SAMPLE PREVIEW

BPS2012

Pharmacology II

Drug Action

Comprehensive Study Notes

HD 85 • Monash University

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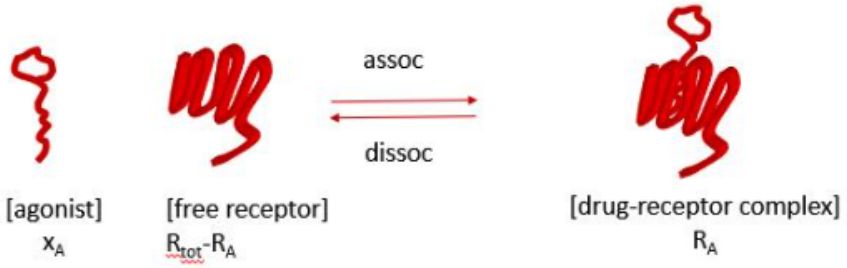
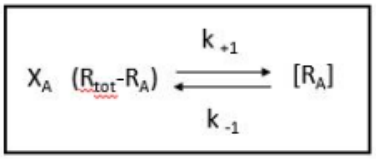
BPS2012 Pharmacology II: Drug Action

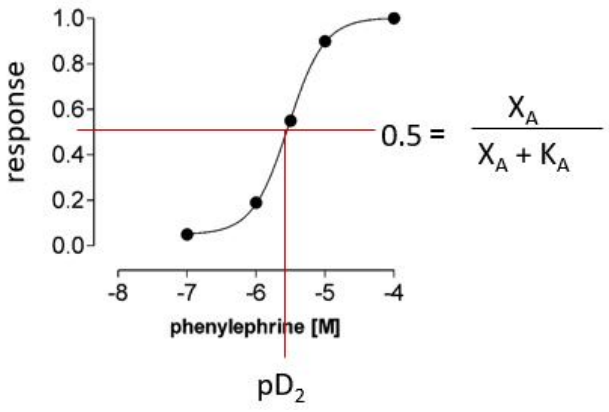
Agonists

- **Receptor occupation / Drug-receptor complex formation**
  - Note: Ligand = agonist or antagonist
  - If the ligand is an agonist, the formation of a ligand-receptor complex initiates a receptor-mediated pharmacological activity
- **Law of mass action**
  - Assumptions:
    - Receptors are free or bound
    - Ligands can freely access receptors
    - Binding is reversible
    - Ligand-receptor complex formation does not change either the receptor or liinverse gand (agonist - receptor binding doesn't change either the receptor or agonist)





  - Forward reaction
    - k1 = association rate constant
    - $k_{+1}(X_A (R_{tot}-R_A))$
  - Backward reaction
    - k2 = dissociation rate constant
    - $k_{-1}(R_A)$
  - Equilibrium
    - $k_{+1}(X_A (R_{tot}-R_A)) = k_{-1}(R_A)$
    - Dissociation constant
      - Concentration of agonist required to produce 50% of the maximal response receptor sites at equilibrium (EC50) = represents affinity of a receptor for an agonist
    - Hill-Langmuir equation

- $P_A = X_A / (K_A + X_A)$
- Ka = EC50 = concentration of drug required to occupy 50% of the receptor sites at equilibrium (equilibrium constant)
    - Refers to the effect of an agonist on receptor sites
- IC50 = concentration of a drug needed to inhibit a response by 50% (half-maximal inhibitory concentration)
    - Refers to potencies of antagonist on receptor sites
- Pa = proportion of receptor occupied / response
- 

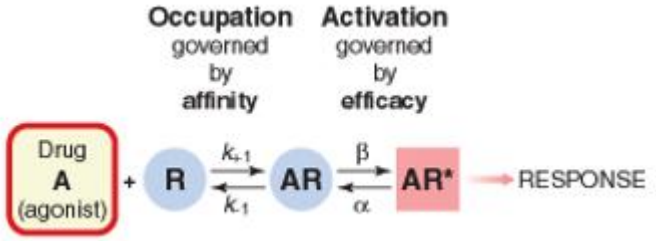
    - pD2 = EC50
- Reasons for a maximal response (maximum response = 1)
    - All receptors are occupied = receptor saturation
    - Internal cellular machinery could be fully responding (contraction mechanism saturated) = saturation

- **Definitions**
    - Affinity → extent to which a ligand binds to a receptor and forms a complex at a given concentration: the strength of binding
    - Potency → proportional to affinity, thus stronger a drug or ligand binds, the less concentration is needed to produce a response
    - Efficacy → ability of the agonist-receptor complex to elicit a response from the cell or tissue. Note: also intrinsic efficacy or activity

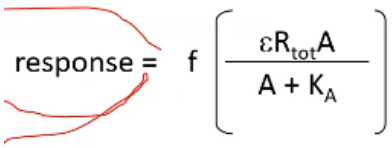
Partial agonists

- Both full and partial agonists bind with equal strength to the receptor
- Full and partial agonists elicit different responses
- Partial agonists are weaker activators of signaling, thus regardless of the concentration, they will never produce a maximal response

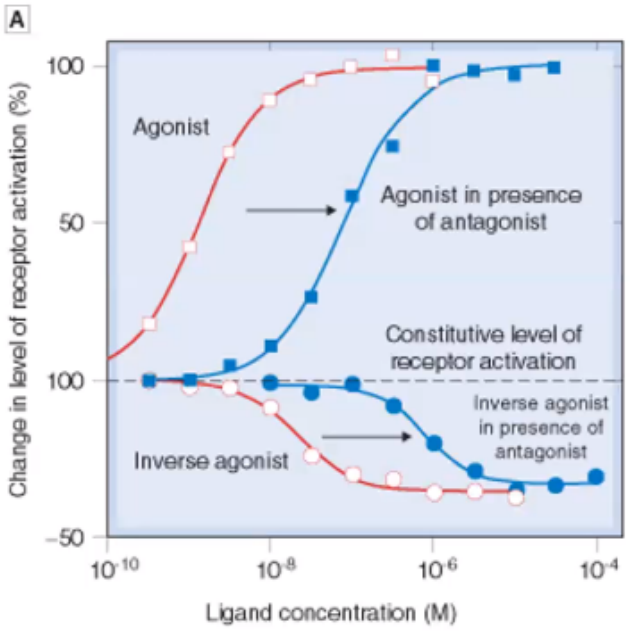
- 1956, Stephenson suggested a measure of agonist activity = efficacy
  - Efficacy = capacity to initiate a response once it occupies a receptor
  - Assumptions to elicit an effect, an agonist must:
    - Bind to a receptor = affinity
    - Activate the receptor = efficacy
- **Two-state model**

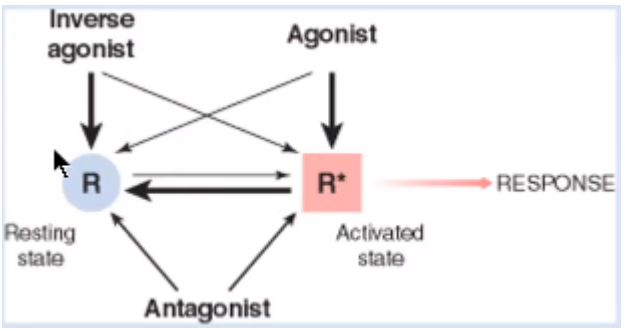


  - Includes both affinity (occupation) and efficacy (activation)
  - Assumes the tendency for the agonist-receptor complex to convert to the agonist-receptor complex's active state depends on the beta-alpha reaction's equilibrium constant.
  - Agonists with high efficacy with have a high beta-alpha, whereas partial agonist that cannot elicit a maximal response has lower efficacy and thus low beta alpha
  - Inverse agonist binds to active complex and actively shifts complex to inactive complex
  - Efficacy = ratio of a partial agonist maximum response / full agonist maximum response
- Response



  - f = transducer function (see basic signalling)*
  - R_{tot} = total number of receptors*
  - ε = intrinsic efficacy**
  - K_A = equilibrium constant**
  - To compare different response curves use this equation
  - * = properties of tissues
  - ** = properties of agonist-receptor interaction
- **Agonist and Inverse Agonist + Constitutive activity**

- An inverse agonist is a ligand that binds to the same receptor-binding site as an agonist and not only antagonizes the effects of an agonist but, moreover, exerts the opposite effect by suppressing spontaneous receptor signaling
- 

    - Constitutive activity = Receptors can be active without an agonist
        - Sometimes “agonists” might switch receptors off
    - Antagonists blocking binding site for agonists and inverse agonists to use
- 

    - Inverse agonist binds preferentially to R and will actively shift receptors from R* to R (active to resting state)
    - Agonist binds preferentially to R (given higher affinity for R) and actively shift receptors from R to R* (resting to active state)
    - The pure antagonist has no preference for (active or resting state) R or R*. When it binds there is no change in the receptor activity
- **Ternary complex model**

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