Pharmacology Lecture - 1

General Pharmacology
Primary Exam Teaching

Pharmacokinetics and Pharmacodynamics

- Volume of distribution - the relationship between the amount of drug in the body to the concentration of the drug found solely in plasma
  - Vd = Amount of drug in body/Concentration
- The Vd is an apparent volume and can exceed any physical volume found in the body because it is the volume necessary to contain the drug homogeneously at the concentration found.
- High Vd = higher concentration in extravascular tissues than vascular tissues e.g. fluoxetine, digoxin, verapamil
- Low Vd = contained within vascular compartment and their Vd is as close as possible to vascular volume e.g. aspirin, amoxicillin

Clearance

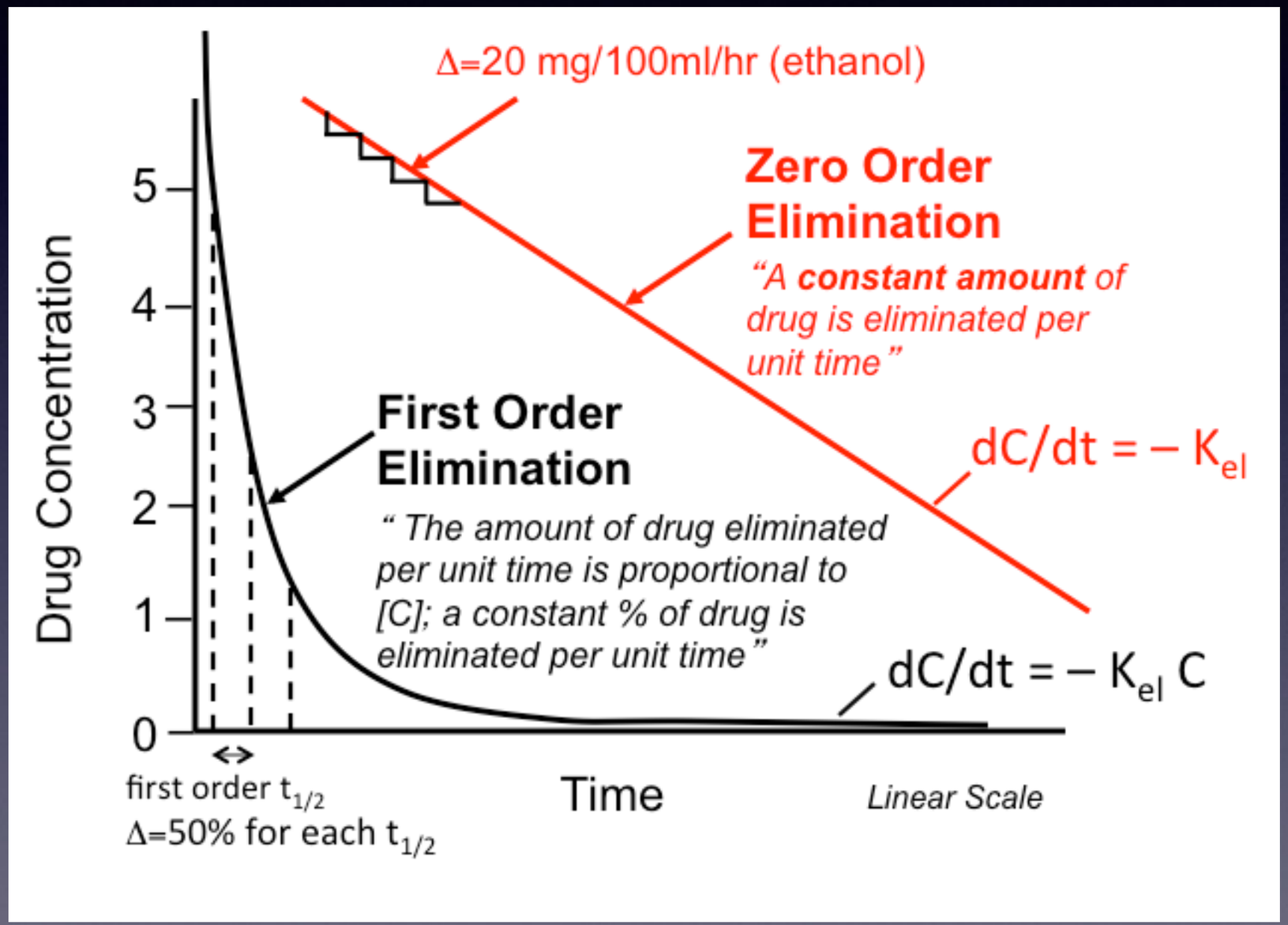
- Clearance - rate of elimination in relation to drug concentration
  - CL = rate of elimination/concentration

- Major sites of elimination are renal and liver
  - Renal excretion = excretion of unchanged drug
  - Liver excretion = biotransformation OR excretion of unchanged drug into bile

Clearance

- Rate of elimination is directly proportional to concentration - FIRST ORDER ELIMINATION - when clearance is first order it can be estimated as area under the curve

- When a constant amount of drug is eliminated per unit of time - ZERO ORDER ELIMINATION


Δ=20 mg/100ml/hr (ethanol)
Zero Order Elimination
"A constant amount of drug is eliminated per unit time"
dC/dt = – K_el
First Order Elimination
" The amount of drug eliminated per unit time is proportional to [C]; a constant % of drug is eliminated per unit time"
dC/dt = – K_el C
Drug Concentration
5
4
3
2
1
0
Time
Linear Scale
first order t1/2
Δ=50% for each t1/2

Clearance

- For most drugs when concentration becomes high enough the elimination will saturated ad will be fixed, independent of concentration e.g. Etoh, Phenytoin and Aspirin

- Rate of elimination = **Vmax x C / Km + C**

- **Vmax = maximum elimination capacity**

- **Km = drug concentration at which the rate of elimination is 50% of Vmax**

- **At concentrations that are high relative to the Km the elimination rate is almost independent of concentration**

Clearance

- Half Life - the TIME required to change the concentration of the drug in the body by one half
- Flow dependent elimination - Some drugs will be largely eliminated on the first pass of the drug through the organ - hence the elimination of the drug will primarily depend on rate of delivery to the organ - these drugs are called HIGH EXTRACTION DRUGS e.g. lignocaine, propranolol

Bioavailability

- Definition: The amount of unchanged drug reaching the systemic circulation following administration by any route.
- IV administration = 100%
- May be less than 100% for 2 reasons
    - EXTENT OF ABSORPTION - lack of absorption from the GIT system
        - RATE OF ABSORPTION
    - FIRST PASS METABOLISM - Following absorption through the gut portal blood goes to the liver prior to systemic circulation.
        - These drugs can be metabolised in the gut wall as well as in the liver and this reduces bioavailability
        - Extraction ratio quantifies this degree of metabolism = Liver clearance/Liver blood flow
        - Drugs with high extraction ratios will show marked variations in bioavailability between subjects because of difference in hepatic function and blood flow.
            - Morphine, propranolol, verapamil, TCA - higher concentrations if blood is shunted past the liver
            - Phenytoi, diazepam, warfarin - have low extraction ratios
- Sublingual, Transdermal and Rectal route bypass first pass metabolism

Dosing

- Maintenance dose - Drug dosing in such a way as to maintain a steady state of drug in the system and thus replace the drug excreted since the preceding dose
    - equals the rate of elimination
        - dosing rate = clearance rate x target concentration
- Loading dose - When time to reach steady state is appreciable - a loading dose may be used to promptly raise plasma concentration
    - Ld = VD x Target Concentration

Biotransformation

- Transforms lipophillic drugs are made more polar and water soluble and hence their excretion is enhanced
- PHASE ONE and PHASE TWO reactions
    - PHASE ONE: Convert the drug into a more polar metabolite by introducing a functional group
        - aromatic hydroxylation, epioxidations
    - PHASE TWO: If phase one metabolites are sufficiently polar they may be readily excreted
        - Normally they need to undergo a reaction where an endogenous substance combines with this new functional group to create a highly polar molecule e.g. glucuronic acid, sulphuric acid

Biotransformation

- Biotransformation reactions occur in the GIT, Lungs, Skin, Kidney and Liver

PHASE 1 reactions

- Microsomal oxidation and Phase one reactions
    - Two key enzymes
        - P450 reductase
        - Cytochrome p450 (CYP34A is the most important one)
        - Enzyme induction - some of these chemically dissimilar p450 drugs, on repeated administration, induce p450 by enhancing the rate of its synthesis or reducing the rate of its degradation.
            - This induction results in an acceleration of substrate metabolism and a decline in the action of the inducer substrate and co administered drugs
            - Enzyme inhibition - Certain drug substrates inhibit P450 enzyme activity

PHASE 2 reactions

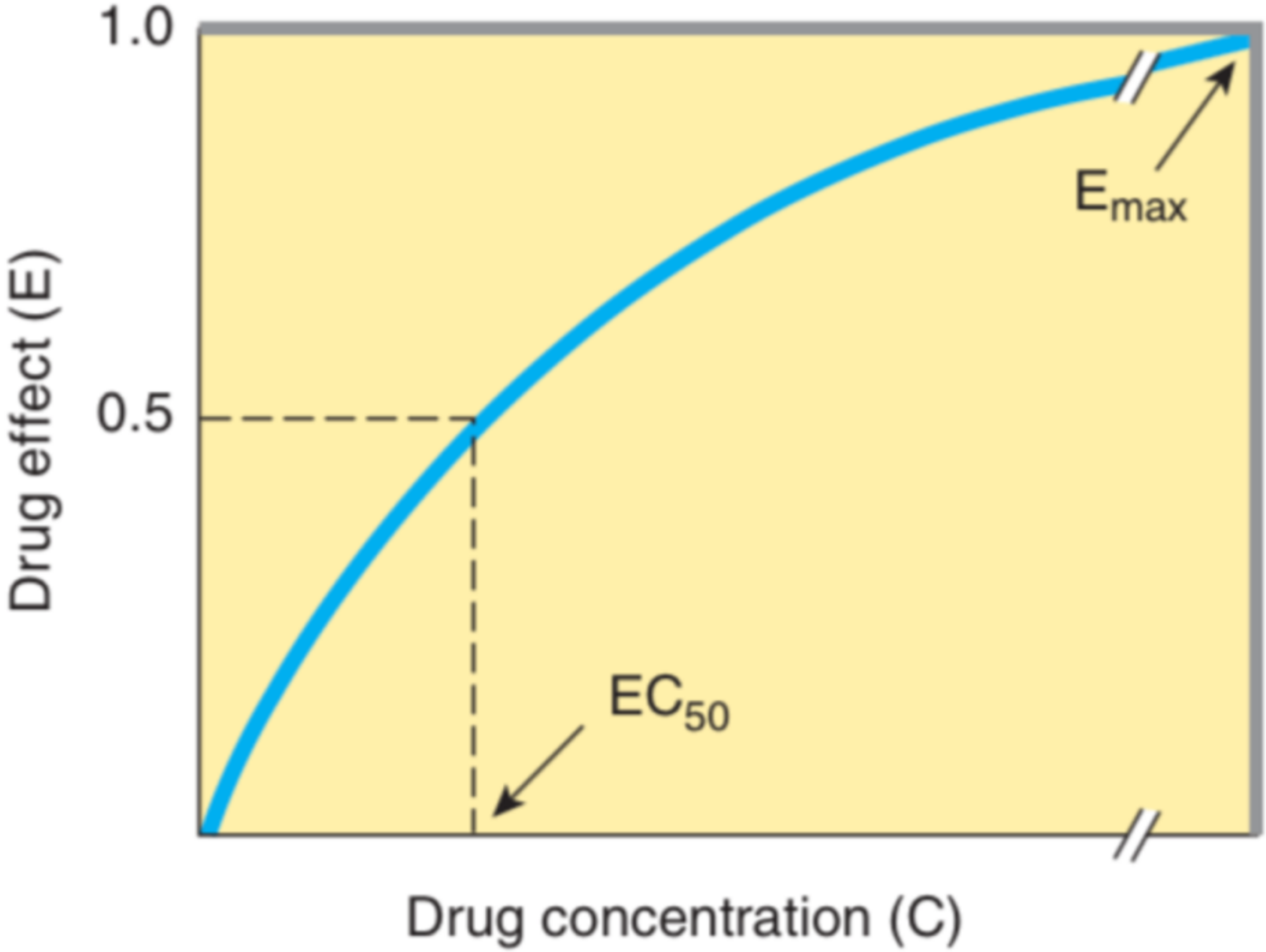
- Conjugation reaction with an endogenous substance - the endogenous substances are highly polar molecules
- A lot of these substrates originate in the diet
- Certain conjugations may lead to the formation of reactive species

Pharmacodynamics

- Receptors - determine the quantitative relation between dose and response and are responsible for selectivity of a drug
- Most receptors are proteins, but can also ben enzymes (di hydrofolate reductase inhibition with methotrexate), transport portents (Na/K ATPase), Structural proteins such as tubular (for colchicine).

Concentration Effect

- Responses to low dose of a drug usually increase in direct proportion to dose. As dose increases, response increment diminishes.
- E = E(max) x C/(C + EC50)
  - E is the effect at concentration C
  - E max - maximal response
  - EC50 is the concentration of drug that produces 50% of maximal effect



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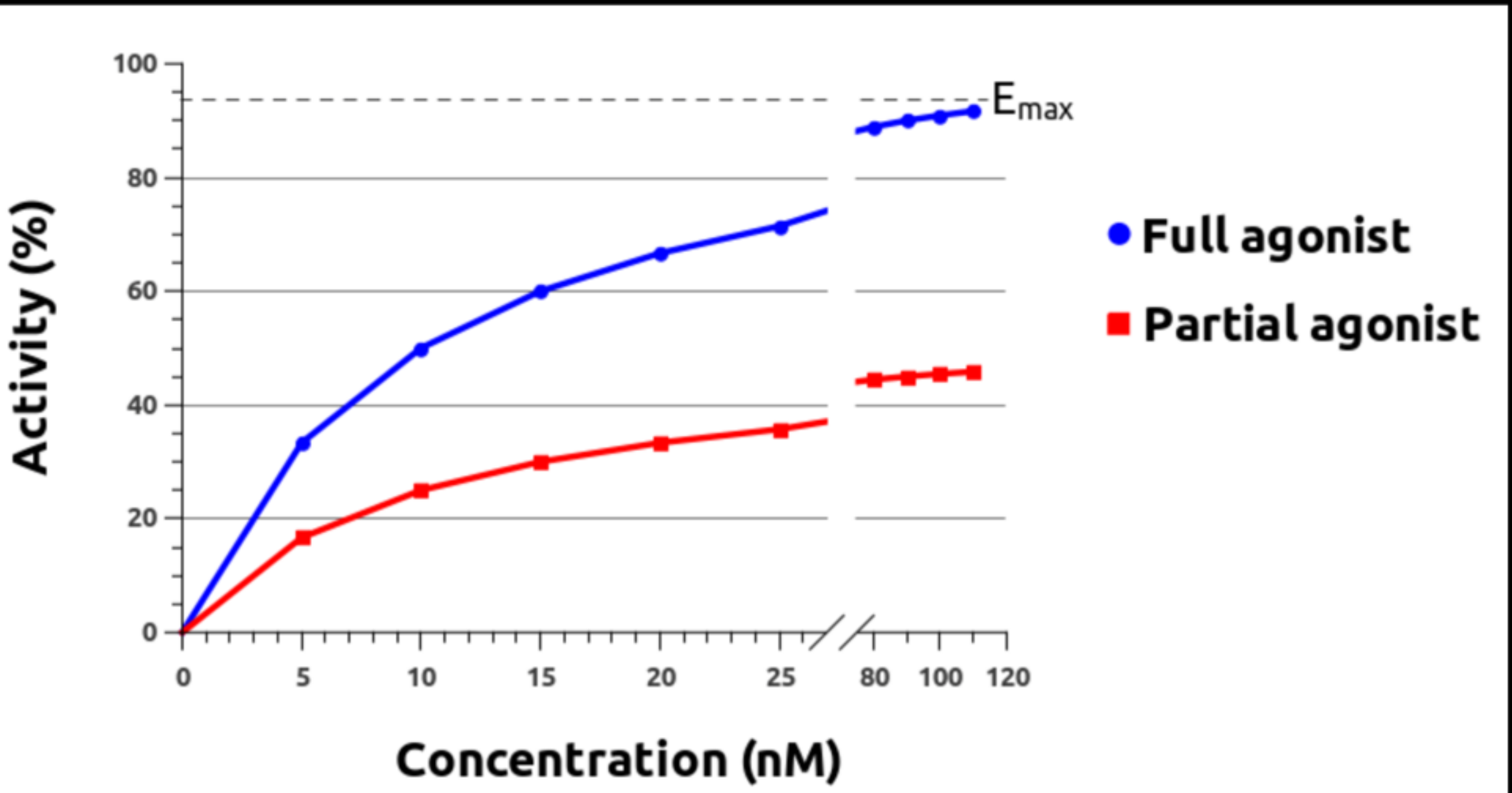
Receptors and Effectors

- Sometimes receptor coupling is linearly related to an effect - but this is often not the case i.e. secondary enzymatic signals)
- SPARE RECEPTORS - Receptors are said to be spares for a given pharmacological response if it is possible to elicit a maximal response at a concentration of agonist that does not result in full receptor occupancy.
    - e.g. myocardial cells exhibit maximal inotropic response to catecholamines even when 90% of receptors are blocked by irreversible antagonists.

Agonists

- Agonist - a chemical that binds to a receptor and activates it to produce a biological response.
- Types of agonist
    - Endogenous and exogenous
    - Physiological agonist - creates the same response but binds a different receptor
    - Full agonists bind and produce a fully efficacious reaction at a receptor e.g. morphine
    - Partial agonists - buprenorphine, bind a receptor, but even at full receptor occupancy do not produce a fully efficacious reaction.
    - Inverse agonist - act on the same receptor but produce an opposite reaction


Activity (%)
100
80
60
40
20
0
E_{max}
Full agonist
Partial agonist
0
5
10
15
20
25
80
100
120
Concentration (nM)

Antagonists

- Antagonists bind a receptor but do not activate the receptor
    - Competitive antagonist - In the presence of a fixed concentration of agonist, increasing concentration of competitive antagonist progressively inhibit the agonist response and vice versa.
    - Increases the agonist concentration required for a given response, shifting the dose response curve to the right

Competitive antagonism

- Two important clinical consequences
  - Degree of inhibition caused by competitive antagonist is related to the concentration of the antagonist an can be different from patient to patient depending on clearance
  - Clinical response depends on concentration of the agonist that is competing for receptor binding.

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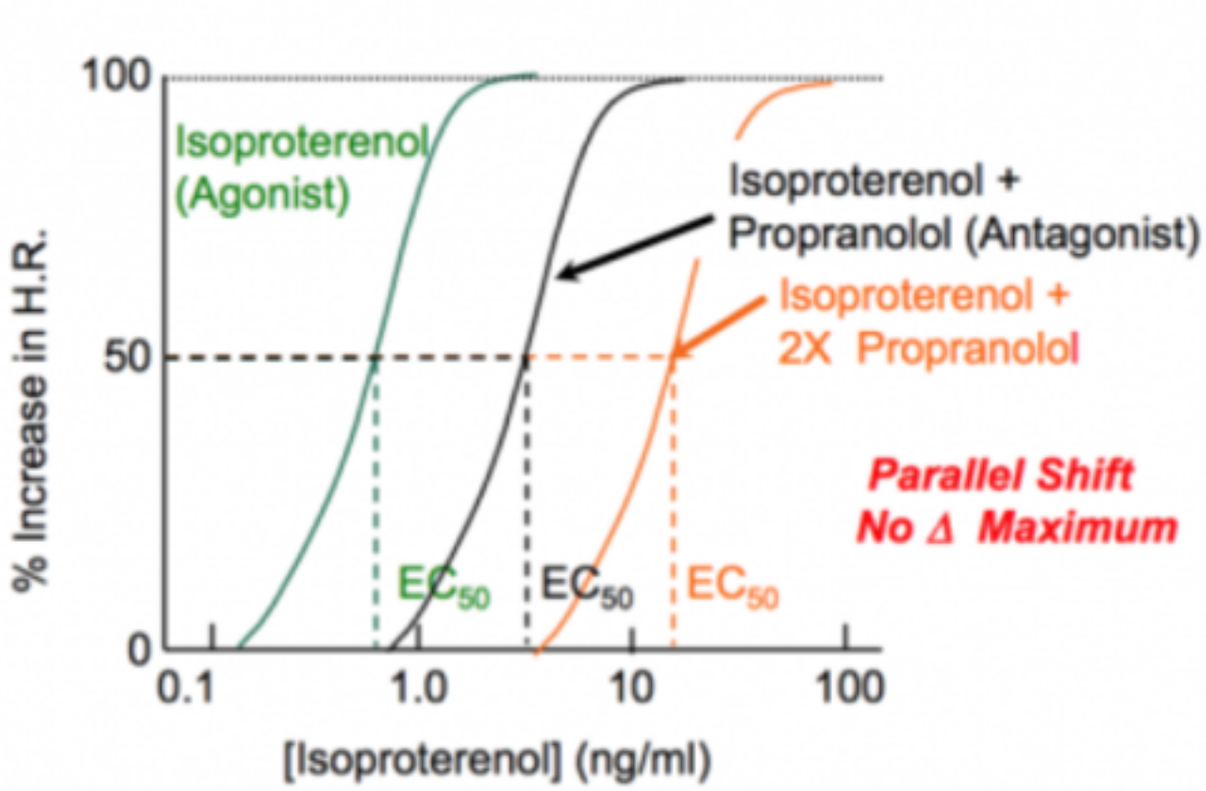
Competitive Inhibition



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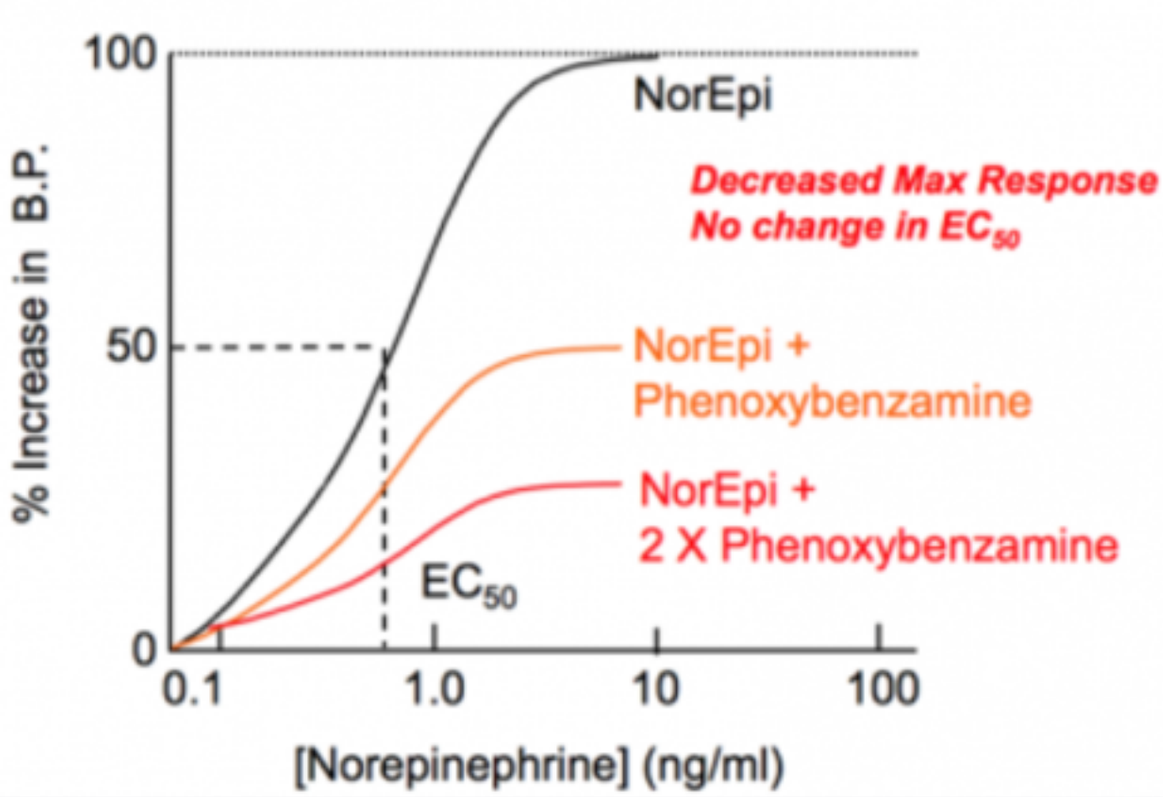
Noncompetitive Inhibition



Irreversible antagonists

- The antagonists bind via covalent mechanisms, after occupancy the number of receptor left may not be enough to generate a maximal response in the presence of an otherwise appropriate dose of antagonist.
- Advantage: Duration of action is independent of its own rate of elimination and more dependent on the rate of turnover of the receptors
- Disadvantage: In overdose, cannot overcome effects by giving more agonist
- E.g. phenoxybenzamine - alpha agonist

Allosteric Modulation

- Binding to a site on the receptor protein separate from the agonist binding site and thereby preventing receptor activation

- eg. Benzodiazepine