Basic Concepts of Pharmacology in Drug Development

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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)
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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,
      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

- acetylcholine
- 5-HT
- noradrenaline
- histamine
- tricyclic antidepressant

5-HT re-uptake transporter
5-HT receptor
synaptic cleft

noradrenaline re-uptake transporter

histamine receptor

post-synaptic membrane
acetylcholinesterase

nerve terminal
mitochondria
MAO

acetate + choline

muscarinic acetylcholine receptor
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
Potency

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

<table>
<thead>
<tr>
<th>Drug</th>
<th>% Drug Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>50</td>
</tr>
<tr>
<td>B</td>
<td>100</td>
</tr>
<tr>
<td>C</td>
<td>0</td>
</tr>
</tbody>
</table>

Potency

more potent ← Potency → less potent

EC50

Log [Drug Concentration]
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.

Competitive Antagonism

![Graph showing competitive antagonism with dose-response curves and dosages](image-url)
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

% Receptor Occupancy 0.1 1.0 10 100
Drug Concentration (Log Scale) 20 40 60 80 100

Nearly linear in this region

Drug Concentration (Linear Scale) 0 20 40 60 80 100

K_D

Drug Concentration (Log Scale) 0.1 1.0 10 100

K_D
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 = $\frac{LD_{50}}{ED_{50}}$
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-U14304 at alpha2 receptors
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

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