Signalling Mechanisms and Drug Action

Signalling Mechanisms

- Five Basic mechanisms:
  - Lipid soluble ligans
  - Ligand related transmembrane enzymes
  - Ligand gated channels
  - G protiens and second messengers
  - Phosphorylation

Lipid Soluble Ligands

- Lipid Soluble Ligands
  - Acts on intracellular receptors
    - e.g. steroids, thyroid hormone
    - Receptor —> stimulates transcription of genes
    - There is a characteristic lag period
    - Effects can persist even after agonist concentrations have decreased to zero

Ligand Regulated Transmembrane Enzymes

- Insulin, EGF
- Receptors have multiple elements
    - Extracellular hormone-binding domain
    - Cytoplasmic enzyme domain
        - These two elements are linked by a hydrophobic segment that crosses lipid membrane
- Mechanism
    - Ligand binds —> Dimerisation of two segments of receptor bring together the tyrosine kinase domains which then become active —> Phosphorylation of downstream proteins
    - RECEPTOR DOWN REGULATION - ligand binding induced endocytosis of receptor and therefore reduces cellular response

Ligad Gated Channels

- Many therapeutic agents act by mimicking or blocking the actions of endogenous ligands that regulate the flow of ions into and out of a cell

- e.g. Ach, GABA, Serotonnin

G - protein coupled receptors

- Extracellular ligands which increase the concentration of second messengers such as cyclic aMP, calcium

- Three separate components in the transmembrane signalling system:

  - Extracellular ligand is detected by the cell surface receptor

  - Receptor triggers activation of G protein located not he cytoplasmic face of the membrane

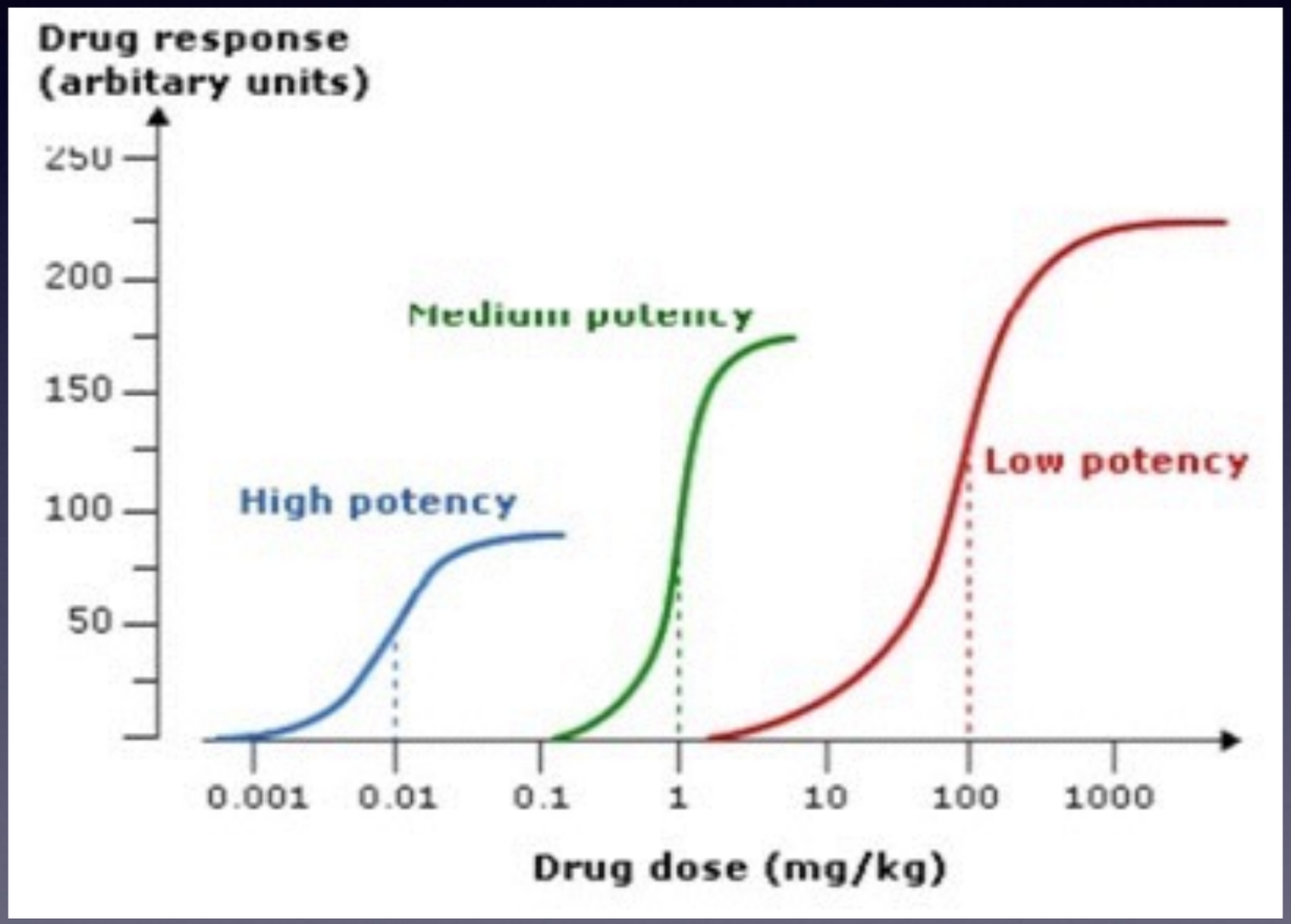
  - Activated G protein changes the activity of an effector element (enzyme or ion channel), which then changes the concentration of the intracellular messenger.

G - protein coupled receptors

- Phosphorylation is a common end point
- Amplification
- Flexible regulation

Drug dose and clinical response

- Potency - concentration of a drug required to produce 50% of that drugs response.
    - Determined by:
        - Affinity of receptors for drug
        - Efficiency with which drug-receptor interaction is coupled with response
        - Hence a drug can be more potent but less efficacious than another drug.


Drug response
(arbitary units)
250
200
150
100
50
Medium potency
High potency
Low potency
0.001
0.01
0.1
1
10
100
1000
Drug dose (mg/kg)

Efficacy

- Limit of dose response interaction

Quantal Dose Response Curve

- For most drugs the doses required to produce a specific quantal effect in individuals follow a bell curve pattern

- Median effective dose is the dose at which 50% of people exhibit the specified response

- By dividing the median toxic dose and the median effective dose you get a therapeutic index

Variations in Drug Responsiveness

- When responsiveness diminishes rapidly to administration of a drug this is called - TACHYPHYLAXIS
- Alterations in concentration of a drug that reaches a receptor
    - Differences in rate of absorption, distribution, distribution and clearance
- Variation in concentration of endogenous receptor ligand - propranolol is more effective in patients with more beta receptors (phaechromocytoma)
- Alteration in number or function of receptor
- Changes in components of response distal to the receptor