl's Essential Psychopharmacology. 4th ed. Figure 3-14.

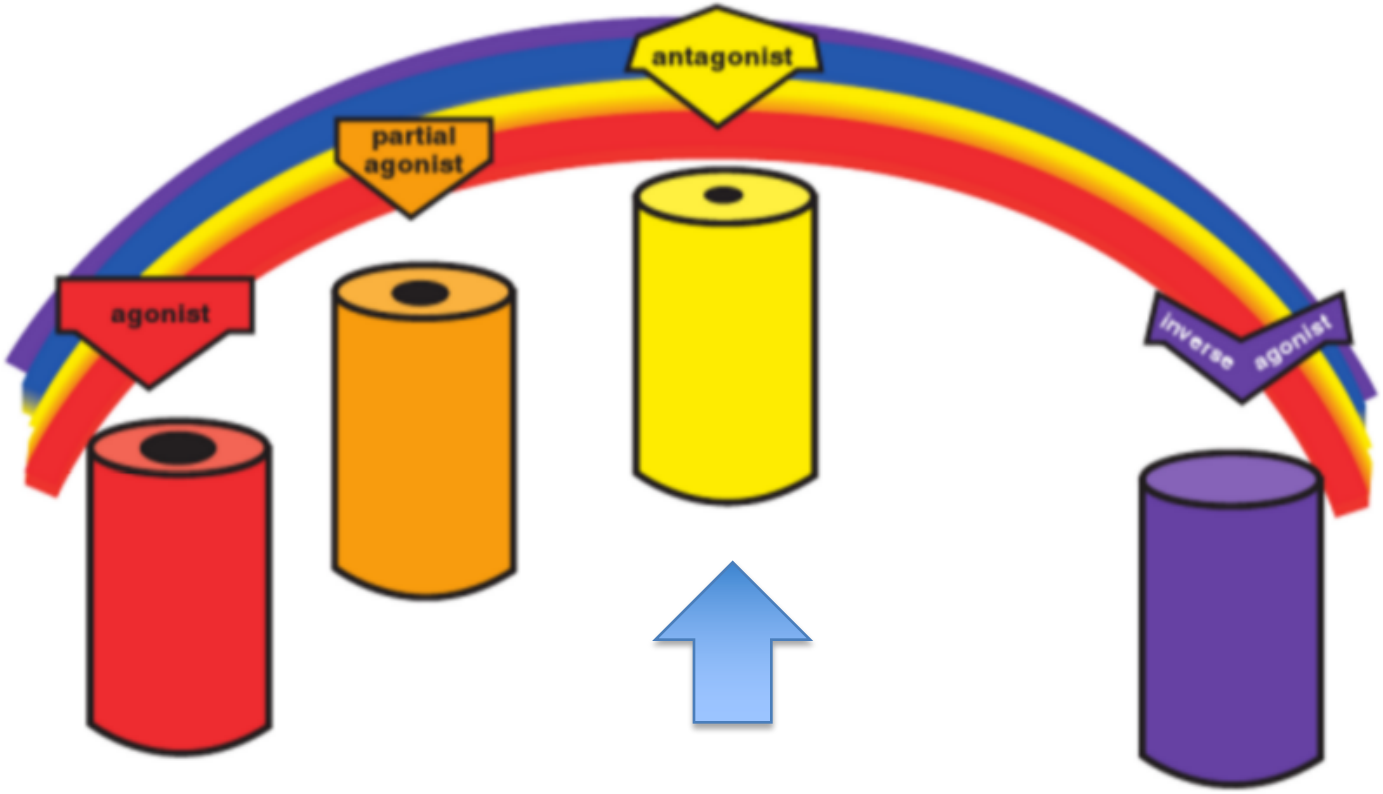
The Agonist Spectrum



- **Agonists: Open channel the maximum amount and frequency allowed by that binding site**
- **Partial Agonist: Increase the degree and frequency of channel opening compared to the resting state, but not as much as a full agonist**
- **Inverse Agonists: Put the ion channel in a closed and inactive state**

Stahl SM. Stahl's Essential Psychopharmacology. 4th ed. Figure 3-4.

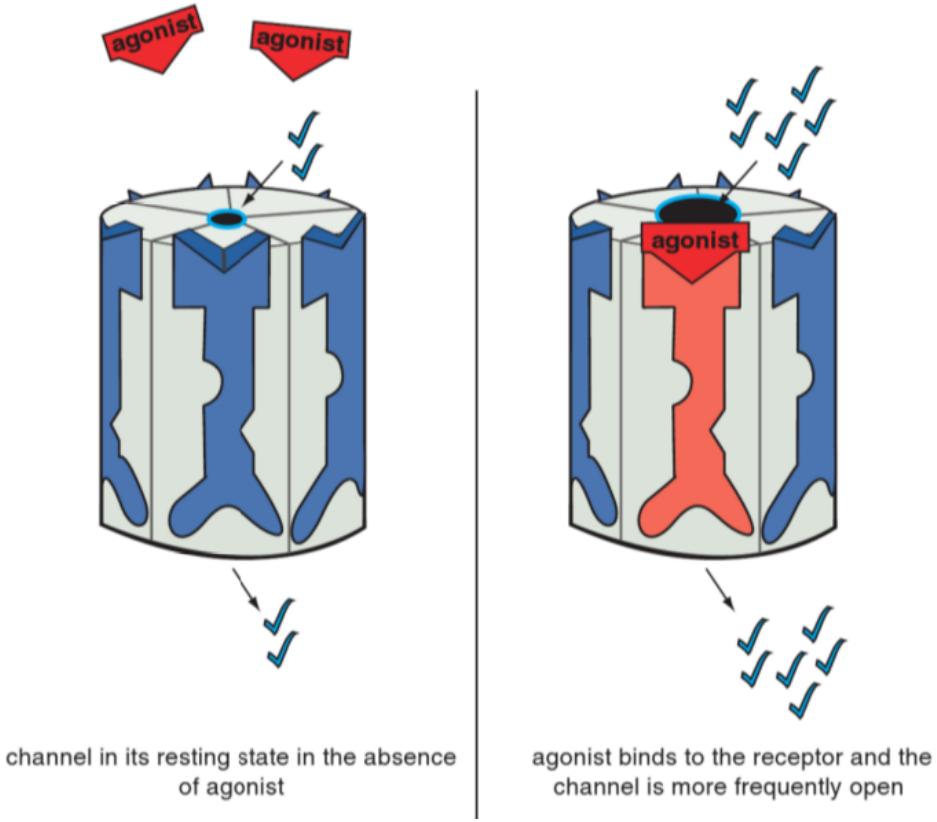
The Agonist Spectrum, continued



- **Antagonists: Retain the resting state with infrequent opening of the channel. Can block anything in the agonist spectrum, returning the ion channel to the resting state in each instance.**

Stahl SM. Stahl's Essential Psychopharmacology. 4th ed. Figure 3-4.

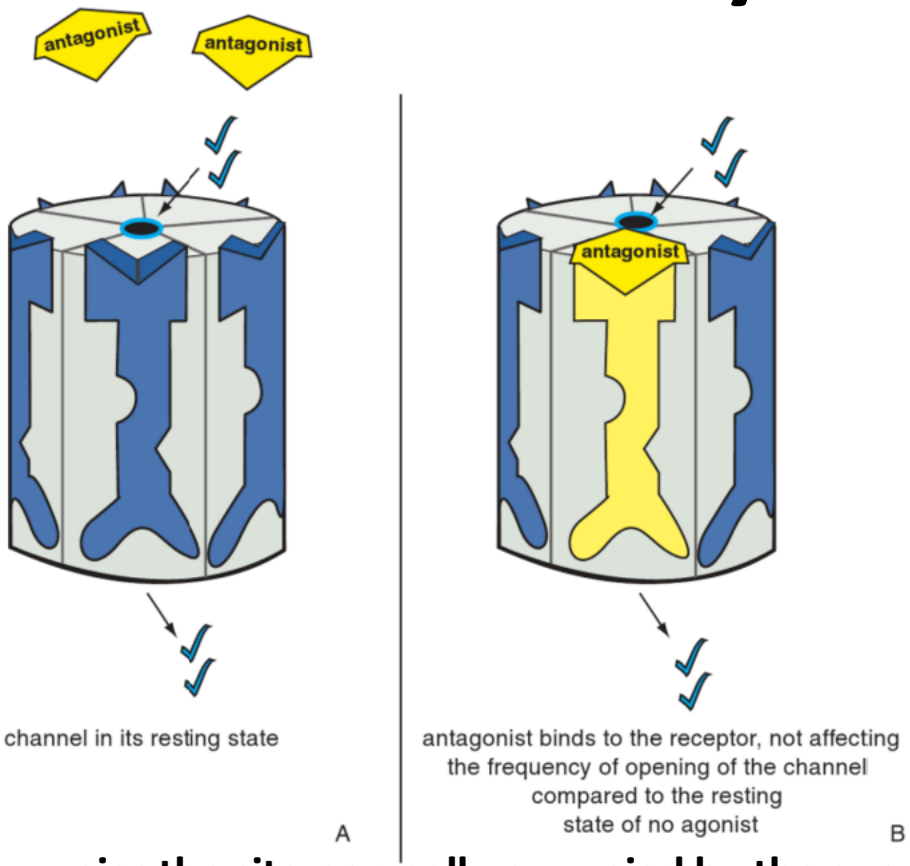
Agonist:
Increased channel opening frequency



In its resting state, the ion channel opens infrequently (constitutive activity). When the agonist occupies its binding site on the ligand-gated ion channel, it increases the frequency at which the channel opens.

Stahl SM. Stahl's Essential Psychopharmacology. 4th ed. Figure 3-5.

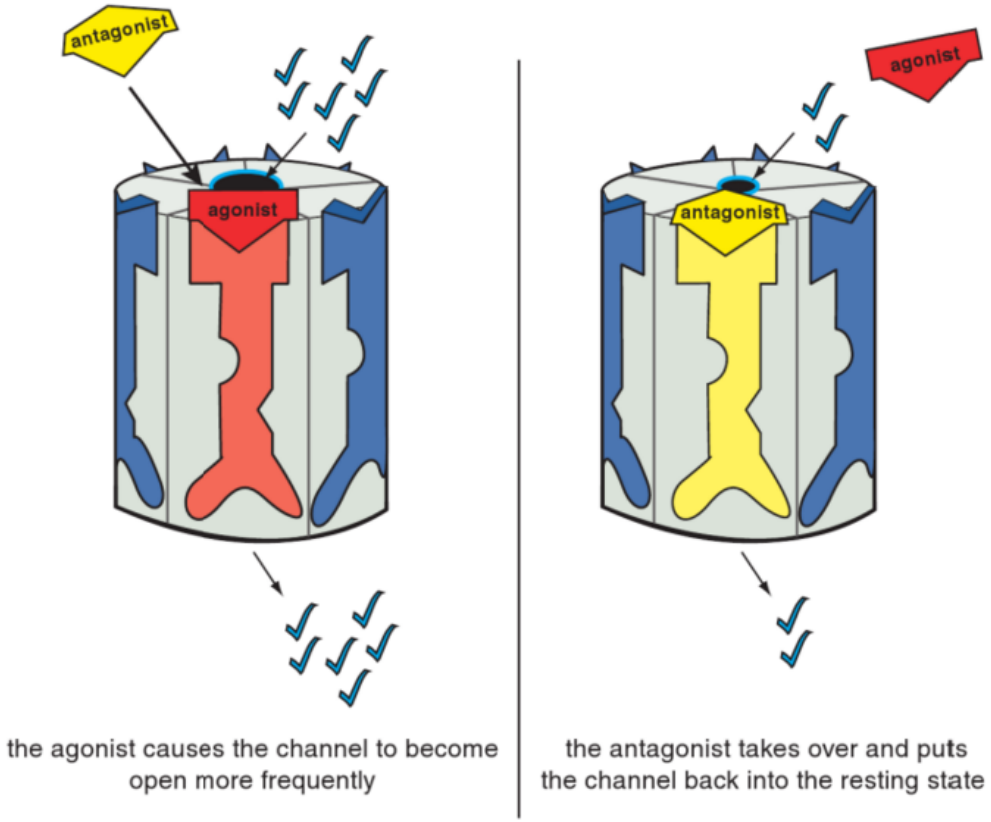
Antagonist: Constitutive activity only



When the antagonist occupies the site normally occupied by the agonist on the ligand-gated ion channel, there is no consequence to this. There is no effect on the degree or frequency of opening of the channel compared to the resting state.

Stahl SM. Stahl's Essential Psychopharmacology. 4th ed. Figure 3-5.

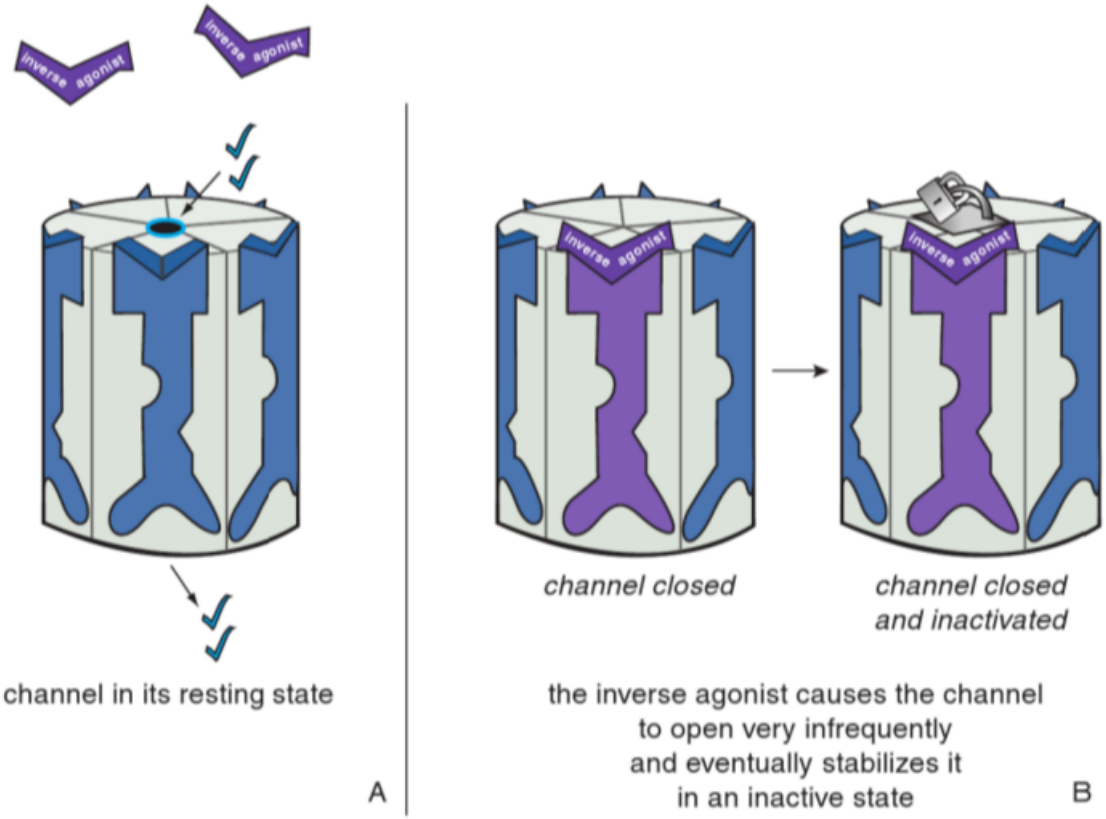
Antagonist in presence of Agonist: Constitutive activity only



In the presence of an agonist, the antagonist shoves the agonist off the binding site, reversing the agonist's actions and restoring the resting state. Thus, the ion channel has returned to its status before the agonist acted.

Stahl SM. Stahl's Essential Psychopharmacology. 4th ed. Figure 3-5.

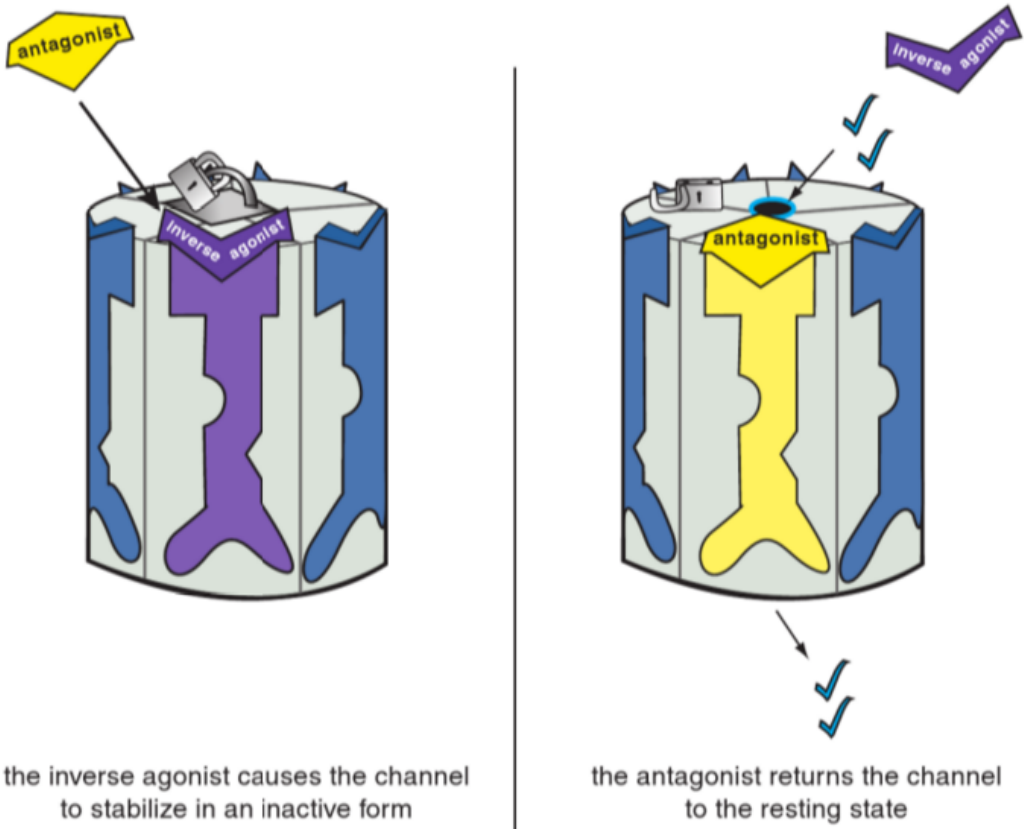
Inverse Antagonist: Closes and Inactivates Channel



When the inverse agonist occupies the binding site on the ligand-gated ion channel, this causes it to close. This is the opposite of what an agonist does! Eventually, the inverse agonist stabilizes the ion channel in an inactive state (represented by the padlock).

Stahl SM. Stahl's Essential Psychopharmacology. 4th ed. Figure 3-5.

Antagonist in presence of Inverse Agonist: Constitutive activity only

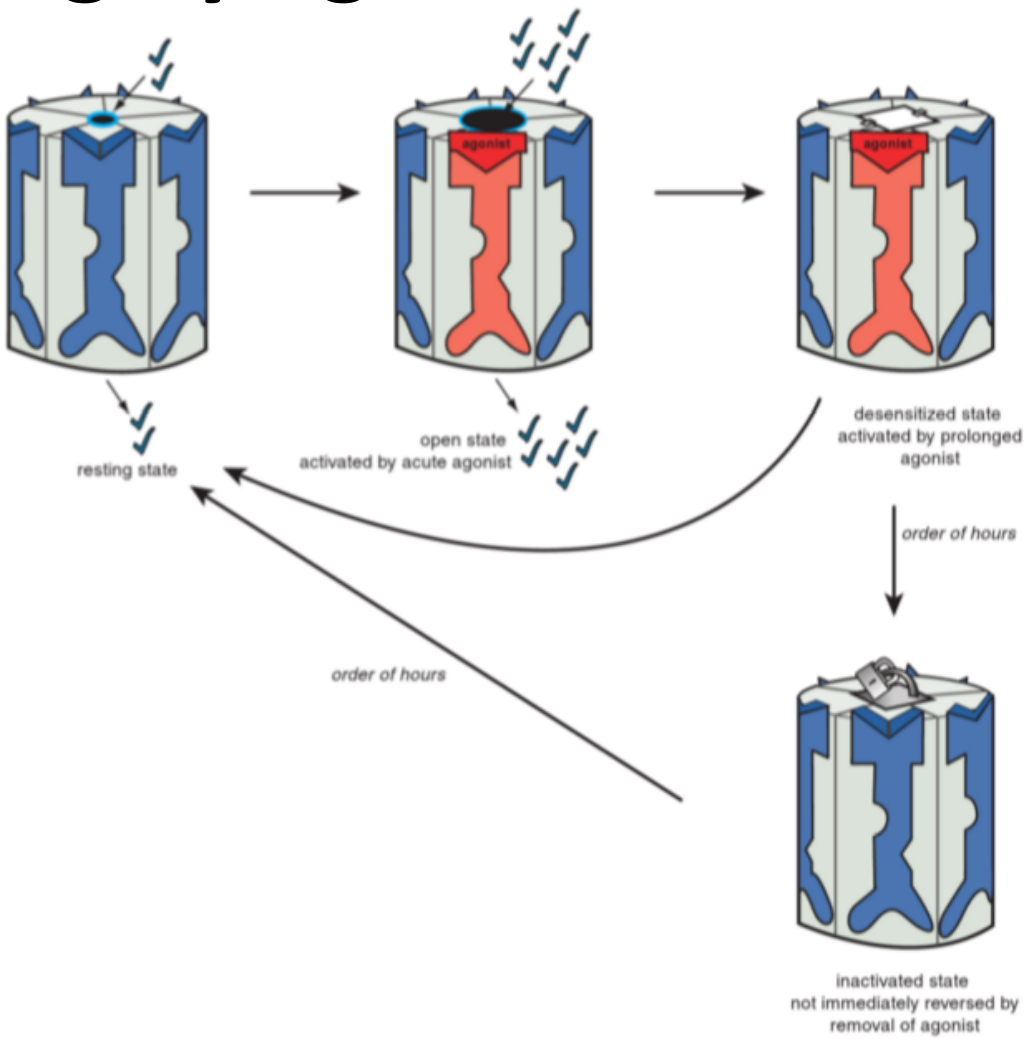


In the presence of an inverse agonist, the antagonist prevails and shoves the inverse agonist off the binding site, returning the ion channel to its resting state. An antagonist reverses the actions of either an agonist or inverse agonist despite the fact that it does nothing on its own.

Stahl SM. Stahl's Essential Psychopharmacology. 4th ed. Figure 3-5.

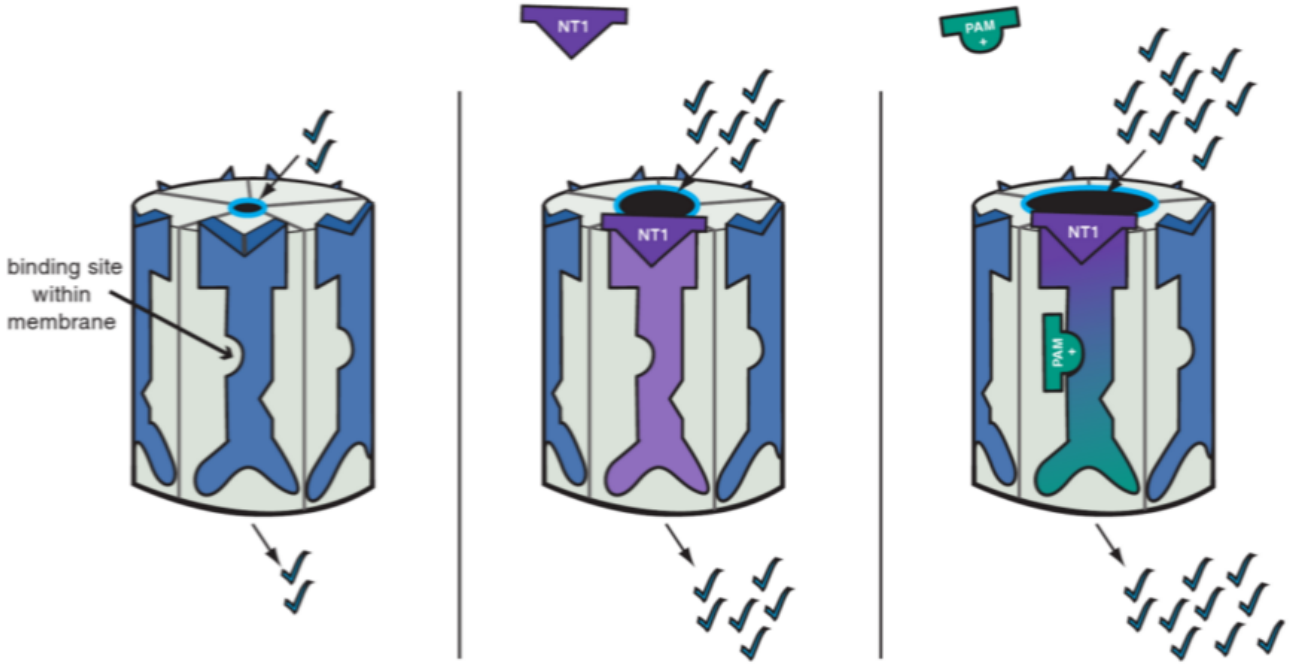
Opening, desensitizing, and inactivating by agonists

- **Prolonged exposure to agonists can cause a ligand-gated ion channel to enter a desensitized state in which it no longer responds to the agonist even if it is still bound.**
  - **Prompt removal of the agonist can reverse this state fairly quickly.**
- **However, if the agonist stays longer, it can cause a conformational change that leads to inactivation of the ion channel.**
  - **This state is not immediately reversed when the agonist is removed.**



Stahl SM. Stahl's Essential Psychopharmacology. 4th ed. Figure 3-15.

Allosteric Modulation: Enhance or block actions of neurotransmitters



When a neurotransmitter binds to receptors making up an ion channel, the channel opens more frequently. However, when BOTH the neurotransmitter and a positive allosteric modulator (PAM) are bound to the receptor, the channel opens much more frequently, allowing more ions into the cell.

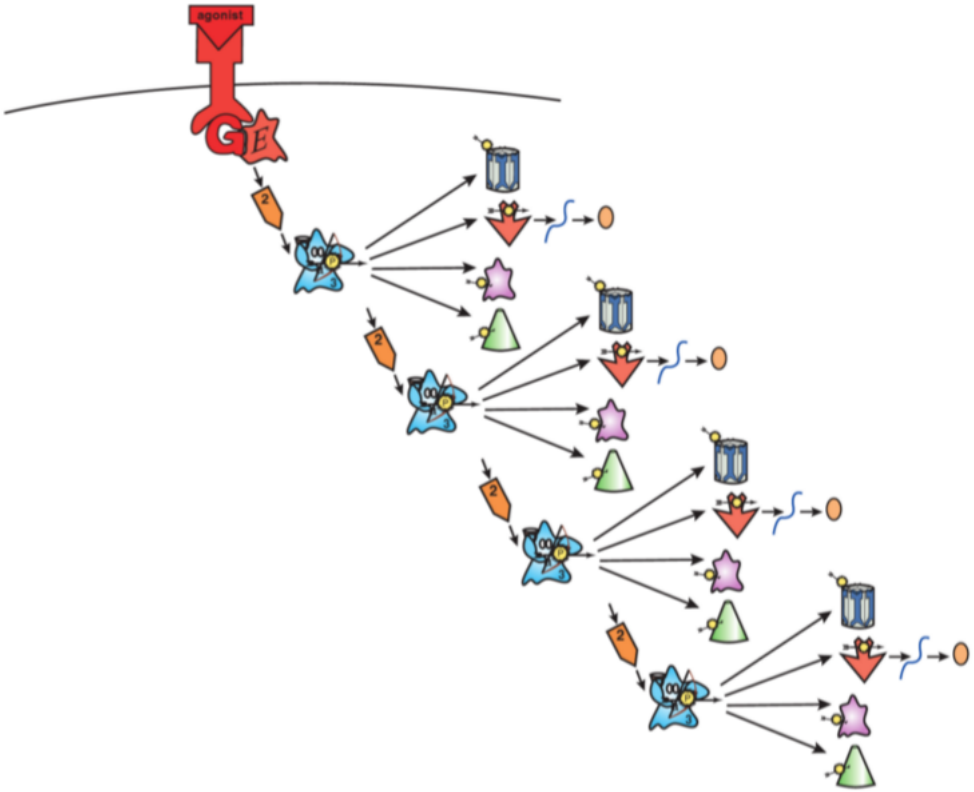
- **Allosteric modulators bind to sites other than the neurotransmitter site on an ion-channel-linked receptor.**
- **Allosteric modulators have no activity on their own – they enhance (positive allosteric modulators) or block (negative allosteric modulators) the actions of neurotransmitters.**

Stahl SM. Stahl's Essential Psychopharmacology. 4th ed. Figure 3-16.

GPCRs: Full Agonists, Partial Agonists, Antagonists

APPENDIX II: PD CONCEPTS

Full Agonist: Maximum Signal Transduction

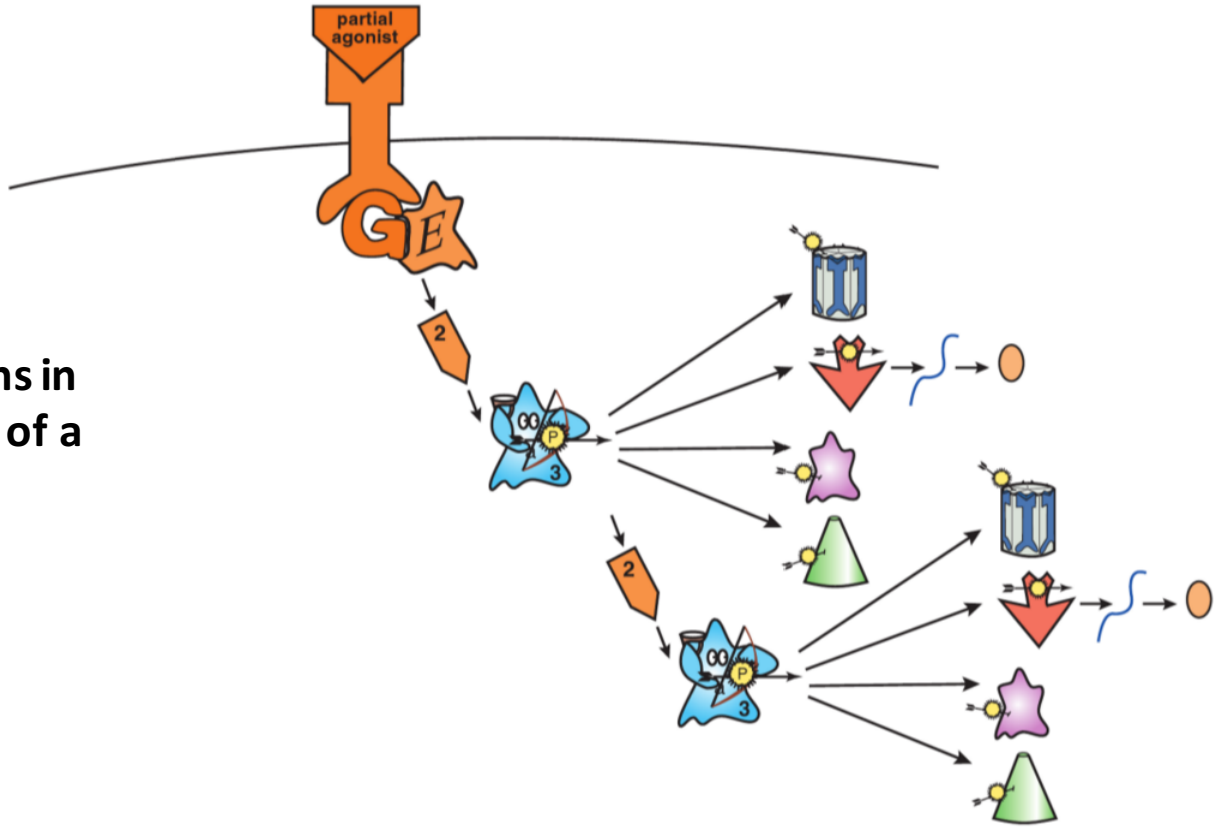


When a full agonist binds to GPCRs, it causes conformational changes that lead to maximum signal transduction. Thus, all the downstream effects of signal transduction, such as phosphorylation of proteins and gene activation, are maximized.

Stahl SM. Stahl's Essential Psychopharmacology. 4th ed. Figure 2-5.

Partial Agonist: Partially Enhanced Signal Transduction

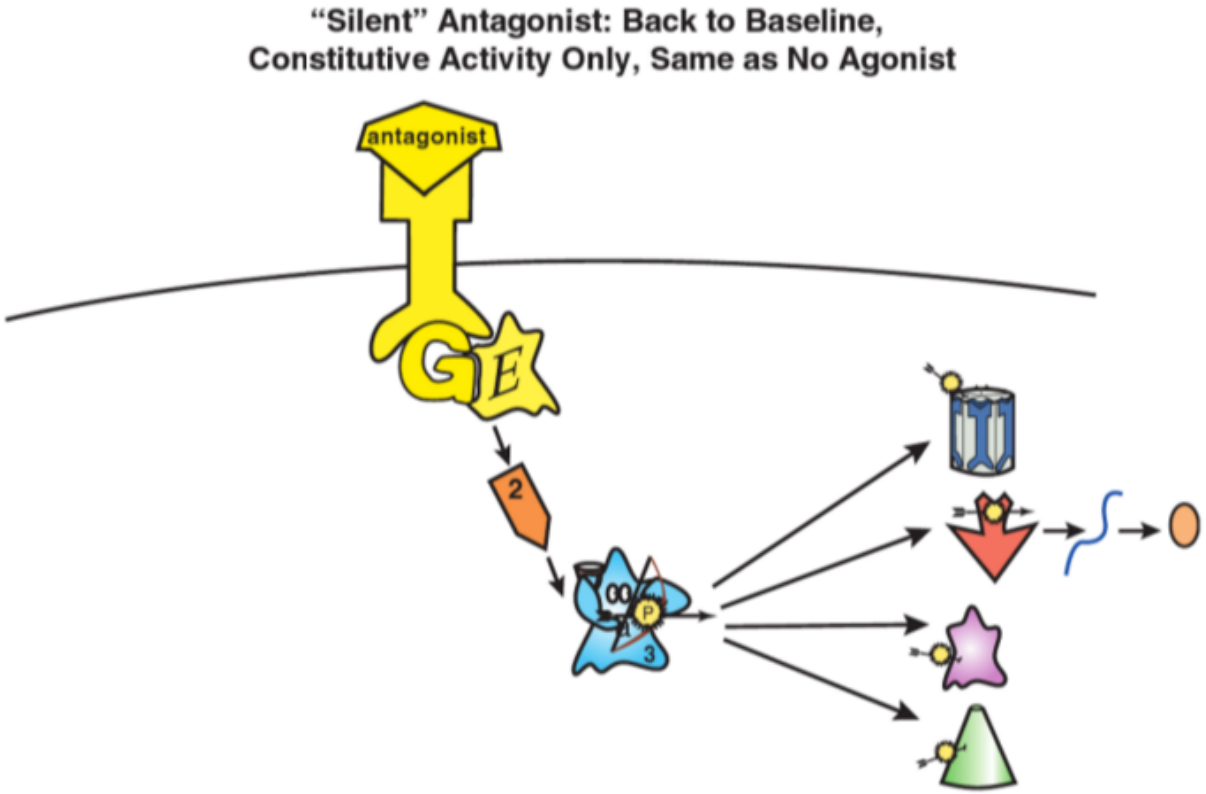
What happens in the presence of a full agonist?



Partial agonists stimulate GPCRs to enhance signal transduction but do not lead to maximum signal transduction the way full agonists do. Thus, in the absence of a full agonist, partial agonists increase signal transduction.

Stahl SM. Stahl's Essential Psychopharmacology. 4th ed. Figure 2-7.

Antagonist: Constitutive Activity Only



An antagonist blocks agonists (both full and partial) from binding to GPCRs, thus preventing agonists from causing maximum signal transduction and instead changing the receptor's conformation back to the same state as exists when no agonist is present.

Stahl SM. Stahl's Essential Psychopharmacology. 4th ed. Figure 2-6.

PK Playing a Role in Validating a PT Intervention

APPENDIX III: IONTOPHORESIS PHARMCOKINETICS

[RESEARCH REPORT]

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J. WILLIAM MYRER, PhD[2] • DENNIS L. EGGETT, PhD[3] • GARY W. MACK, PhD[2]

The Time Course of Dexamethasone Delivery Using Iontophoresis Through Human Skin, Measured via Microdialysis

Iontophoresis is a transdermal drug-delivery system that uses a direct or galvanic current to transfer ions through the skin to underlying tissues. Dexamethasone sodium phosphate (Dex-P) delivered via iontophoresis is commonly used in physical medicine and rehabilitation to treat tendinopathies; however, this procedure has been shown to exhibit inconsistent clinical outcomes.[1,8,19,21-23,25,28,32]

Using animal models, initial research out accumulation in venous blood.[5] How-

studies to humans difficult.

In vivo human studies have been limited by an inability to monitor tissue levels of Dex-P with minimally invasive techniques. For example, researchers have used indirect methods, such as assessing skin blanching characteristics[2] and venous blood draws,[30] to examine Dex-P delivery. One group of researchers directly

Rigby JH et al. J Orthop Sports Phys Ther. 2015;45(3):190-7. PMID: 25679344. A DME

Effects of Physical Therapy on Absorption

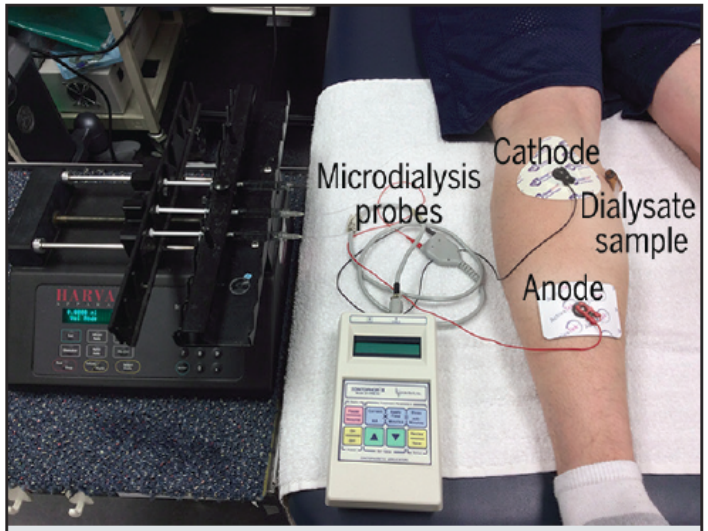

FIGURE 2. Iontophoresis treatment of dexamethasone sodium phosphate with in vivo drug concentration collected via microdialysis probes. The microdialysis probes were perfused with sterile saline at a rate of 1.2 µL/min.

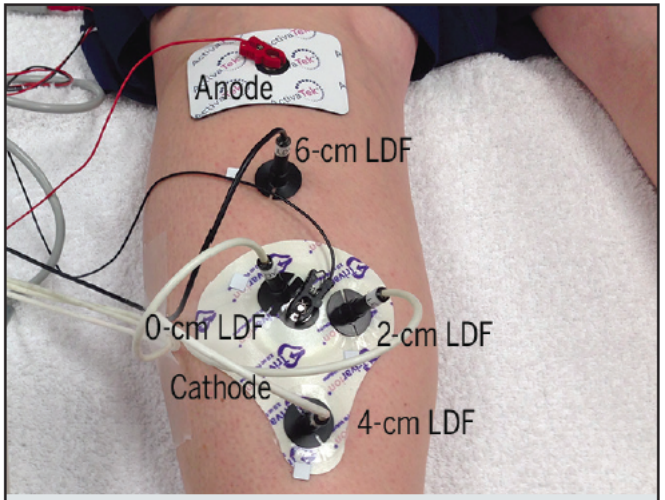

FIGURE 3. Placement of LDF probes to measure skin perfusion during iontophoresis treatment. The LDF probes were placed inside the drug chamber (0 cm), just outside the drug chamber (2 cm), and 4 and 6 cm from the center of the drug electrode. Abbreviation: LDF, laser Doppler flowmetry.

64 healthy male participants randomized to six groups:

- 1-mA current, 1-mm probe depth
- 1-mA current, 4-mm probe depth
- 2-mA current, 1-mm probe depth
- 2-mA current, 4-mm probe depth
- In vivo retrodialysis
- Skin perfusion flowmetry

A DME

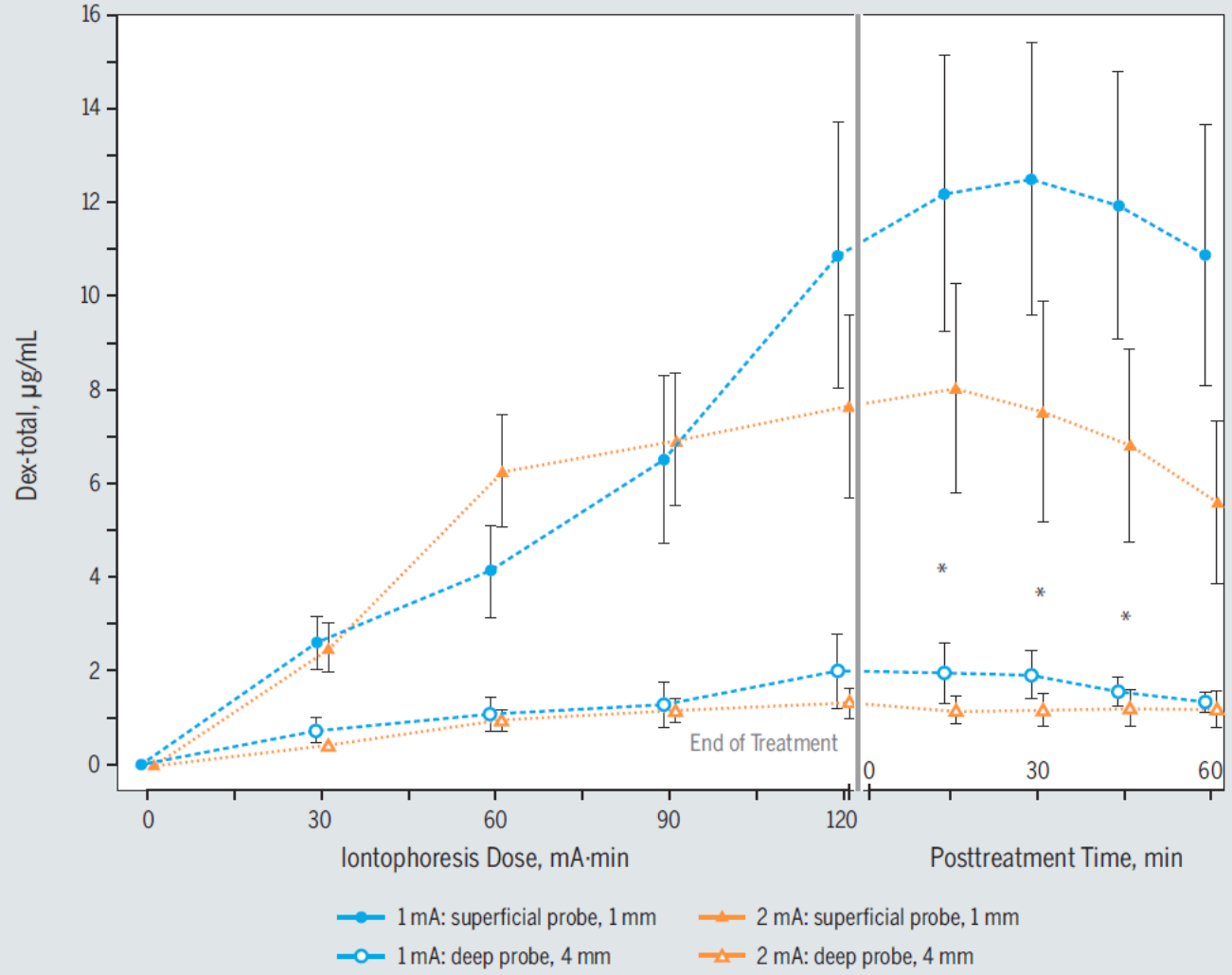

FIGURE 4. Dex-total (dexamethasone sodium phosphate + dexamethasone + dexamethasone-21-oic acid) concentrations between 1- and 2-mA intensities and different depths over a 120-mA·min iontophoresis dose. Values are mean ± 1 standard error of measurement for 8 participants in each group. *Significant difference of Dex-total between 1 and 4 mm within the 1-mA intensity conditions ($P<.05$).

A DME