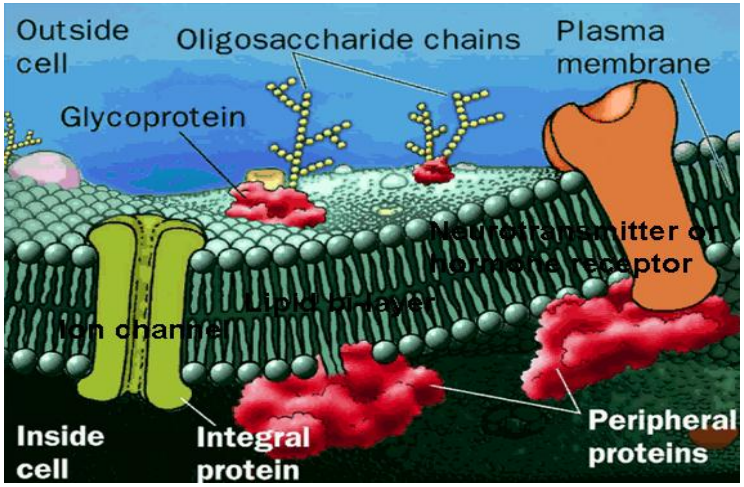
Basic Concepts of Pharmacology in Drug Development

Bob Lyon, PhD
Procter and Gamble Healthcare
Mason, OH

American Translators Association
San Diego, CA October 26, 2012



Agenda

- Overall Goals:
  - Gain an understanding of how drugs work
  - Gain an understanding of pharmacologic theory and practice
  - Gain an understanding of how drugs may be evaluated

- Terminology:

  - Mechanisms of Action
  - Agonists and Antagonists
  - Releasing Agents and Uptake Blockers
  - Potency
  - Efficacy
  - Dose Response
  - Therapeutic Index
  - Radioligand Binding Methods

Overview of Drug Development

- Basic Research:
  - Therapeutic target identified (e.g., 5-HT1A receptor: anxiety)
  - Chemical synthesis of new molecules that are specific for this receptor
  - In vitro screening (high throughput) to identify leads
  - Pharmacology evaluation: agonist, antagonist, potency
  - Lead selection
- Pre-Clinical Development of the Lead:
  - Animal pharmacology
  - Animal safety (rat, dog, monkey)
  - In vitro safety (screening endpoints)
  - Submit an IND (Investigational New Drug Application) to FDA
- Clinical Development:
  - Phase 1 Studies: Pharmacokinetics and initial safety
  - Phase II studies: Proof of Concept and Dose Ranging
  - Phase 3 Studies: Large efficacy/safety studies in intended population
  - File NDA and global submissions
- Phase 4: FDA commitments?
- Time: Up to 10 years. Cost: ca. $500 million (depends on drug class)

Drug Development: Focus for Today is Basic Research Principles and Terminology

- Basic Research:
  - Therapeutic target identified (e.g., 5-HT1A receptor: anxiety)
  - Chemical synthesis of new molecules that are specific for this receptor
  - In vitro screening (high throughput) to identify leads
  - Pharmacology evaluation: agonist, antagonist, potency
  - Lead selection

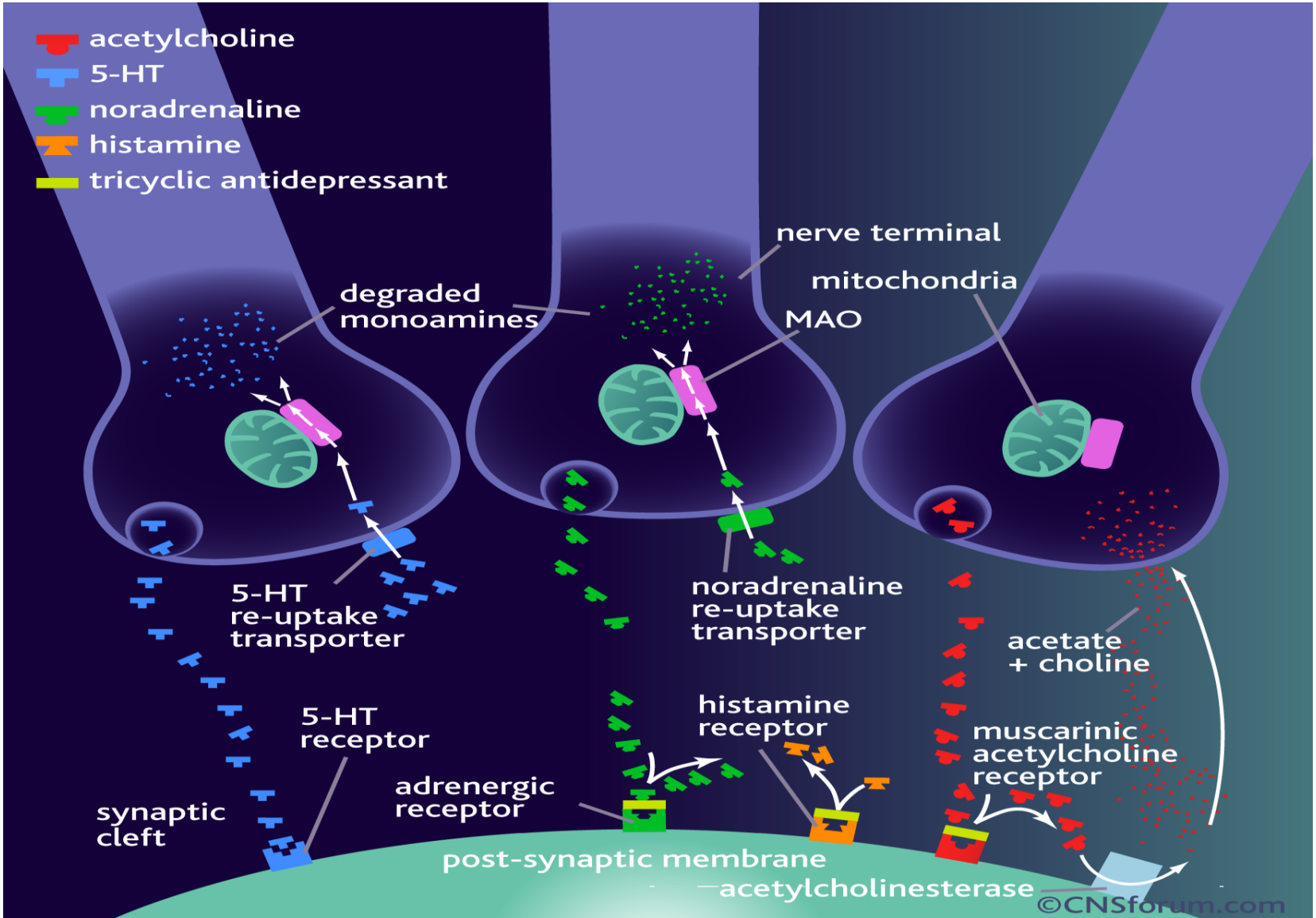
Terminology

- Drug: An exogenous substance that brings about a change in biologic function through its chemical action.
  - Phenylephrine, Dextromethorphan, Ibuprofen (OTC)
  - Bisoprolol, Risedronate, Simvastatin (Rx)
- Pharmacology: study of the effects of drugs on the body or system, or “what the drug does to the body”
  - Classical Pharmacology: in vitro/ in vivo testing
  - Molecular Pharmacology: cloned receptors/dna etc.

Drug Mechanisms of Action (MOA)

- Drugs produce their effects in a number of ways:
  - **Receptor-based**: stimulate or block a receptor
    - Phenylephrine activates alpha$_1$ adrenergic receptors
    - Ipratropium blocks the action of acetylcholine at cholinergic receptors
  - **Releasing Agents**: release neurotransmitter from nerve (cocaine)
  - **Re-uptake Blockers**: block the re-uptake of NT into nerve
  - **Enzyme-based**: activate or inhibit an enzyme
    - Monoamine oxidase inhibitors (MAO inhibitors): Iproniazid
    - ACE Inhibitors (anti-hypertensives): Captopril
  - **Activate or Inhibit Ionic channels**:
    - Calcium channel blockers for hypertension
    - Batrachotoxin: sodium channel activator
  - **Genetic Activation/Inhibition**:
    - Steroids

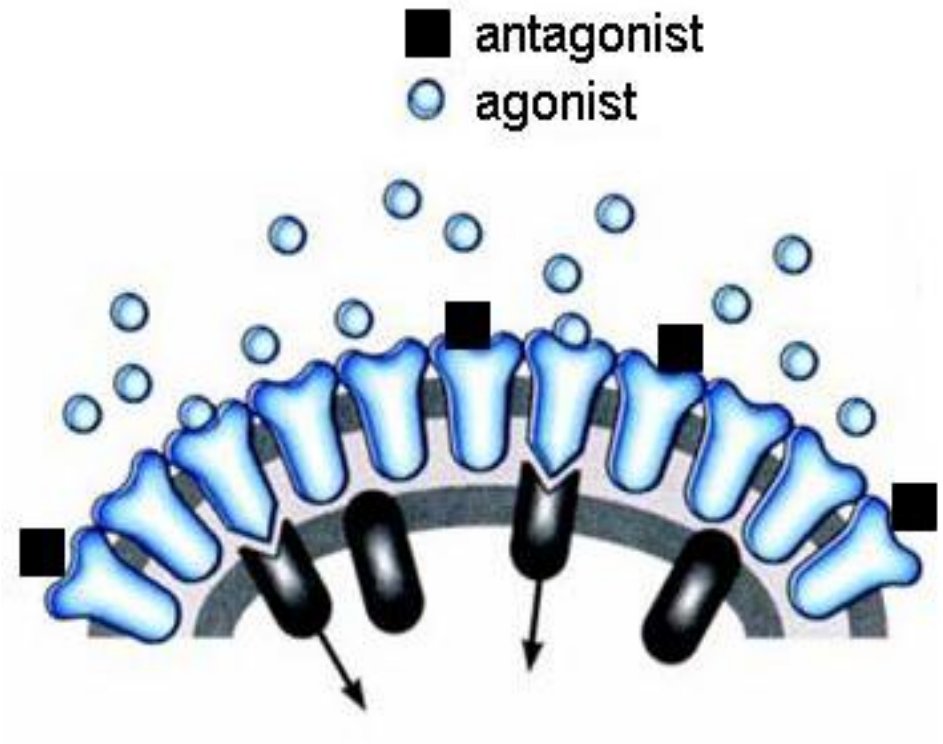
Drug Mechanisms of Action



Drug Action

- Agonists:
  - Mimic the action of an endogenous substance
    - Example: Norepinephrine
  - Activate or stimulate a receptor to produce a response
  - May be full agonists or partial agonists
  - Full agonist produces 100% of maximal response
  - Partial agonists produce < 100% of maximal response
  - EC50: dose that produces 50% of maximal response
- Antagonists:
  - Block the action of an endogenous substance
    - Example: Anti-cholinergic agents block acetylcholine
  - Competitive Antagonism: can be overcome (with more agonist)
  - Non-competitive Antagonism: cannot be overcome with more agonist

Receptor Agonists and Antagonists



Potency

- Potency: "A much misunderstood concept"
  - Potency is simply a **dose-related phenomena**
    - Potency has nothing to do with efficacy
    - Potency refers to dose: what dose do I need to get a certain response?
    - A low-potency drug can produce a full or maximal response
    - A very potent drug might only produce a partial response
    - Potency measured as EC50 (dose that produces 50% max response)
  - How can I achieve a maximal agonist response?
    - Give a small dose of a potent compound
    - Give a large dose of a less potent compound
  - Caveat: potent compounds MAY have less potential for side effects
    - Depends on pharmacology of the compound

Efficacy

- Efficacy: also a much misunderstood concept
  - Simply the level of response a drug can achieve relative to the maximal effect
  - Not related to potency
    - A full agonist may have low potency
    - A partial agonist may have high potency
  - Efficacy measured as % of full response: Emax
  - Full agonist: 100% response
  - Partial Agonist: < 100% response

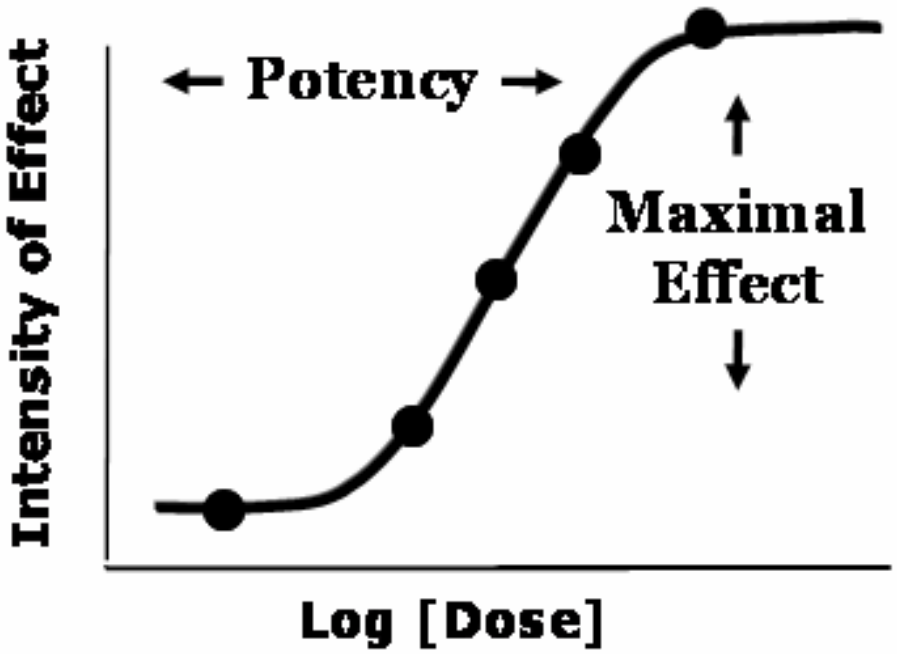
Dose-Response

- Now combine potency and response:
- Dose-Response Concept:
  - Concept that increasing dose will give increasing response
  - Based on Receptor Occupancy Theory
  - A full response will be achieved when all receptors are occupied
  - (Spare Receptor Theory: alternative concept)

The Dose-Response Curve

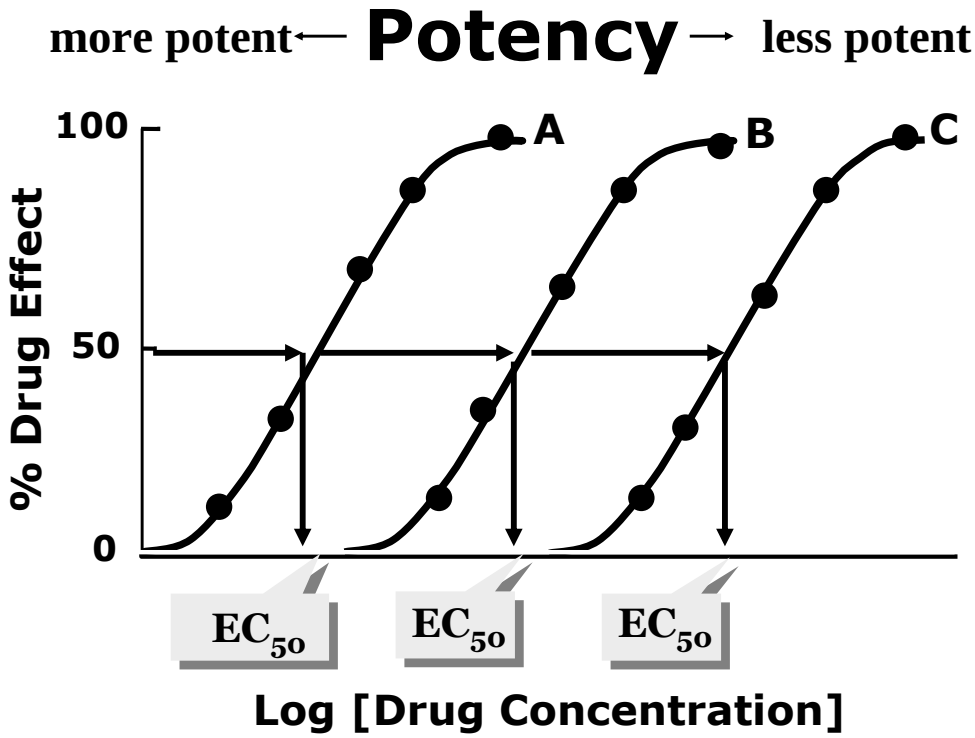
- The concept is that as we increase dose, we increase response
- Dose is plotted on a log scale (x-axis)
- % effect is plotted on the y-axis
- The result is a sigmoidal (S-shaped) curve
- Potency and maximal effect can be determined from this plot

Log Dose-Response Curve



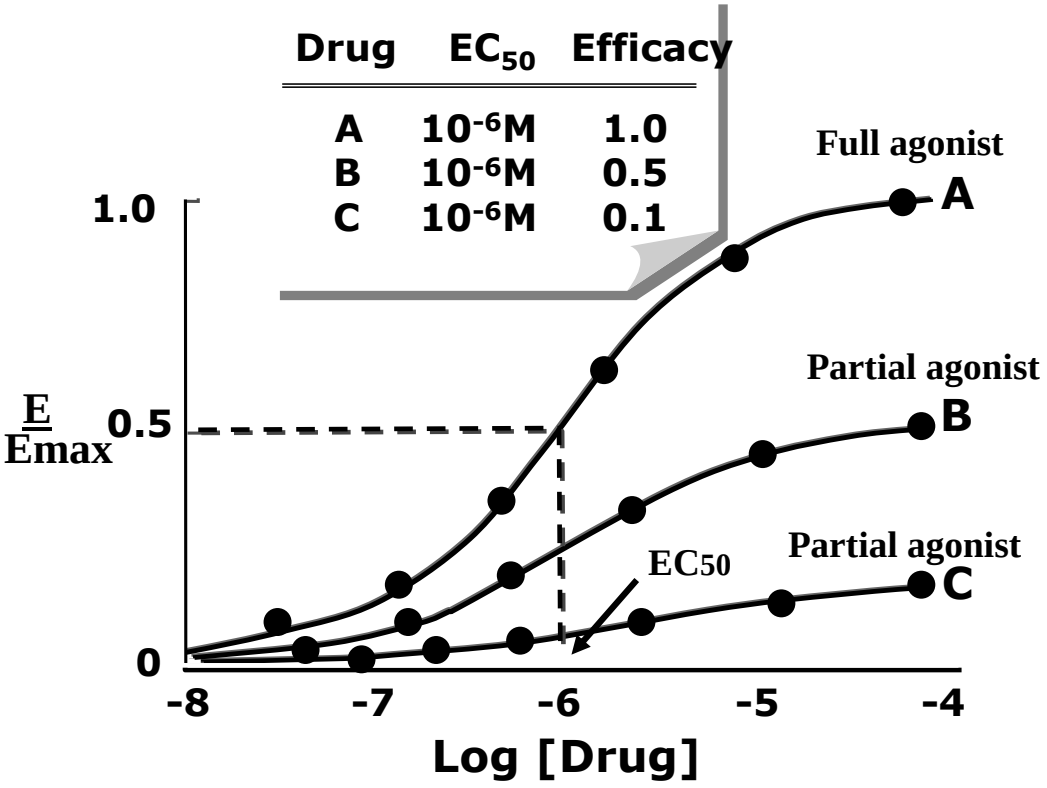
Potency

The potency of a series of drugs may be compared and the EC50 determined. The maximaum achieved effect (Emax) can also be determined.



Partial Agonists

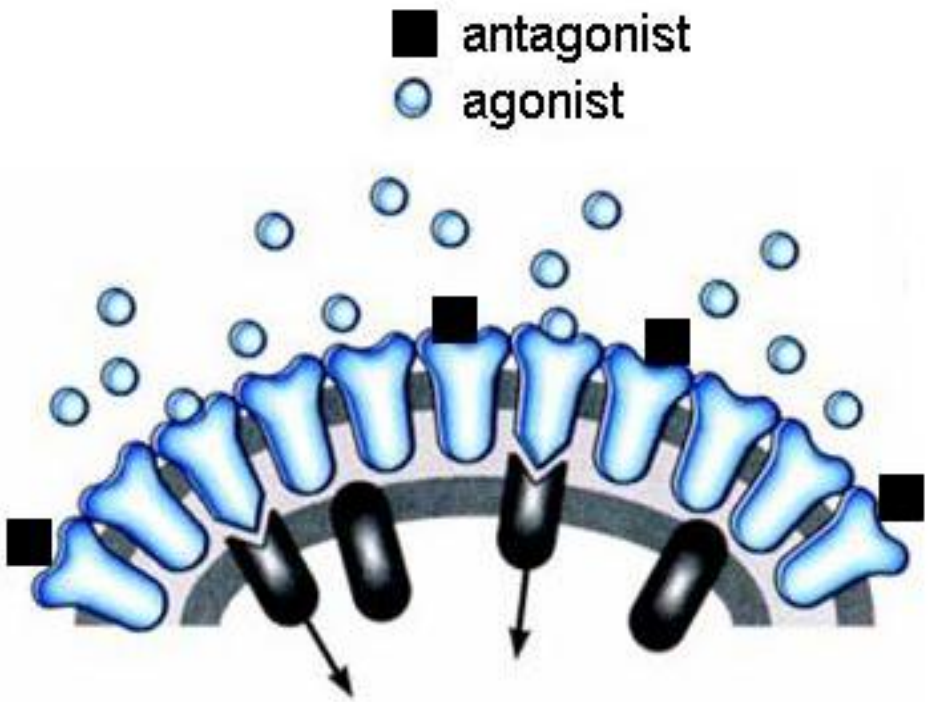
Partial agonists do not produce a full response, but they may have the same potency.



Antagonists

- Block the action of an endogenous substance
  - Example: Anti-cholinergic agents block acetylcholine
- Competitive Antagonism: can be overcome (with more agonist)
- Non-competitive Antagonism: cannot be overcome with more agonist

Antagonists: Block an Effect



Antagonists

Some questions for understanding:

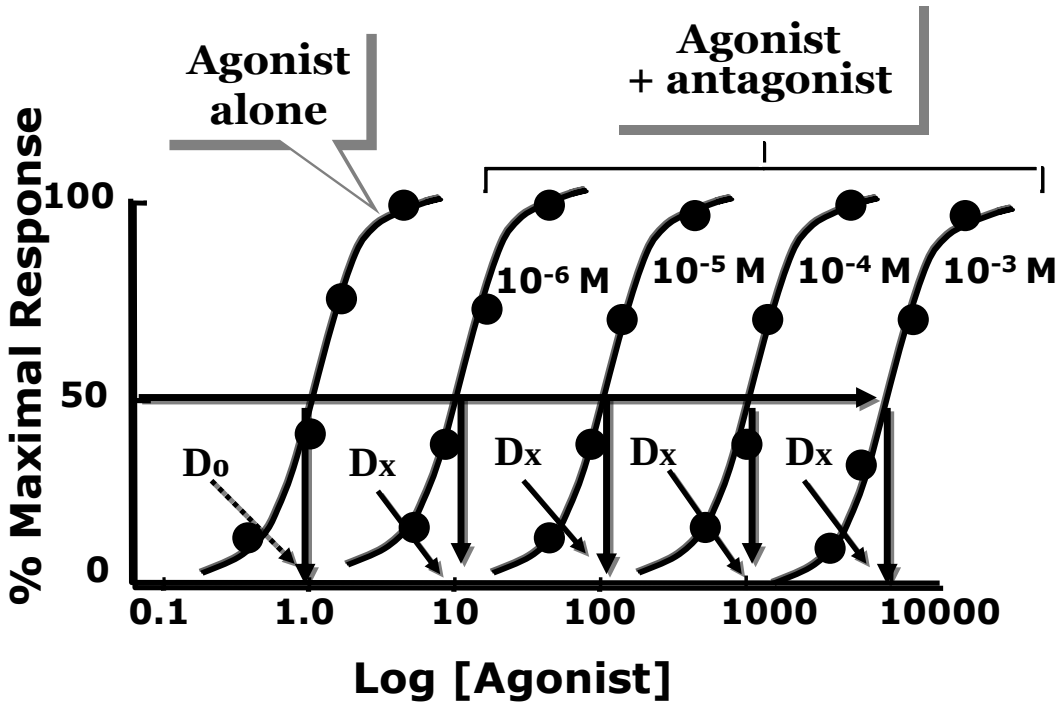
What is the dose-response for an antagonist?

What does that dose-response look like?

What is the EC50 and Emax of an antagonist?

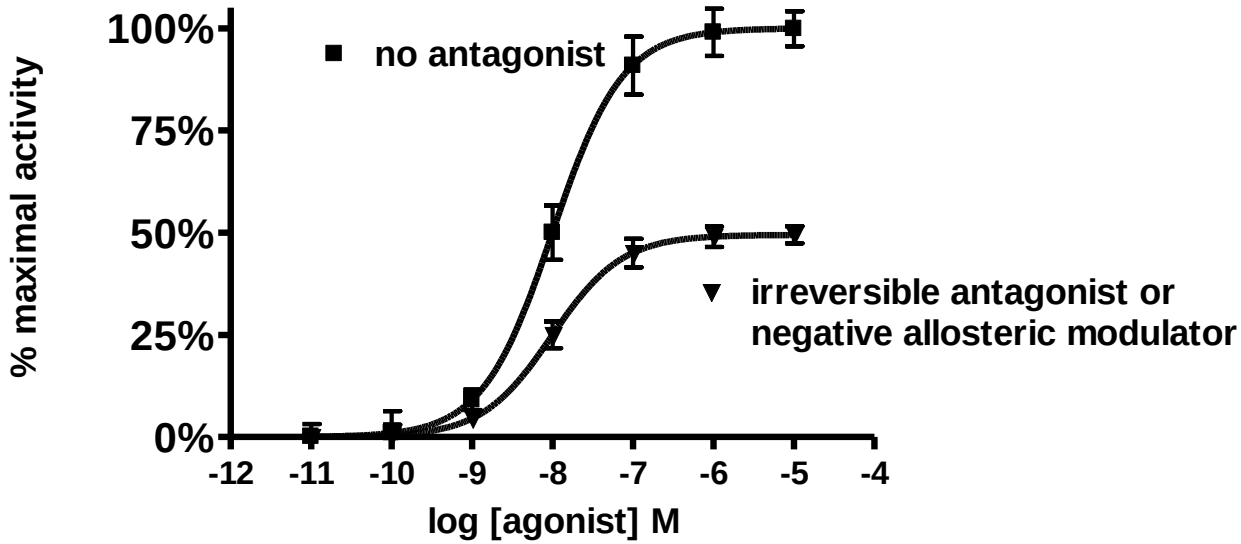
Competitive Antagonists

Shift the agonist dose-response curve. Emax remains the same.



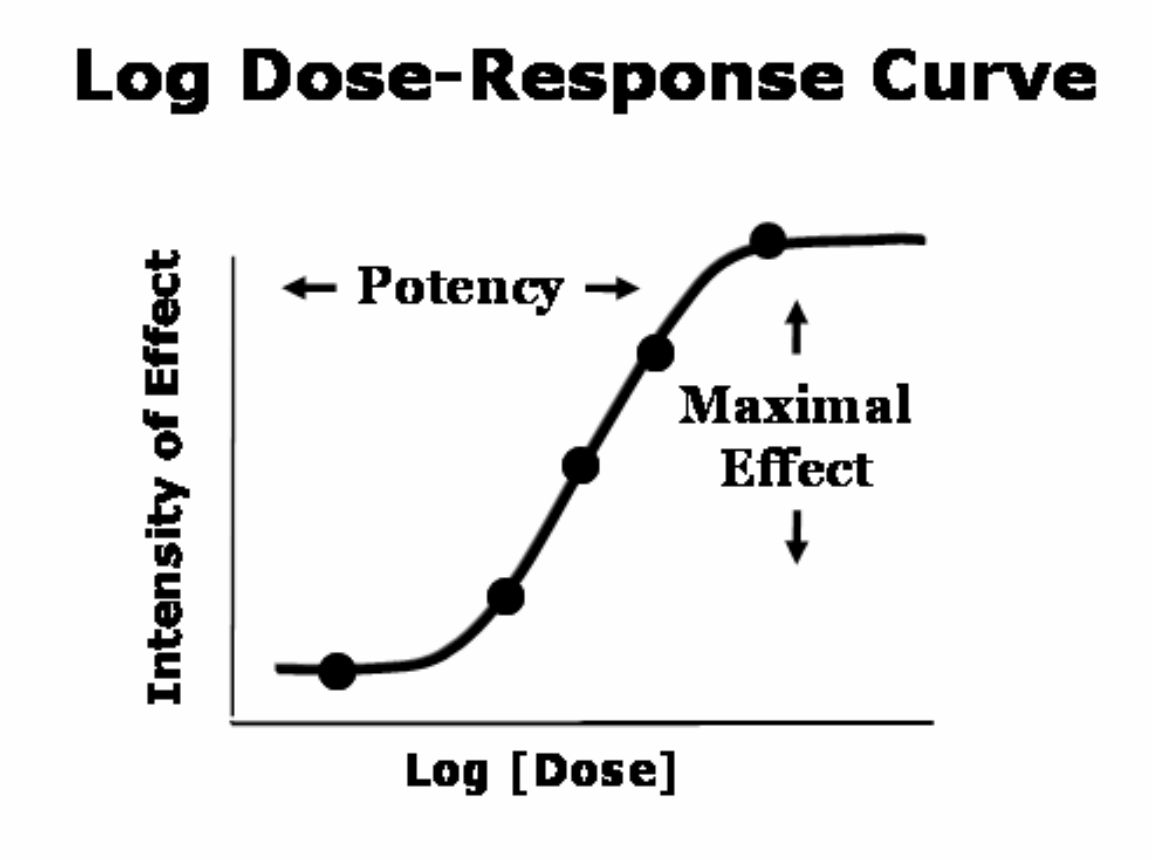
Non-Competitive Antagonism

Non-competitive antagonists decrease the Emax.

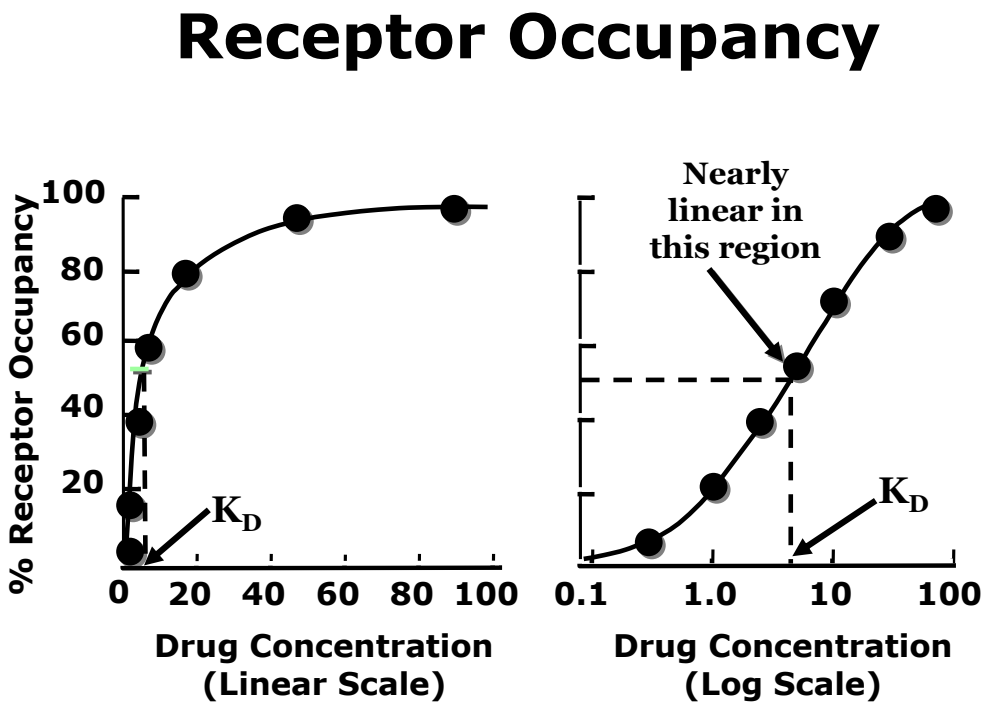


Negative allosteric modulators and irreversible antagonists reduce the maximal effect of an agonist

Log-Dose Response Curve
Relating this to Receptor Occupancy



Receptor Occupancy Predicts Response

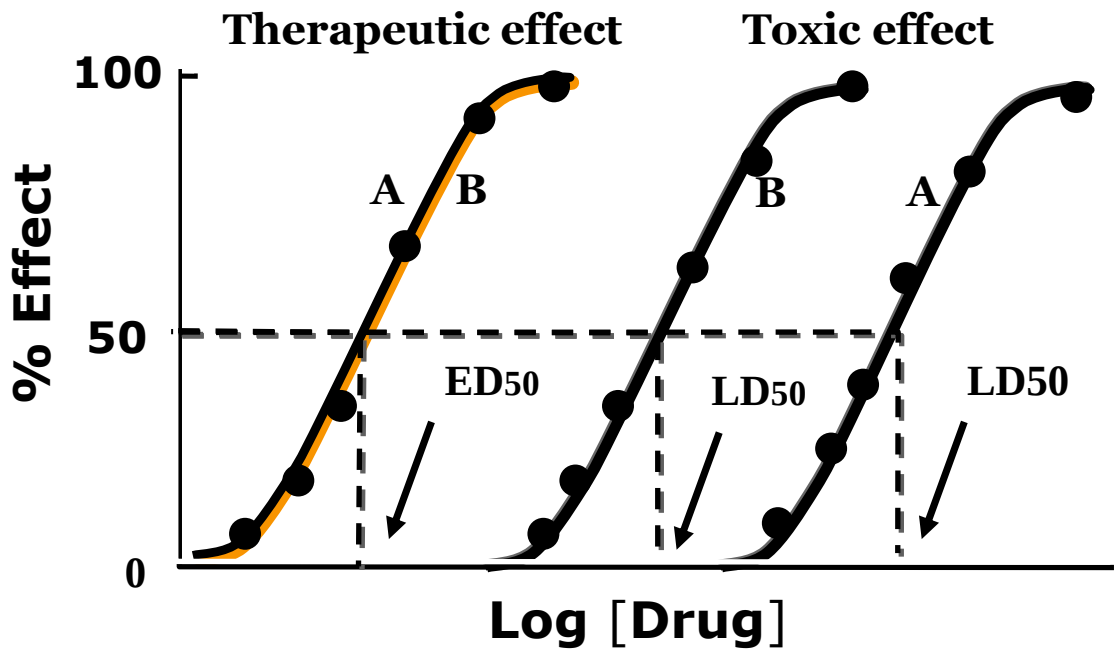


Receptor Occupancy Theory

- Progressive response with progressive receptor occupancy
- 10% occupancy = 10% effect
- 50% occupancy = 50% effect
- 100% occupancy = 100% effect
- Does not explain partial agonists
  - Spare receptor theory
  - Receptor coupling
  - Agonist high and low affinity states

Therapeutic Index: Combining a Therapeutic and a Toxic Dose Response ED50 and LD50

Therapeutic Index = LD_{50}/ED_{50}



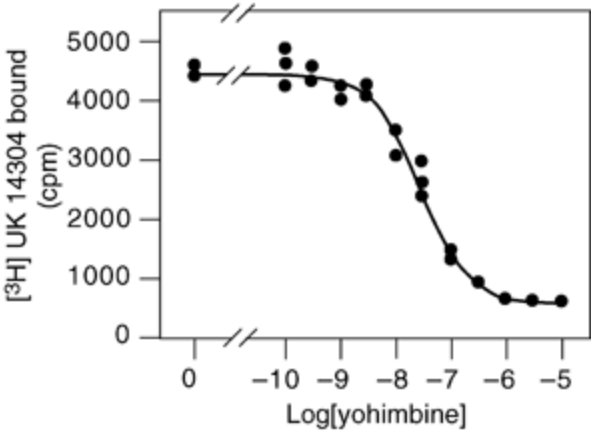
Radioligand Binding Methods: Studying Receptor Pharmacology

- High affinity (high potency) compound or drug
  - Selective or specific for a given receptor
  - Radio-labeled (tritium, iodine etc)
- Incubated with tissue/cells that express the given receptor
  - Radio-labeled drug binds to the receptor population
- Test drugs “compete” for this binding
- Assay the loss of radiolabelled drug
  - Calculate potency of competing drug
  - IC50 values; Ki values

Radioligand Binding Competition Study

- Yohimbine competing for 3H-UK14304 at alpha2 receptors

Log [competitor](M)	Binding (cpm) in triplicate		
−12.0	4549	4380	4554
−10.0	4604	4803	4213
−9.5	4353	4278	4508
−9.0	4192	4156	3972
−8.5	4053	4420	4191
−8.0	3453	3018	3024
−7.5	2587	2946	2367
−7.0	1295	1405	1402
−6.5	886	880	888
−6.0	591	612	603
−5.5	580	559	555
−5.0	521	545	555



Pharmacology Evaluations

- Radioligand Binding Studies:
  - Can determine “affinity” for receptor
- In vitro Pharmacology:
  - Can determine agonist/antagonist, potency and efficacy of a test drug
- In vivo Pharmacology:
  - Can determine full pharmacology profile of a test drug
  - Animals don’t talk: need clinical data to determine full response profile
  - Especially true for psychoactive drugs
- Clinical Studies:
  - Effects of drugs on people and populations
  - Animals do not speak; subtle effects of a drug may be missed in animal studies
  - Especially true for psychoactive drugs, which we will discuss next

Overall Drug Development Process

- Basic Research:
  - Therapeutic target identified (e.g., 5-HT1A receptor: anxiety)
  - Chemical synthesis of new molecules that are specific for this receptor
  - In vitro screening (high throughput) to identify leads
  - Pharmacology evaluation: agonist, antagonist, potency
  - Lead selection
- Pre-Clinical Development of the Lead:
  - Animal pharmacology
  - Animal safety (rat, dog, monkey)
  - In vitro safety (screening endpoints)
  - Submit an IND (Investigational New Drug Application) to FDA
- Clinical Development:
  - Phase 1 Studies: Pharmacokinetics and initial safety
  - Phase II studies: Proof of Concept and Dose Ranging
  - Phase 3 Studies: Large efficacy/safety studies in intended population
  - File NDA and global submissions
- Phase 4: FDA commitments?
- Time: Up to 10 years. Cost: ca. $500 million (depends on drug class)

Questions?