PHARMACODYNAMICS

(a) ***To explain the concept of drug action with respect to:***
- ***Receptor theory***
- ***Enzyme interactions***
- ***Physico-chemical interactions***

(b) ***To explain receptor activity with regards to:***
- ***Ionic fluxes***
- ***Second messengers and G-proteins***
- ***Nucleic acid synthesis***
- ***Evidence for the presence of receptors***
- ***Regulation of receptor number and activity***

(c) ***To define and explain dose-effect relationships of drugs with reference to:***
- ***Graded and quantal response***
- ***Therapeutic index***
- ***Potency and efficacy***
- ***Competitive and non-competitive antagonists***
- ***Partial agonists, mixed agonist-antagonists and inverse agonists***

(d) ***To describe efficacy and potency with reference to dose-response curves.***

(e) ***To explain the Law of Mass Action and describe affinity and dissociation constants.***

(f) ***To describe the theories of mechanism of action of general anaesthetic agents.***

(g) ***To describe the mechanisms of adverse drug effects.***

(A) **Overview of Pharmacodynamics**:

Pharmacodynamics is the study of a drug's biochemical and physical effects in the body, and the mechanisms by which these effects occur (Ie. "what the drug does to the body")

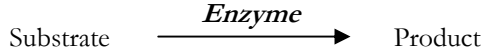
Of note:

- A drug's biochemical and physical effect is determined by the intrinsic sensitivity or responsiveness of receptors within the body to a drug
- Intrinsic sensitivity/responsiveness of a receptor to a drug is evaluated by measuring the plasma/effect-site [drug] required to evoke a specific drug response → this relationship varies b/t individuals (Ie. at a similar plasma [drug], some will have a therapeutic response, some will have no response, some will have toxic response)
- The link b/t a drug's chemical structure and its provoked effects → forms basis of "Structure-activity relationship"

(B) **Mechanism of Drug Action**:

(1) Chemical interaction:
- (a) Neutralisation reaction (Eg. antacids neutralise gastric acid)
- (b) Chelating agents (Eg. sugammadex chelates rocuronium)

(2) Enzymes:
- Enzymes are biological catalysts:



- Drugs usually inhibit enzymes (Ie. AChEi, CAi, ACEi), resulting in ↑ [substrate] normally metabolised by the enzyme and ↓ [product] of the reaction → this interaction is either:
    - (i) Competitive or reversible (Eg. edrophonium vs AChE)
    - (ii) Non-competitive or irreversible (Eg. organophosphates vs AChE)

(3) Voltage-gated ion channels:
- Voltage-gated ion channels are membrane-bound protein complexes implicated in the conduction of electrical impulses in excitable tissues (Eg. muscle, nerves, glands) → they open and close an ion channel in response to Δs in voltage across the cell membrane:
    - (i) Channel is closed at RMP (-60 to -80 mV)
    - (ii) Channel undergoes conformational change when cell membrane depolarises (Ie. MP becomes +ve) → ion channel opens and ion flux occurs
    - (iii) Channel closes again when RMP is restored
- Drugs usually inhibit VG ion channels (Ie. LA inhibit VG Na^+ channels on nerves, CCBs inhibit L-type VG Ca^{2+} channels on vascular SM)

(4) Receptors:
- Receptor → protein-based moiety that contains a region that binds a natural ligand (or drug) to bring about a response
- They are located either:
    - (i) Within the cell membrane → ligand is poorly lipid-soluble (Ie. cannot cross cell membrane)
    - (ii) Intracellularly → ligand is lipid-soluble (Ie. can cross cell membrane)
- Drug-receptor binding can invoke 3 responses:
    - (i) Elicits an effect → agonist response
    - (ii) Prevent the action of a natural ligand → antagonist response
    - (iii) Reduce a constitutive effect of a receptor → inverse agonist response
- There are 5 classes of receptors:
    - (a) Ligand-gated ion channels:
        - Receptor is part of membrane-spanning complex of protein subunits that can form a channel through the membrane → generally found in excitable tissue (Eg. nerve, muscle, glands)
        - Ligand (or drug) binds to receptor to regulate flow of ions through the channel (Ie. "inotropic" receptor interaction):
            - (i) Ligand or drug binds to receptor and induces conformational change in structure of membrane protein complex → this leads to opening of ion channel and ↑ membrane permeability to certain ions
            - (ii) Ions flow across membrane channel occurs along its electrical and [ ] gradients → alters membrane potential (Ie. depolarises or hyperpolarises) → elicits cellular effect
        - There are 3 families:
            - (i) Pentameric family – Possess 5x membrane-spanning subunits (Eg. nAChR, GABA-A receptor, 5-HT3R, glycine receptor)

- (ii) Inotropic glutamate – Glutamate is an excitatory NT in CNS that acts on various ligand-gated ion channels → include NMDA, AMPA and Kainate receptors
- (iii) Inotropic purinergic receptors – ATP acts on PX1/PX2 receptors → involved in pain and mechano-sensation

- (b) <u>G-protein coupled receptors (GPCR)</u>:
  - A membrane-bound protein with a serpentine structure (7x helical regions traversing cell membrane) associated with a heterotrimeric G-protein (α, β, γ subunits – α subunits binds either GTP or GDP) on the intracellular aspect of cell membrane
  - Ligand (or drug) binds to GPCR extracellularly → induces conformational change that activates G-protein, which triggers a cascade of intracellular signalling mechanisms (Ie. "metabotropic" receptor interaction):
    - (i) G-protein is "inactive" in its resting state – GDP is bound to α-subunit, which is associated with a βγ-dimer
    - (ii) G-protein is "activated" by ligand-bound GPCR – GTP replaces GDP on α-subunit → causes α-GTP subunit to dissociate from βγ-dimer → it then activates or inhibits effector protein (adenylyl cyclase (AC) or phospholipase C (PLC)) or an ion channel

      Note – βγ-dimer can elicit cellular effects via other intermediary mechanisms

    - (iii) α subunit possesses an intrinsic GTPase enzyme – GTP is hydrolysed to GDP → regenerates an α-GDP subunit which reassociates with βγ-dimer → G-protein returns to "inactive" resting state
  - Each GPCR interacts with a specific G-protein complex (which is determined by variations in its α-subunit) → this influences the IC signalling cascades triggered by ligand-GPCR interaction:

Type	Cellular event triggered	Example
Gs	α-subunit of G-protein activates AC → ↑ cAMP synthesis → cAMP binds protein kinase A (PKA) to produce cellular effect (Ie. Δ gene transcription, Δ ion permeability of membrane)	β1, β2, β3 receptors, H2 receptor
Gi	α-subunit of G-protein inhibits AC → ↓ cAMP synthesis → ↓ PKA activation → cellular effect	α2 receptor, M2 and M4 receptors
Gq	α-subunit of G-protein activates PLC → cleaves membrane phospholipid (phosphatidyl-inositol biphosphate; PIP2) into: - (i) Inositol tri-phosphate (IP3) → causes Ca^{2+} release from ER - (ii) Diacylglycerol (DAG) → activates protein kinase C	α1 receptor, M1, M3 and M5 receptors, H1 receptor

Important to note – GPCR have important characteristics:
- (i) Signal amplification – Single GPCR stimulates ≈ 100x G-proteins and each G-protein can activate several 2nd messenger systems
- (ii) Tachyphylaxis – Phosphorylation of GPCR intracellularly at carboxyl-terminal encourages binding of protein (β-arrestin) → signals removal of receptor from cell membrane

  - (c) <u>Membrane guanylyl cyclase</u>:
    - Membrane-bound receptors a/w an intrinsic guanylyl cyclase
    - Ligand or drug (Eg. ANP) binds to receptor → activates intrinsic guanylyl cyclase → ↑ cGMP → phosphorylation of IC enzymes → cellular effects

      Note – Nitric oxide (and its donors SNP/GTN) exert its effects by stimulating *cytoplasmic* guanylyl cyclase instead (and NOT membrane-bound guanylyl cyclase)

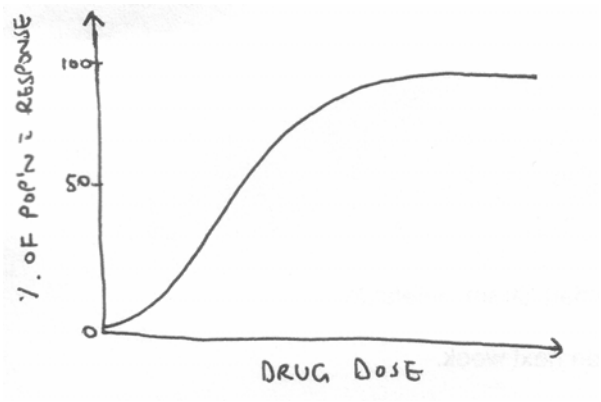
- (d) Tyrosine kinase receptors:
  - Transmembrane receptor-enzyme complex that consists of – (i) extracellular ligand-binding domain (2x α-subunits) and (ii) membrane-bound domain (2x β-subunits) associated with a cytoplasmic enzyme (Tyrosine kinase)
  - Ligand (Eg. IGF) or drug (Eg. insulin) binds to the α-subunits (extracellular domains) which causes the β-subunits (membrane-bound domains) to dimerise → IC tyrosine residues on β-subunits are then phosphorylated leading to activation of tyrosine kinase → this phosphorylates various IC proteins that elicits a cellular effect
- (e) Intracellular receptors:
  - Ligands acting on these receptors are lipid soluble (Eg. steroid and thyroid hormones) → cross cell membrane and bind to receptors within the cytoplasm
  - These receptors act as "ligand-regulated transcription factors":
    - (i) Normally, receptors reside within the cytoplasm → held in the inactive form by association with inhibitory proteins
    - (ii) Binding of hormone (or drug) induces conformational change that activates receptor (by releasing inhibitory protein) → receptor-ligand complex translocates to nucleus and associates with DNA promoter sequences → alter gene transcription
  - Effects are delayed (as proteins must be synthesised) BUT have a long duration of action (as proteins have a long t ½)

(C) **Dose-Response Curves**:

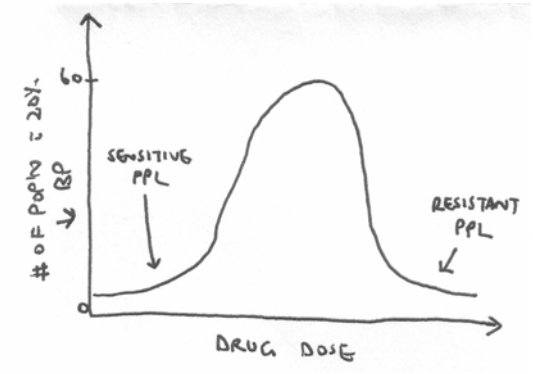
Types of dose-response curves:

(1) *Quantal dose-response curve*:

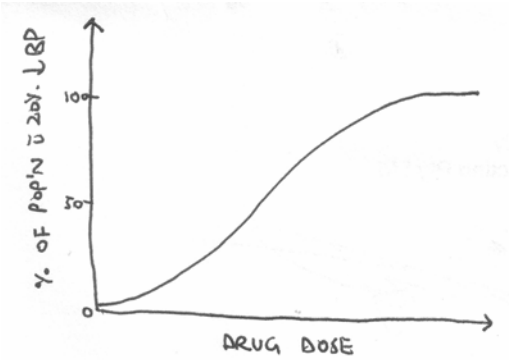
- Derived from a "population" → describes the relationship b/t (i) drug dose and (ii) the frequency of "quantal response" (Ie. all-or-none response to the drug) in a population



- Basis of curve:
  - Minimal drug dose that produces a "quantal response" (Ie. drug dose that causes 20% ↓ in BP) is not the same across a population → it obeys a "normal distribution"



  - Cumulative graph of this normal distribution can be transformed into a "frequency distribution curve" → forms quantal dose-response curve

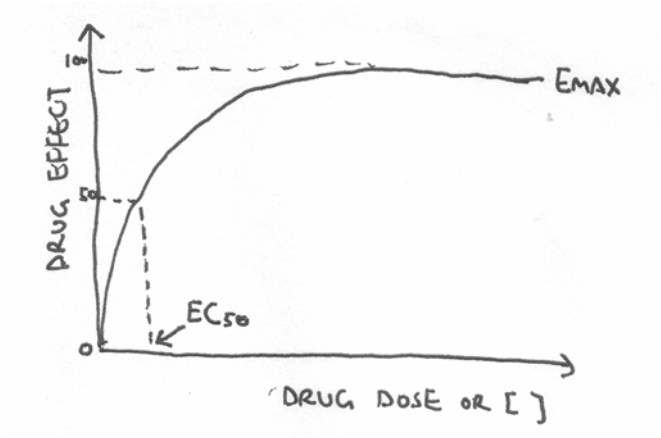


Important pharmacodynamic parameters derived from this curve include:

- (i) ED_{50} – Effective dose for 50% of population (Ie. median effective dose)
- (ii) LD_{50} – Lethal dose for 50% of population (Ie. median lethal dose)
- (iii) Therapeutic index (see below)
- (iv) Margin of safety (see below)

(2) *Graded dose-response curve*:

- Derived from an "individual" → describes the relationship b/t (i) drug dose (or [ ]) and (ii) intensity of drug effect
- Forms a "hyperbolic curve":



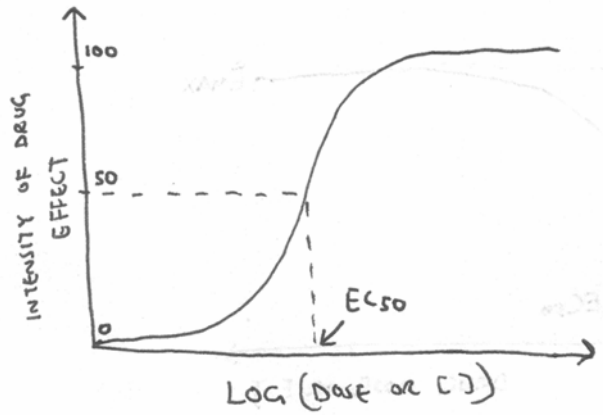
$$E = \frac{E_{MAX} \times C}{(C + EC_{50})}$$

Where:
- E = Effect at drug concentration (C)
- C = Drug concentration
- E_{MAX} = Maximal intensity of drug effect
- EC_{50} = [drug] that produces half the response b/t the baseline and maximum response

Note – Intensity of drug effect increases with drug dose whereby:
- (i) At low [drug] → ↑ intensity of drug effect occurs rapidly
- (ii) At higher [drug] → ↑ intensity of drug effect occurs slowly
- (iii) At a high enough [drug] → maximal intensity of drug effect (E_{MAX}) is reached

Important to note – This hyperbolic relationship is the result of the dynamics of drug-receptor interaction (See "Law of Mass Action" below)

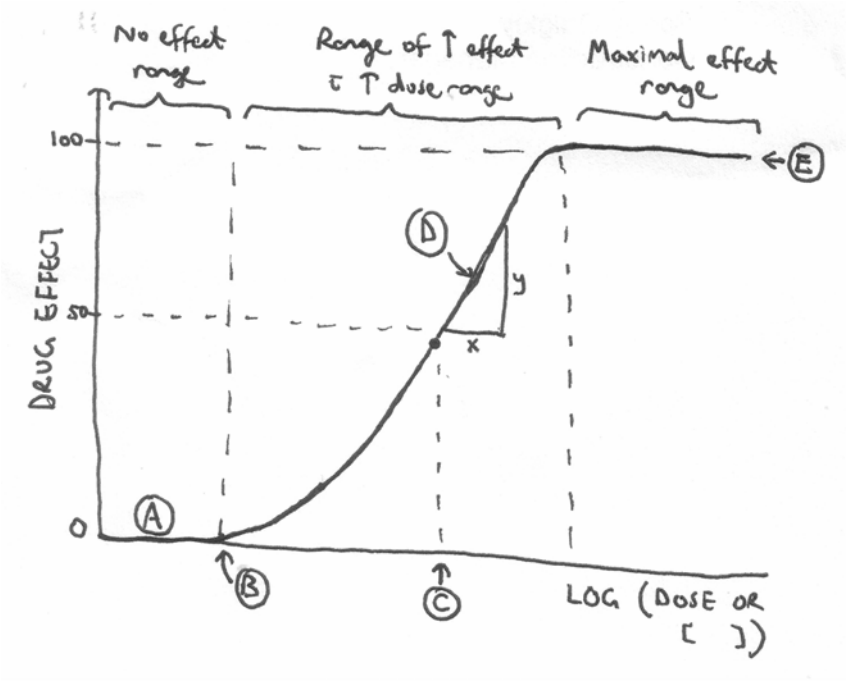
- This curve is often transformed into a "*Log dose-response curve*" → demonstrates relationship b/t (i) log of drug dose (or [ ]) and (ii) intensity of drug effect



Note – This transforms the curve into a "sigmoidal" one that has the following effects:
- (1) Linear at mid-portion (Ie. b/t 20-80% of max. drug effect) where the drug is generally within the therapeutic dose or [ ] range
- (2) Permits display of wide range of doses by expanding the scale at low drug doses (where drug effect changes rapidly) and compressing it at high drug doses (where drug effect changes slowly)
- (3) Facilitates comparison b/t drugs that act at the receptor (Ie. efficacy and potency of different drugs)

Important pharmacodynamic parameters derived from a log-dose response curve:
- (A) – "Baseline response" → drug effect is usually zero when drug dose (or [ ]) is zero (BUT it can be > 0 if intrinsic receptor activity exists)
- (B) – "Threshold dose" → drug dose or [ ] below which there is no appreciable ↑ in receptor activity with agonist binding

- (C) – "EC_{50}" (measure of "potency") → drug dose or [ ] that produces half the response b/t the baseline and maximum response
- (D) – Slope of curve is linear at this mid-portion (b/t 20-80% of max. drug effect) → steepness of slope influenced by # of receptors that must be occupied before drug response occurs ("Receptor occupancy theory"):
    - (i) Steep slope – Drug must occupy majority of receptors before any drug effect is seen → thus, small ↑ dose produces large ↑ response
    - (ii) Shallow slope – Small response is seen when few receptors are occupied, but maximal response is seen only when all receptors are occupied → thus, a much larger ↑ dose is required to cause the same ↑ in response
- (E) – "E_{MAX}" (measure of "efficacy") → Maximal intensity of drug effect

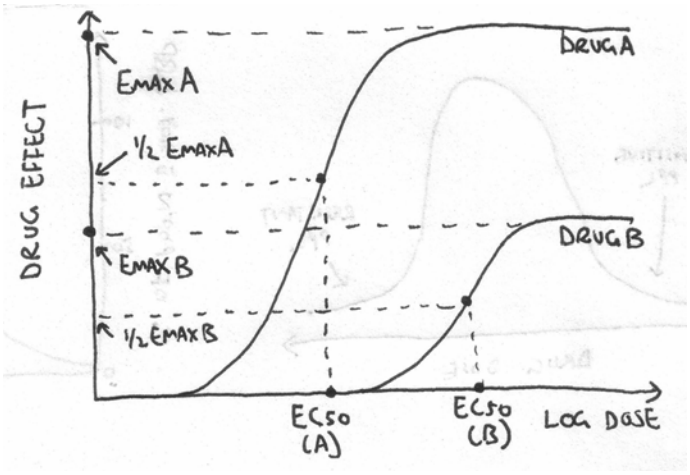


Efficacy and Potency:

(1) *Efficacy*:
- Defined as the ability of drug to elicit the maximal effect (E_{MAX}) when bound to receptor
- Measured by height of plateau phase (or E_{MAX}) in "log dose-response curve" → ↑ height of plateau phase (or E_{MAX}) = ↑ efficacy
- It reflects "intrinsic activity" of the drug (Ie. magnitude of effect drug has once bound):
    - Full agonists → 100% efficacy (or IA = 1)
    - Partial agonists → efficacy b/t 0 and 100% (or 0 < IA < 1)
    - Antagonists → 0% efficacy (or IA = 0)
- It is vital when selecting drugs (Ie. paracetamol and morphine are both analgesics but with different efficacy)

(2) *Potency*:
- A comparative measure b/t drugs that have the same action on a receptor (Ie. have same log dose-response curve slopes) → refers to the different doses of two drugs needed to produce the same drug effect (Ie. more potent drug evokes a ↑ response at a ↓ dose)
- Measured by the EC_{50} in "log dose-response curve" → ↑ EC_{50} = ↓ potency
- It reflects the "affinity" of the drug for the receptor → ↑ receptor affinity = ↓ K_D or ↑ K_A = ↑ potency
- It is not as vital when selecting drugs (cf. efficacy), as long as the effective dose can be administered conveniently

Example:



"Drug A" is more efficacious than "Drug B" ($E_{MAX\ A} > E_{MAX\ B}$)

"Drug A" is also more potent than "Drug B" ($EC_{50\ A} < EC_{50\ B}$)

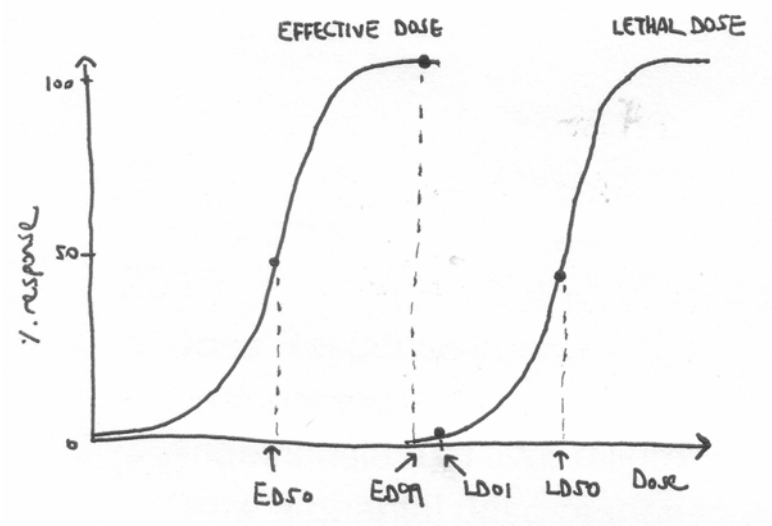
Therapeutic Index and Margin of Safety:

(1) *Therapeutic index* (TI):
- TI is used to evaluate safety and usefulness of a drug for a given indication → it describes the relationship between the drug dose needed to produce an undesired effect and the drug dose needed to produce a desired effect
- It is derived from the "quantal dose-response curve" as the ratio of the median lethal dose (LD_{50}) to the median effective dose (ED_{50}):

$$TI = \frac{LD_{50}}{ED_{50}} \longrightarrow$$ Safe drugs have ↑ TI (Ie. LD_{50} is >>> ED_{50})

(2) *Margin of safety* (MOS):
- MOS is used to evaluate safety and usefulness of a drug for a given indication → it describes the extent of overlap between the quantal dose response curves for effective and lethal dose
- It is derived from the "quantal dose-response curve" as the ratio of the lethal dose for 1% of population (LD_{01}) to the effective dose for 99% of population (ED_{99}):

$$MOS = \frac{LD_{01}}{ED_{99}} \longrightarrow$$ Dangerous drugs have MOS < 1

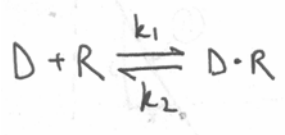


(D) **Drug-Receptor Interaction**:

(I) Dynamics of drug-receptor binding:

Drug-receptor binding:

- A drug (D) generally binds to a receptor (R) via a "reversible" reaction:



k_1 = Rate constant for forward reaction
k_2 = Rate constant for reverse reaction

- This drug-receptor interaction occurs by various physicochemical bonds:
  - (i) Ionic bond – Electrostatic forces existing b/t groups of opposite charge
  - (ii) Hydrogen bond – Bond b/t hydroxyl or amino groups and an electronegative carboxyl or oxygen group
  - (iii) van der Waal forces – Weak bond b/t 2 different atoms (or groups of atoms)
  - (iv) Covalent bond – Strong bond formed by sharing of electron pairs b/t atoms → Nb. this bond is generally "irreversible" (cf. above bonds)

"Law of Mass Action":

- The rate of a reaction is proportional to the [ ] of reacting compounds → such that:
  - (i) Rate of forward reaction: $V_1 = k_1 \bullet [D] \bullet [R]$
  - (ii) Rate of reverse reaction: $V_2 = k_2 \bullet [DR]$
- Thus, at equilibrium the reactions occur at the same rate in both directions (Ie. $V_1 = V_2$) such that:

$$K_D \text{ (equilibrium dissociation constant)} = \frac{k_2}{k_1} = \frac{[D] \bullet [R]}{[DR]} \quad \text{(units: mmol/L)}$$

$$K_A \text{ (equilibrium association constant)} = \frac{k_1}{k_2} = \frac{[DR]}{[D] \bullet [R]} \quad \text{(units: L/mmol)}$$

> Important to note – K_A is the reciprocal of K_D → reflects the affinity of drug for the receptor (Ie. ↑ K_A or ↓ K_D = ↑ receptor affinity by drug)

Pharmacological effect of drug-receptor binding:

> "Receptor Occupancy Theory":
> - Intensity of drug effect is proportional to fraction of receptors occupied by the drug → such that maximal effect occurs when all receptors are occupied by the drug
> - Note – This theory is discredited as it does NOT apply to drugs with intrinsic activities < 1 (Ie. antagonist, partial agonists, inverse agonist)

- Pharmacological effect of drug-receptor binding depends on:
  - (1) Properties of the drug:
    - (i) Affinity (Ie. how avidly a drug binds to a receptor) → determined by K_A or K_D of drug (such that ↑ K_A or ↓ K_D affinity
    - (ii) Intrinsic activity (IA; Ie. magnitude of effect drug has once bound) → drugs have IA b/t 0 and 1 (Nb. inverse agonists have IA b/t -1 and 0)

Note:
- Full agonist – High receptor affinity *and* full intrinsic activity (IA = 1)
- Partial agonist – High receptor affinity *but* fractional intrinsic activity (0 < IA < 1)
- Inverse agonist – High receptor affinity *but* with –ve intrinsic activity → either full or fractional (-1 ≤ IA < 0)
- Antagonist – High receptor affinity *but* has no intrinsic activity (IA = 0)

- (2) State of receptor activation – Receptors exist in an equilibrium b/t an (i) "active form" and (ii) "inactive form", which is altered by the presence of a drug

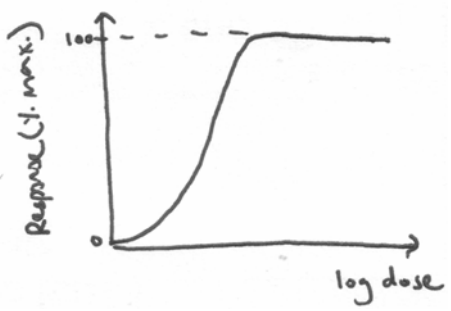
Note:
- Absence of drug – Equilibrium favours most receptors being in "inactive form"
- Antagonist – Drug binds to both receptor forms but does not alter equilibrium b/t "active" and "inactive"
- Full agonist – Drug binds receptors → shifts equilibrium entirely towards receptor being in "active form"
- Partial agonist – Drug binds receptors → shifts equilibrium partly towards receptors being in "active form" (Ie. fraction of receptors in "active form" cf. full agonist)
- Inverse agonist – Drug binds receptors → shifts equilibrium towards most receptors being in "inactive form"

Concentration of receptors:
- [ ] of receptors in cell membrane is dynamic:
  - (i) Down-regulation – There is ↓ [receptors] to attenuate the intensity of receptor stimulation with excess ligand or drug binding
  - (ii) Up-regulation – There is ↑ [receptors] to maintain the intensity of receptor stimulation with absence of ligand or drug binding

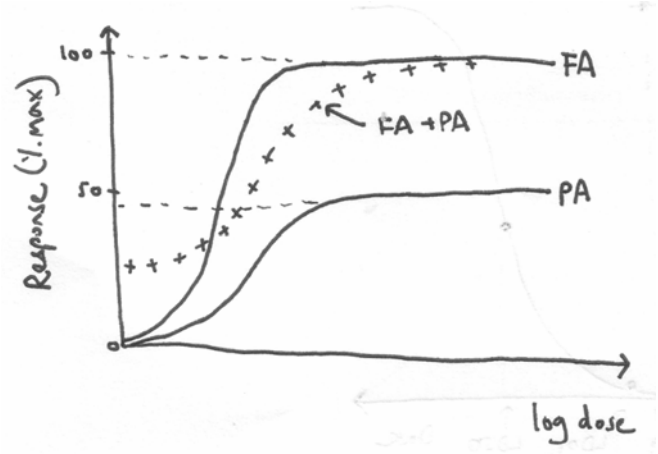
"Spare receptors":
- "Spare receptors" are present when a maximal response is achieved with occupation of only a fraction of receptors
- Eg. nAChR at NMJ → maximal agonist response (Ie. muscle contraction) can still be achieved when up to 75% of receptors are occupied by an antagonist so long as an agonist binds to the remaining 25% of receptors → these spare receptors provide a margin of safety in maintaining NMJ transmission (Ie. protects against toxins to NMJ)

(II) Types of drug-receptor interactions:

(1) *Receptor agonism*:
- (a) Full agonist (Eg. phenylephrine or noradrenaline at α1 receptor)
  - Drug exhibits high receptor affinity and full intrinsic activity (IA = 1) → shifts receptor equilibrium entirely towards the "active form"
  - This can generate a maximal response from receptor binding (Ie. 100% efficacy) with sufficient drug dosing



- (b) Partial agonist (Eg. buprenorphine at μ receptor)
    - Drug exhibits high receptor affinity but with fractional intrinsic activity ($0 < IA < 1$) → shifts receptor equilibrium partly towards "active form"
    - This generates a submaximal response from receptor binding (cf. full agonist), EVEN with very high doses (Ie. maximal receptor occupancy)



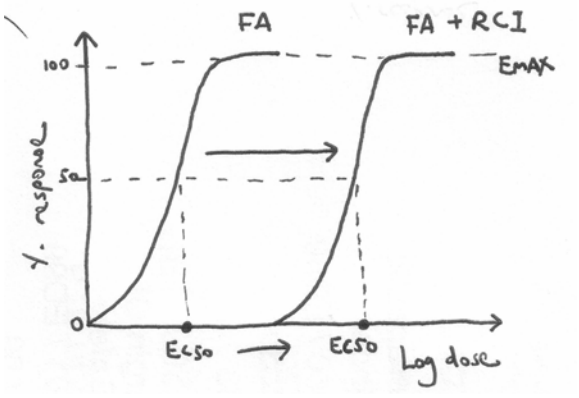
> Important to note – When used with a full agonist, a partial agonist can exert either an agonist or antagonist effect:
> - (i) Additive agonist effect → when used with low doses of a full agonist
> - (ii) Competitive antagonist effect → when used with high doses of full agonists (Ie. full agonist needs to displace partial agonist to restore maximal effect)

- (c) Inverse agonist (Eg. naloxone at μ receptor)
    - Drug exhibits high receptor affinity but with –ve fractional intrinsic activity ($-1 \leq IA < 0$) → shifts receptor equilibrium towards "inactive form"
    - This generates an effect opposite to that of an endogenous agonist (in either full or partial manner)

> Suggested mechanism – Receptor demonstrates "constitutive" action (Ie. low level of activity in absence of ligand due to small presence of receptors naturally in "active form") → inverse agonists bind them and ↓↓↓ presence of receptors constitutively in "active form" → produces effect opposite of an agonist

(2) *Receptor antagonism*:

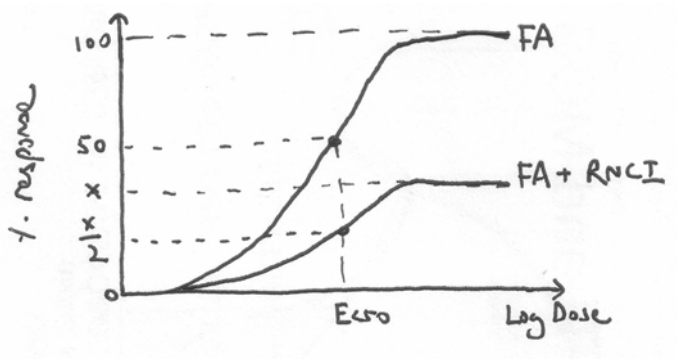
- All antagonists exhibit high receptor affinity but no intrinsic activity ($IA = 0$) → does not alter receptor equilibrium b/t "active" and "inactive" forms → thus, no response is generated from receptor binding
- Binding can be either:
    - (a) Reversible:
        - (i) Competitive (Eg. NDMR at nAChR)
            - Drug competes with agonist for same receptor site in a reversible manner
            - Antagonism can be overcome by ↑ [agonist], such that E_{MAX} can be achieved if enough agonist given → this is b/c the relative amounts of agonist and antagonist (combined with their receptor affinity) determine their ratio of receptor occupation



Note – Efficacy (E_{MAX}) is maintained assuming enough agonist is given, but potency is ↓ (as EC_{50} is ↑ and curve is shifted to right)

Important to note – "Dose-ratio" is the extent by which the curve is shifted → it is determined as the factor by which [agonist] must be ↑ to produce equivalent responses in presence and absence of the competitive inhibitor

- (ii) Non-competitive (Eg. ketamine at NMDA receptor)
  - Drug binds to a separate site as agonist in a reversible manner and generally does NOT alter binding of agonist to its receptor site → antagonism results from preventing receptor activation through conformational distortion
  - Antagonism CANNOT be overcome by ↑ [agonist]



Note – Efficacy (E_{MAX}) is ↓, but potency (or EC_{50}) is unchanged

Important to note – "Allosteric modulators":
- Allosteric modulators have reversible activity but do not fit neatly as either a competitive or non-competitive antagonist → these drugs bind to a separate site as the agonist, BUT alter binding characteristics of agonist without having any discernible effects of its own
- They can be either:
  - (i) –ve allosteric modulators – ↓ activity of agonist (Eg. Bz at GABA-A receptor)
  - (ii) +ve allosteric modulators – ↑ activity of agonist

- (b) Irreversible (Eg. phenoxybenzamine at α receptor)
  - Drug binds irreversibly to same site as agonist or at a separate site → prevent agonist binding or reduce agonist activity
  - Antagonism CANNOT be overcome by ↑ [agonist]

(E) **Mechanism of General Anaesthetic Agents**:

Overview of general anaesthesia (GA):

- General anaesthesia → defined as altered physiological state characterised by reversible loss of consciousness, analgesia of entire body, amnesia and some degree of muscle relaxation
- Multiple agents can produce GA → Xe, N_2O, volatile agents, IV induction agents, Etc.

Site of GA action:

GA agents act at various sites in CNS:

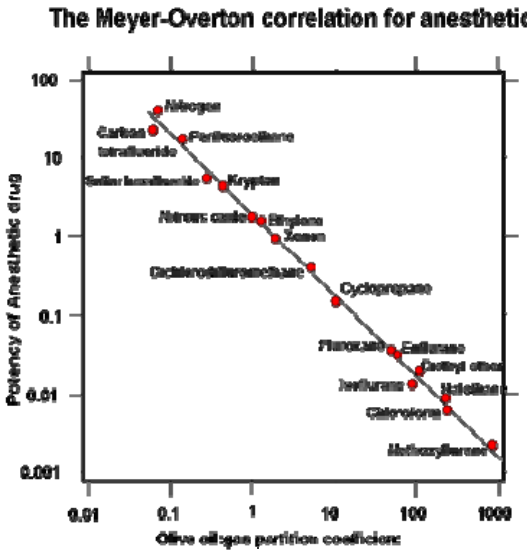
- (1) Macroscopically → in brain (esp at reticular activating system, cerebral cortex, hippocampus, Etc.) and spinal cord (esp at level of dorsal horn interneurons)

> Note – Different aspects of GA relate to different sites of action → LOC and amnesia are mediated by cortical sites, while suppression of purposeful withdrawal from pain is mediated by subcortical sites of action (Eg. spinal cord, brainstem)

- (2) Microscopically → mainly affects synaptic transmission (pre- and post-synaptically), rather than axonal conduction

Mechanisms of GA:

- (1) "Meyer-Overton rule"
  - Anaesthetic potency of inhalational agents correlates directly with their lipid solubility → implies GA results from molecules dissolving at specific lipophilic sites



- (2) "Critical volume hypothesis"
  - Neuronal membranes contain hydrophobic sites in cell membrane → GA agent binds to these sites and expand bilayer membrane to critical state, effectively altering their membrane function
- (3) "Fluidisation theory of anaesthesia"
  - GA agent binds to neuronal cell membrane and significantly modifies its structure (Ie. causing hydrophobic membrane proteins to undergo conformational changes → inhibits synaptic or neuron function by disrupting ion channel function (Ie. alters electrolyte permeability of membrane)
- (4) Binding of ligand-gated ion channels:
  - (i) GABA-A receptor – Most GA agents (Eg. propofol, barbiturates, volatiles, Bz) enhance GABA-A mediated-inhibition of the CNS → potentiation of GABA-A receptor activity (by ↑ channel opening time) correlates with anaesthetic potency
  - (ii) Glycine receptor – Volatiles potentiate action of glycine
  - (iii) NMDA receptor – Ketamine, N_2O, Xe non-competitively inhibit excitatory glutamatic neurotransmission